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ORIGINAL ARTICLE

Dissociating Parieto-Frontal Networks for Phonological and Semantic Word Decisions: A Condition-and-Perturb TMS Study

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Abstract

Left posterior inferior frontal gyrus (pIFG) and supramarginal gyrus (SMG) are key regions for phonological decisions, whereas angular gyrus (ANG) and anterior IFG (aIFG) are associated with semantics. However, it is less clear whether the functional contribution of one area changes in the presence of a dysfunctional area within the network. Using repetitive transcranial magnetic stimulation (rTMS), we first tested whether perturbing one area would disrupt behavior. Second, we applied a condition-and-perturb approach, combining parietal offline rTMS with frontal online rTMS to investigate how the functional contribution of a frontal region changes in the presence of a dysfunctional parietal region. We found that rTMS over SMG or pIFG delayed phonological decisions, but this was not enhanced by combining supramarginal rTMS with pIFG rTMS. In contrast, semantic decisions were only impaired when angular rTMS was combined with aIFG rTMS. We infer that offline rTMS caused a dysfunction of ANG which increased the functional relevance of aIFG for semantic decisions and sensitized this network to the disruptive effects of aIFG rTMS. The results provide causal evidence that ANG and aIFG contribute to semantics and that the functional significance of one area within this network depends on the functional integrity of the other.

Key words: inferior frontal gyrus, language, parietal cortex, transcranial magnetic stimulation, virtual lesion

Introduction

Successful human communication critically depends on efficient language comprehension and production. This involves the automatic analysis of the sound patterns of a particular language (its phonology) as well as the analysis of the meaning of that language (its semantics). Functional neuroimaging studies in healthy volunteers showed that phonological decisions (decisions about the sound structure of a word) engage left posterior inferior frontal gyrus (pIFG) and supramarginal gyrus (SMG) (Price et al. 1997; Poldrack et al. 1999; Devlin et al. 2003). Conversely, semantic decisions (decisions about the meaning of a word) consistently recruited left anterior IFG (aIFG) and angular gyrus (ANG) (Devlin et al. 2003; Vigneau et al. 2006; Binder et al. 2009). One idea arising from these studies is that phonological and semantic decisions might be implemented in functionally different networks, with SMG and pIFG contributing to phonological decisions (phonological network), and ANG and aIFG contributing to semantic word decisions (semantic network). A critical question is how the functional contribution of one area changes in the presence of a dysfunctional node within the same network.

Studies on patients with structural lesions provided evidence for a causal contribution of distinct parietal and frontal regions to phonological and semantic processing (Corbett et al. 2009; Dewarrat et al. 2009). Similarly, findings obtained in repetitive transcranial magnetic stimulation (rTMS) studies targeting single regions are consistent with the notion of separate parieto-frontal networks each comprising 2 different and mutually exclusive nodes. According to these studies, left pIFG contributes to phonological decisions whereas the aIFG is more engaged in semantic decisions (Devlin et al. 2003; Gough et al. 2005; Romero et al. 2006). Although a functional-anatomic double dissociation for phonological versus semantic processing has been suggested for the inferior parietal cortex (Stoeckel et al. 2009), recent rTMS studies have only provided evidence for a critical contribution of left SMG to phonological decisions (Romero et al. 2006; Hartwigsen, Baumgaertner et al. 2010; Sliwinska et al. 2012) whereas rTMS over ANG during semantic decisions did not disrupt task processing (Hartwigsen, Baumgaertner et al. 2010). Neither studies drawing from structural lesions nor those relying on unifocal virtual lesions are suited to address the question of relative contribution and functional interaction between different network nodes.

To uncover the functional contribution of parietal and frontal network nodes subserving phonological and semantic decisions, we performed 2 experiments. Experiment 1 tested whether a unifocal perturbation of a frontal or parietal area alone was already sufficient to disrupt task processing. Experiment 2 combined offline rTMS before a task over a parietal area with online rTMS during a task over a frontal area. This condition-and-perturb rTMS approach was adopted to investigate how the functional contribution of a frontal region changes in the presence of a dysfunctional parietal region (Hartwigsen et al. 2012). We hypothesized that the acute lesion effect induced by online rTMS over the critical frontal node within a network might be enhanced if the respective parietal region was conditioned with offline rTMS. Specific predictions can be found in the "Experimental Design" section.

Materials and Methods

Subjects

The initial sample size was set to $n = 20$. Note that data quality of the T1-weighted MR image was not sufficient for 1 subject. Two other subjects decided not to continue with the TMS procedure during or after their initial TMS session since they felt uncomfortable with the stimulation procedure. Hence, the remaining 17 native German speakers (7 females, age range: 23–30 years, mean age: 25.7 years) with no history of neurological disorders or head injury were included in Experiment 1, which was designed to examine the effect of unifocal offline or online rTMS over different parietal and frontal nodes. A total of 17 different native German speakers (9 females, age range: 20–30 years, mean age: 24.7 years) participated in Experiment 2 in which we investigated the effect of combined offline and online rTMS over parieto-frontal networks. All subjects were right-handed (laterality index >95%) according to the Edinburgh Handedness Inventory (Oldfield 1971) and were naive to TMS. Written informed consent was obtained before the experiment. The study was performed according to the guidelines of the Declaration of Helsinki and approved by the local Ethics committee of the Medical Faculty of the University of Leipzig.

Experimental Design

Parieto-frontal contributions to semantic and phonological processing were probed in 2 experiments. Both experiments used the same tasks and stimuli. To avoid extensive repetition of the same stimulus set and habituation effects, each experiment employed a different group of healthy participants. Both groups underwent 4 experimental sessions with an inter-session interval of at least 5 days between all sessions.

Motivated by the previous rTMS studies on the role of different parietal and inferior frontal regions in semantic versus phonological processing (Devlin et al. 2003; Gough et al. 2005; Romero et al. 2006; Hartwigsen, Baumgaertner et al. 2010; Hartwigsen, Price et al. 2010), we used a condition-and-perturb approach combining offline rTMS over a parietal area with online rTMS over a frontal site. Specifically, this enabled us to investigate how the functional contribution of left inferior frontal gyrus to phonological and semantic decisions changes in the presence of a dysfunctional parietal area. To render the rTMS procedures comparable for both experiments, we always targeted parietal areas with offline rTMS and perturbed frontal areas with online rTMS for both effective versus sham rTMS. We chose to condition the parietal areas with offline rTMS and perturb the frontal nodes with online rTMS as recent functional-anatomic models on language processing generally assume that information is first analyzed and stored in temporo-parietal areas and then mapped to frontal nodes (Baddeley 1992; 2003a,b; Hickok and Poeppel 2004, 2007). Particularly, this enabled us to investigate whether the parietal nodes would be able to compensate for the rTMS-induced disruption of the frontal areas (and vice versa) unless they were additionally conditioned with offline rTMS. Note that it was not possible to target both areas of interest with online rTMS as the distance between the parietal and frontal areas was too small to allow for simultaneous coil placement.

Experiment 1: Effects of Unifocal Offline or Online rTMS over Different Parietal and Frontal Nodes

In this experiment, we investigated whether a unifocal lesion over either an inferior parietal (i.e., ANG and SMG) or an inferior frontal node (i.e., aIFG and pIFG) was already sufficient to significantly disrupt semantic or phonological decisions.

Experiment 1 used a 4 × 2 within-subject factorial design with 4 different rTMS sites (offline rTMS over ANG, offline rTMS over SMG, online rTMS over aIFG and online rTMS over pIFG) and 2 tasks (phonological and semantic decisions). Each participant participated in 4 sessions and received rTMS over different parietal and frontal nodes for phonological and semantic processing (Fig. 1*A*–*D*). The order of sessions was counterbalanced across subjects to the best possible degree. Note that complete counterbalancing of the session order was not possible with 17 subjects included in each experiment. To match Experiment 1 as closely as possible with Experiment 2, each rTMS application was combined with sham rTMS. Specifically, offline rTMS over ANG and SMG was combined with sham online rTMS over aIFG or pIFG and online rTMS over aIFG and pIFG was combined with sham offline rTMS over ANG or SMG. The full within-subject factorial design enabled us to test for main effects and interactions between the factors task and rTMS while controlling for stimulus and repetition effects.

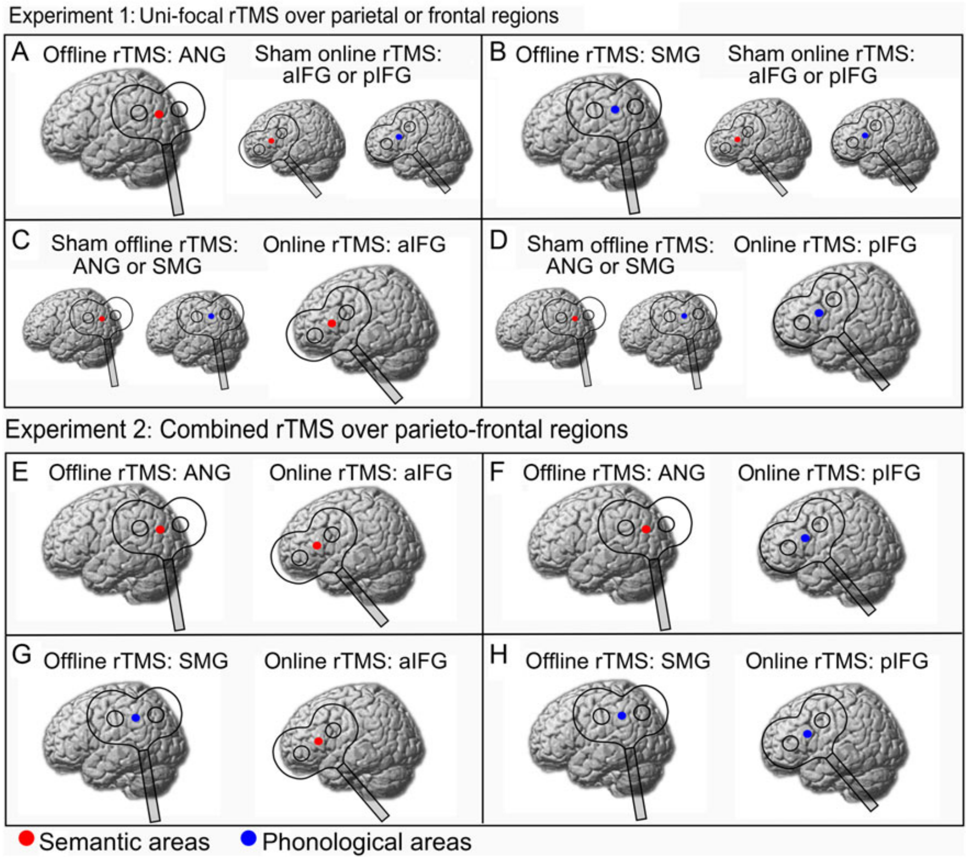

Figure 1. rTMS sites for the parieto-frontal networks targeted with unifocal rTMS (*A–D*) and combined rTMS over parietal and frontal areas (*E–H*). Experiment 1: (*A*) In 1 session, offline rTMS of left ANG during quiet wakefulness was combined with subsequent sham online rTMS of either left anterior or posterior inferior frontal gyrus (aIFG or pIFG; counterbalanced across subjects). (*B*) In another session, offline rTMS of left SMG preceded sham online rTMS of either aIFG or pIFG. (*C*) Sham offline rTMS of ANG or SMG (counterbalanced across subjects) was followed by online rTMS of left aIFG. (*D*) Sham offline rTMS of ANG or SMG was combined with online rTMS of pIFG. Experiment 2: (*E*) Semantic network: In 1 session, offline rTMS was applied to ANG and subsequent online rTMS targeted aIFG. (*F*) Offline rTMS of ANG was combined with online rTMS over pIFG. (*G*) Offline rTMS over SMG preceded online rTMS over aIFG. (*H*) Phonological network: Offline rTMS over SMG was combined with online rTMS to pIFG.

Based on the results from previous studies (Devlin et al. 2003; Gough et al. 2005; Hartwigsen, Baumgaertner et al. 2010; Hartwigsen, Price et al. 2010), our first hypothesis was that a focal perturbation of either left pIFG or SMG (combined with sham rTMS) should affect the speed or accuracy of phonological but not semantic decisions. The role of left aIFG and ANG in semantic processing is less clear. Although some rTMS studies reported prolonged reaction times after rTMS of aIFG (Devlin et al. 2003; Gough et al. 2005), our previous studies (Hartwigsen, Baumgaertner et al. 2010; Hartwigsen, Price et al. 2010) did not find evidence for a causal contribution of left aIFG or ANG to semantic processing. Consequently, 1 hypothesis was that a unifocal lesion to either aIFG or ANG was sufficient to increase the speed or error rates during semantic relative to phonological processing. An alternative hypothesis was that a unifocal lesion over either area was not sufficient to disrupt semantic processing since the respective other intact area might have compensated for the rTMS-induced disruption.

Note that the previous studies described earlier had already demonstrated that SMG and pIFG contribute to phonological decisions whereas aIFG and ANG were associated with semantic processing. Consequently, the main aim of the current experiment was not to contrast phonological and semantic decisions per se but rather to investigate how much each area of the respective network is critical to semantic or phonological processing.

Experiment 2: Effects of Combined Offline and Online rTMS over Different Parieto-Frontal Networks

This experiment used a $2 \times 2 \times 2$ within-subject factorial design with 2 different offline rTMS sites in the left inferior parietal cortex (rTMS over ANG vs. SMG), 2 online rTMS sites in left IFG (rTMS over aIFG vs. pIFG) and 2 tasks (phonological and semantic decisions). Each participant received 4 combinations of conditioning and perturbing rTMS over different parieto-frontal nodes for phonological and semantic processing with the order of sessions being counterbalanced across subjects to the best possible degree (Fig. 1*E–H*).

The condition-and-perturb experiment was used to investigate whether conditioning a parietal region with offline rTMS would increase the perturbing effect of online rTMS over a frontal area. We expected that the parietal area might to some degree be able to compensate for the acute rTMS-induced frontal lesion effect and maintain task-function unless it was additionally perturbed by offline rTMS. More specifically, we expected that offline conditioning of SMG might sensitize the phonological network to disruption of left pIFG by online rTMS during phonological decisions, whereas the disruptive effect of online rTMS over aIFG during semantic word decisions might be enhanced by offline conditioning of left ANG. Consequently, for phonological versus semantic decisions, our hypothesis was that the virtual lesion effect would be enhanced after combined rTMS over both pIFG and SMG relative to rTMS over either region alone combined with a semantic area (i.e., ANG or aIFG). For semantic decisions, we expected that combined rTMS over both aIFG and ANG should increase the total lesion load and might thus disrupt semantic relative to phonological processing.

Tasks

Subjects performed 2 tasks on the same set of auditorily presented word stimuli in both experiments (Fig. 2). In the phonological task, subjects categorized the words as having 2 or 3 syllables. The semantic task required participants to decide whether a word represented a natural or man-made item. Tasks were blocked to ensure a constant cognitive set. Subjects were instructed to respond as quickly and accurately as possible by pressing a button on a response pad with their left middle or index finger (Fig. 2C).

Stimuli

We used 120 German nouns for stimulus presentation. The stimuli were taken from previous studies (see [Hartwigsen, Baumgaertner et al. 2010; Hartwigsen, Price et al. 2010] for more details). Only highly frequent, unambiguous nouns from the CELEX lexical database for German (Centre for Lexical Information, Max Planck Institute for Psycholinguistics, The Netherlands) were selected. In total, 60 two-syllable nouns and 60 three-syllable nouns were selected. All words represented natural or man-made items (i.e., 50% of the 2-syllable words and 50% of the 3-syllable words, respectively).

Procedure

As a prerequisite for neuronavigated rTMS, all subjects underwent structural MR imaging (Siemens Verio 3-Tesla scanner; Siemens). This included a high-resolution T1-weighted anatomical scan for each subject (MPRAGE; 170 slices, voxel size = $1 \times 1 \times 1.5$ mm^3, matrix = 240×240 $pixel^2$, TR = 1.3 s, TE = 3.46 ms).

Subjects performed a practice session with 3 trials of the phonological and semantic task each. The stimuli used for the practice session were not included in the main experiment. During the practice session, sound volume was individually adjusted for each subject. Stimuli were presented via in-ear headphones equipped with earplugs to shield the subject from the rTMS-induced noise.

Each experimental session started with individual stereotactic co-registration and the determination of the active motor threshold (see "Transcranial Magnetic Stimulation" for details). Neuronavigated rTMS was subsequently applied over different left hemisphere parieto-frontal nodes in 4 sessions (Fig. 1). The order of sessions was counterbalanced across subjects (to the degree possible), and all sessions were performed at least 5 days apart to prevent any carry-over effects of the stimulation procedures.

The main experiment started with the application of the offline rTMS protocol (Fig. 2*A*,*B*). After a rest period of 5 min to allow for the unfolding of the inhibitory stimulation effect (Huang et al. 2005), the TMS coil was moved to either aIFG or pIFG and subjects had to decide whether an auditorily presented German noun (e.g., "Tunnel") consisted of 2 or 3 syllables (phonological task) or represented a natural or man-made item (semantic task) in 2 blocks (Fig. 2C). The order of blocks was counterbalanced across

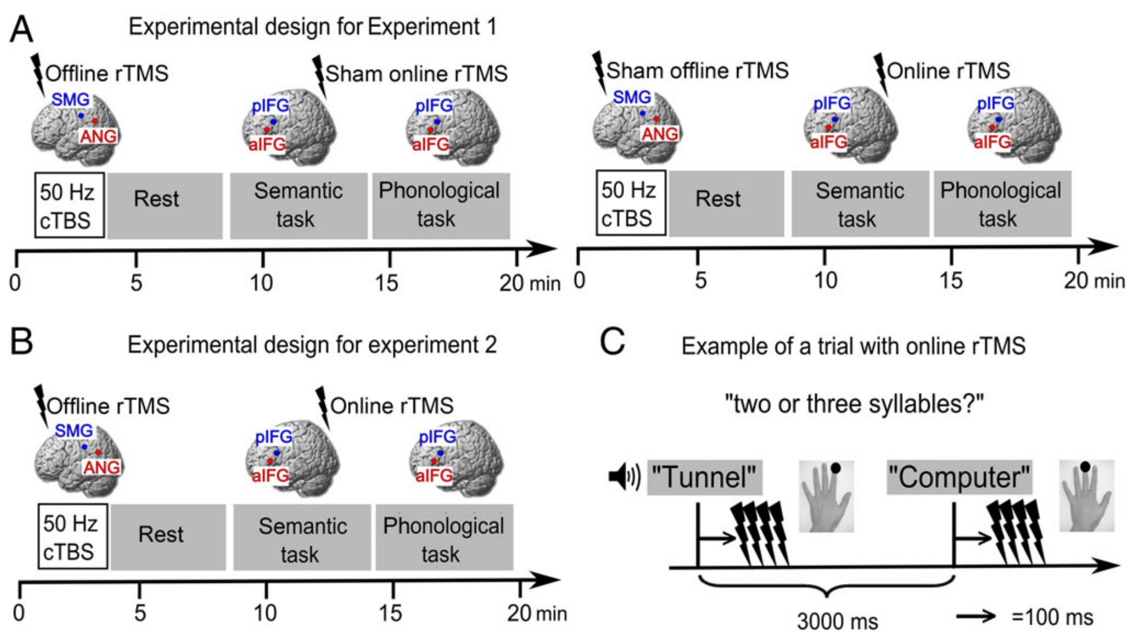

Figure 2. Experimental design. (*A*) Experiment 1. Left panel: After a training session, subjects received 50 Hz of offline continuous theta burst stimulation (cTBS) either over SMG or ANG in different sessions. A rest period of 5 min was included to allow for the unfolding of the cTBS effect. Afterward, subjects performed the semantic and phonological tasks while receiving high-frequency sham online rTMS over either the aIFG or pIFG in different sessions. The order of semantic and phonological blocks was counterbalanced across subjects. Right panel: In 2 additional sessions, subjects received sham offline cTBS over ANG or SMG and online rTMS over aIFG or pIFG. (*B*) Experiment 2. Subjects received a combination of effective offline and online rTMS in 4 different sessions without any sham rTMS. In all other aspects, this experiment was identical to Experiment 1. (*C*) Each trial had a duration of 3000 ms. During each trial, an auditory word was presented and subjects responded via button press with their left hand. 10 Hz online rTMS (or sham rTMS in 2 sessions of Experiment 1) was applied 100 ms after word onset during each trial. Subjects responded with their left index or middle finger.

subjects. During each 3-s trial, a four-pulse train of perturbing 10 Hz online rTMS was applied 100 ms after word onset.

Mean stimulus duration was 0.78 s (range = 0.74–0.87 s). Across the whole experiment, participants were asked to fixate a cross that was presented on a computer screen that was positioned in front of the subjects' head at a distance of ~60 cm. Stimulus presentation and response recording was controlled via E-PRIME software (Psychology Software Tools, Inc.; version 2.0).

Transcranial Magnetic Stimulation

We used frameless stereotaxy (Brainsight 2, Rogue Research, Montreal) based on the coregistered individual T1-weighted MR image to navigate the TMS coil and maintain the exact location and orientation throughout the experimental sessions.

Neuronavigated rTMS was performed by using the mean Montreal Neurological Institute (MNI) coordinates determined previously (i.e., SMG: $x, y, z = -45, -39, 45$ mm; ANG: $x, y, z = -42, -66, 28$ mm; aIFG: $x, y, z = -45, 27, 12$ mm and pIFG: $x, y, z = -47, 6, 21$ mm [Hartwigsen, Baumgaertner et al. 2010; Hartwigsen, Price et al. 2010]). Individual stimulation sites were determined by calculating the inverse of the normalization transformation and transforming these coordinates from standard to individual space for each subject using Matlab 7.1 (The Mathworks, Inc.).

For offline rTMS, the coil was placed over either SMG or ANG, and a total of 600 pulses of 50 Hz continuous theta burst stimulation (cTBS) (Huang et al. 2005) were applied in trains of 3 stimuli at an inter-burst interval of 200 ms for 40 s. The coil was positioned with the handle pointing lateral and perpendicular to the midline over left SMG or ANG, with the second phase of the biphasic pulse inducing a lateral to medial current flow (Hartwigsen, Baumgaertner et al. 2010; Fig. 1). Following Huang et al. (2005), stimulation intensity for cTBS was set to 80% of individual active motor threshold of the left primary motor hand area. AMT was defined as the lowest stimulus intensity producing an MEP of ~150–200 µV in the tonically active first dorsal interosseus muscle at 20% of maximum contraction.

After cTBS, the coil was moved to aIFG or pIFG and fixed over either stimulation site (Fig. 1). The coil was placed tangentially on the head with the handle pointing at 45° to the sagittal plane, with the second phase of the biphasic pulse inducing a posterior to anterior current flow (Hartwigsen, Price et al. 2010). Stimulation intensity for online rTMS was set to 90% of the active motor threshold as in our previous study that targeted the inferior frontal gyrus (Hartwigsen, Price et al. 2010). Note that we were not able to use higher stimulation intensities in our study because subjects had reported substantial discomfort and muscle contractions at stimulus intensities of >100% active motor threshold in a pilot study when rTMS was given over aIFG [see Hartwigsen, Price et al. 2010].

During each experimental trial, a four-pulse train of biphasic stimuli was applied at a rate of 10 Hz 100 ms after word onset. A figure-of-eight-shaped coil (MC-CB-60; outer diameter 7.5 cm) connected to a MagPro X100 stimulator (Medtronic) was used in all rTMS conditions, and the overall application of rTMS pulses was within the recommended safety limits (Rossi et al. 2009). For sham rTMS, we used a specially designed figure-of-eight-shaped placebo coil (MCF-P-B-65; outer diameter 7.5 cm) that creates a sound level identical to the MC-CB-60 coil but provides an effective field reduction of 80%.

Data Analyses

Behavioral Data

Repeated-measures ANOVAs were used to separately investigate the effects of rTMS on reaction times in both experiments and error rates in Experiment 2 since Kolmogorov–Smirnov tests had indicated that the normal distribution was not violated. The Greenhouse-Geisser correction was used to correct for non-sphericity when appropriate. Error rates for Experiment 1 were investigated with non-parametric Wilcoxon signed-rank tests since these data were not normally distributed, precluding the use of an ANOVA.

An α-level of 0.05 (two-tailed) was considered significant for all comparisons in the ANOVAs. Two-tailed Bonferroni–Holm-corrected *post hoc* paired *t*-tests further explored differences among conditions. The required threshold for each comparison is given in brackets in the Results section. All statistical analyses were performed with SPSS (version 20).

Results

Experiment 1: Effects of Unifocal Offline or Online rTMS over Different Parietal and Frontal Nodes

This experiment used a two-way repeated-measures ANOVA with the factors rTMS (4 levels: aIFG, pIFG, ANG and SMG, each combined with sham rTMS) and task (2 levels: semantic vs. phonological decisions) to test for the disruptive effects of unifocal rTMS over parietal and frontal areas (combined with sham rTMS). rTMS differentially influenced reaction times for phonological and semantic decisions (see Table 1 for mean reaction times and error rates). This was evidenced by a significant

Table 1 Mean reaction times and error rates for Experiments 1 and 2

rTMS condition	Semantic word judgments		Phonological word judgments	
	RTs ± SEM(ms)	ERs ± SEM (%)	RTs ± SEM(ms)	ERs ± SEM (%)
Experiment 1: unifocal rTMS over parietal and frontal areas				
Offline: ANG and online: sham	972.48 ± 41.68	0.0255 ± 0.0073	972.07 ± 34.33	0.0588 ± 0.0228
Offline: SMG and online: sham	953.46 ± 42.68	0.0294 ± 0.0083	1070.33 ± 51.96	0.0480 ± 0.0108
Offline: sham and online: aIFG	1007.93 ± 42.89	0.0255 ± 0.0072	985.00 ± 36.41	0.0353 ± 0.0116
Offline: sham and online: pIFG	958.76 ± 37.34	0.0316 ± 0.0108	1057.75 ± 46.13	0.0657 ± 0.0150
Experiment 2: combined offline and online rTMS over parietal and frontal areas				
Offline: ANG and online: aIFG	1060.67 ± 26.61	0.0445 ± 0.0068	949.43 ± 26.16	0.0269 ± 0.0064
Offline: ANG and online pIFG	987.35 ± 26.06	0.0402 ± 0.0095	1047.74 ± 28.19	0.0412 ± 0.0076
Offline: SMG and online: aIFG	988.43 ± 34.07	0.0333 ± 0.0090	1029.63 ± 47.84	0.0431 ± 0.0105
Offline: SMG and online: pIFG	972.48 ± 29.84	0.0402 ± 0.0094	1074.92 ± 40.59	0.0422 ± 0.0044

a/pIFG, anterior/posterior inferior frontal gyrus; ANG, angular gyrus; ERs, error rates (in %); RTs, reaction times (in milliseconds); SEM, standard error of the mean; SMG, supramarginal gyrus.

rTMS by task interaction ($F_{3,48} = 4.93$; $P = 0.005$). *Post hoc* paired *t*-tests revealed significantly prolonged reaction times for phonological relative to semantic decisions after either offline rTMS of SMG ($t_{16} = 3.52$; $P = 0.003$; Bonferroni–Holm corrected: $P < 0.00625$) or online rTMS of pIFG ($t_{16} = 3.11$; $P = 0.007$; Bonferroni–Holm corrected: $P < 0.008$, Fig. 3A). Accordingly, we found longer phonological reaction times relative to semantic reaction times after offline rTMS over SMG compared with offline rTMS over ANG ($t_{16} = 3.21$; $P = 0.006$; Bonferroni–Holm corrected: $P < 0.0071$) (Fig. 3A). Phonological reaction times were also delayed by online rTMS of pIFG relative to online rTMS of aIFG (not significant, $t_{16} = 1.99$; $P = 0.064$; required Bonferroni–Holm-corrected threshold: $P < 0.01$). In contrast, there was no significant difference between phonological and semantic reaction times after offline rTMS of ANG ($t_{16} = 0.48$; $P = 0.64$) or online rTMS of aIFG ($t_{16} = 0.56$; $P = 0.58$). Finally, semantic reaction times were delayed after online rTMS of aIFG relative to pIFG (not significant, $t_{16} = 1.80$; $P = 0.09$; required Bonferroni–Holm-corrected threshold: $P < 0.0125$). There were no significant differences in semantic reaction times after offline rTMS of ANG compared with offline rTMS of SMG ($t_{16} = 0.01$; $P = 0.99$).

We did not find any non-specific rTMS effects on reaction times (i.e., no significant main effect of rTMS) or overall difference in reaction times between semantic and phonological decisions (i.e., no significant main effect of task).

In 2 additional one-way repeated-measures ANOVAs with the factor rTMS (4 levels: aIFG, pIFG, ANG and SMG, each combined with sham rTMS) as independent variable and phonological "or" semantic reaction times as dependent measures, we explored the task-specific effects of rTMS separately for each task. The ANOVA on phonological decisions revealed a significant main effect of rTMS ($F_{1.99,\ 31.83} = 5.86$; $P = 0.007$, see Fig. 3A). In contrast, the one-way ANOVA on semantic decisions was not significant ($P = 0.48$). For details on the *post hoc t*-tests, please refer to the Supplementary Material, Results and Fig. 3A. In sum, these analyses confirmed the results from the two-way ANOVA reported earlier.

Analyses of error rates supported the results from the reaction time measures. Hence, we found higher error rates for phonological relative to semantic decisions after online rTMS of pIFG ($Z = 2.70$; $P = 0.006$; Bonferroni–Holm corrected; $P < 0.00625$). Accordingly, Wilcoxon tests indicated significantly higher error rates for phonological decisions after rTMS over pIFG compared with rTMS of aIFG ($Z = 2.62$; $P = 0.007$; Bonferroni–Holm corrected; $P < 0.0071$), but no other comparison reached significance (all $P > 0.18$) (Fig. 3B).

Experiment 2: Effects of Combined Offline and Online rTMS over Different Parieto-Frontal Networks

This experiment tested whether conditioning a parietal region with offline rTMS would increase the perturbing effect of online rTMS over a frontal area.

First, these analyses replicated the findings from the unifocal rTMS experiment that rTMS over either SMG or pIFG selectively delayed phonological but not semantic reaction times (see Table 1 for mean reaction times and error rates). This was evidenced by an interaction between task and offline rTMS ($F_{1,16} = 12.63$; $P = 0.002$; pooled across the factor online rTMS; Fig. 4A) and task and online rTMS ($F_{1,16} = 20.76$; $P = 0.0001$; pooled across the factor offline rTMS; Fig. 4B). For details on the respective *post hoc t*-tests, please refer to the Supplementary Material, Results section and Fig. 4.

As a main novel finding, there was a significant three-way interaction between task, offline rTMS and online rTMS ($F_{1,16} = 5.43$; $P = 0.02$). This interaction was caused by the effects

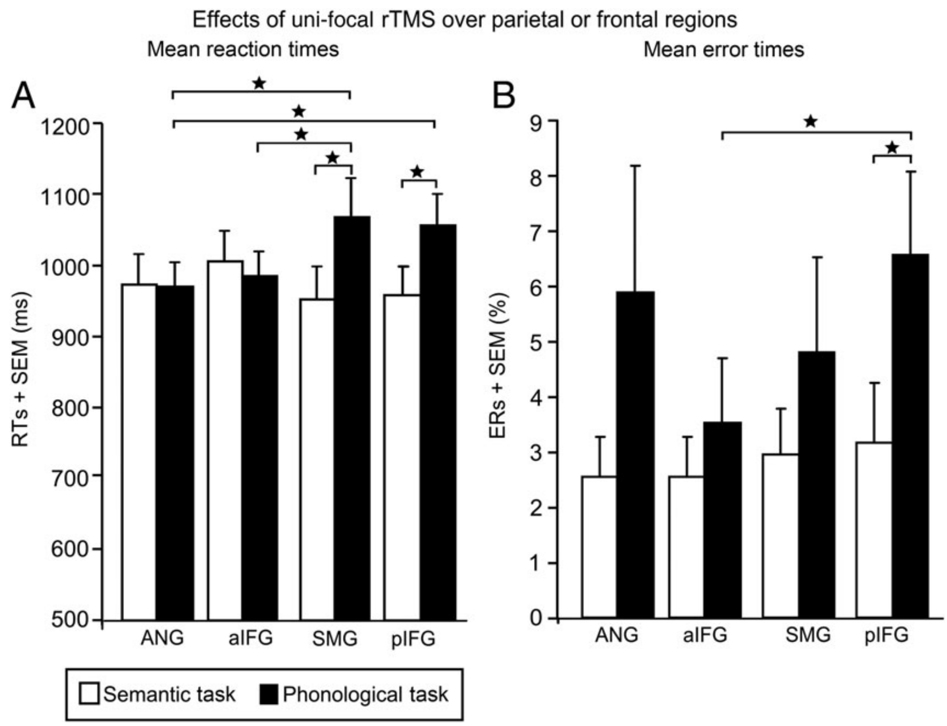

Figure 3. Effects of unifocal rTMS over angular gyurs (ANG), anterior/posterior inferior frontal gyrus (a/pIFG) and SMG (each combined with sham rTMS). (*A*) The significant effects of rTMS on mean reaction times (RTs). (*B*) Effects of unifocal rTMS on mean error rates (ERs). *$P < 0.05$, corrected for multiple comparisons with the Bonferroni–Holm correction; a/pIFG, anterior/posterior inferior frontal gyrus; ANG, angular gyrus; SMG, supramarginal gyrus; SEM, standard error of the mean.

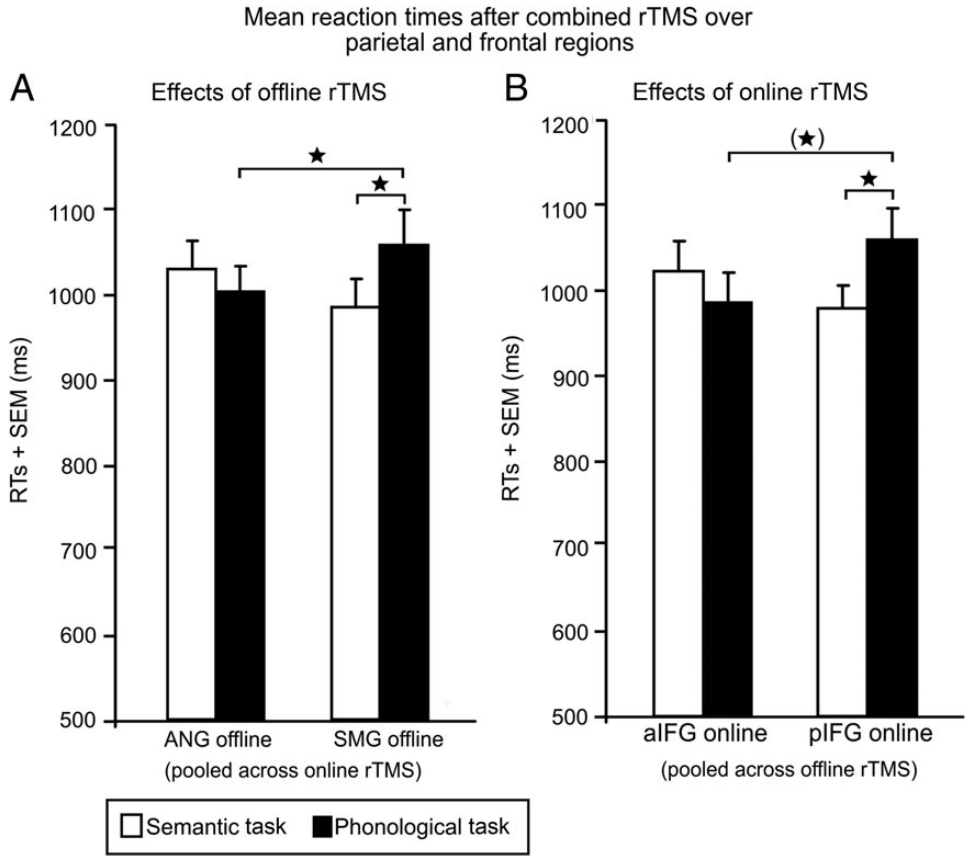

Figure 4. Effects of combined offline and online rTMS on mean reaction times (RTs). (*A*) The significant two-way interaction between task and offline rTMS (pooled across online rTMS). (*B*) The significant two-way interaction between task and online rTMS (pooled across offline rTMS). *$P < 0.05$; two-tailed; corrected for multiple comparisons with the Bonferroni–Holm correction; (*)$P < 0.05$, does not survive the Bonferroni–Holm correction; a/pIFG, anterior/posterior inferior frontal gyrus; ANG, angular gyrus; SMG, supramarginal gyrus; SEM, standard error of the mean.

of rTMS on semantic decisions. Semantic decisions were only delayed when offline rTMS of left ANG preceded online rTMS of left aIFG (Fig. 5A). Accordingly, *post hoc* paired *t*-tests showed significantly longer RTs for semantic decisions relative to phonological decisions after combined rTMS over both ANG and aIFG ($t_{16} = 3.84$; $P = 0.001$; Bonferroni–Holm corrected; $P < 0.0071$). This difference was not significant when online rTMS of aIFG was preceded by offline rTMS over SMG ($t_{16} = 1.32$; $P = 0.20$). In contrast, when offline rTMS of ANG was combined with online rTMS of pIFG, we found longer RTs during phonological relative to semantic decisions ($t_{16} = 2.82$; $P = 0.012$; being at threshold with the Bonferroni–Holm correction requiring a $P < 0.012$), presumably indicating an "online" virtual lesion effect of rTMS over pIFG on phonological decisions. Finally, phonological decisions were significantly prolonged after combined rTMS over both phonological areas (i.e., SMG and pIFG) relative to combined rTMS over both semantic areas (i.e., ANG and aIFG) ($t_{16} = 3.13$; $P = 0.006$; Bonferroni–Holm corrected; $P < 0.0083$). This effect on reaction times was task specific since phonological decisions were significantly prolonged relative to semantic decisions after combined rTMS of both SMG and pIFG ($t_{16} = 4.23$; $P = 0.0001$; Bonferroni–Holm corrected; $P < 0.00625$).

The three-factorial ANOVA yielded no main effects, indicating that neither the site of online or offline rTMS had unspecific effects on reaction times. Overall, reaction times were thus comparable for semantic and phonological decisions.

Again, we performed 2 additional one-way repeated-measures ANOVAs with the factor rTMS (4 levels: ANG-aIFG, ANG-pIFG, SMG-aIFG and SMG-pIFG) to investigate the effects of combined offline and online rTMS on task processing separately for each task. These ANOVAs revealed significant main effects of rTMS for both phonological reaction times ($F_{3,48} = 3.82$; $P = 0.016$) and semantic reaction times ($F_{3,48} = 4.87$; $P = 0.04$). Please refer to the Supplementary Material, Results section for the respective *post hoc t*-tests (see also Fig. 5A).

A repeated-measures ANOVA on error rates revealed no main effects but again a significant three-way interaction for task, offline rTMS and online rTMS ($F_{1,16} = 4.57$; $P = 0.045$; Fig. 5B). *Post hoc* paired *t*-tests only showed a trend toward higher error rates for semantic relative to phonological decisions after combined rTMS over both ANG and aIFG ($t_{16} = 2.05$; $P = 0.049$, does not survive the Bonferroni–Holm correction requiring a $P < 0.00625$). Otherwise, none of the pair-wise comparisons yielded a significant difference in error rates between conditions (all $P > 0.10$). A follow-up one-way repeated-measures ANOVA on semantic error rates only revealed a trend for a difference between the 4 rTMS conditions ($F_{2.20,35.34} = 2.49$; $P = 0.07$). The respective one-way ANOVA on phonological error rates was not significant ($F_{3,48} = 1.02$; $P = 0.39$).

Note that previous studies argued that ANOVAs are not well-suited to analyze binary (categorical) data and might lead to spurious results. Consequently, logit-mixed models were

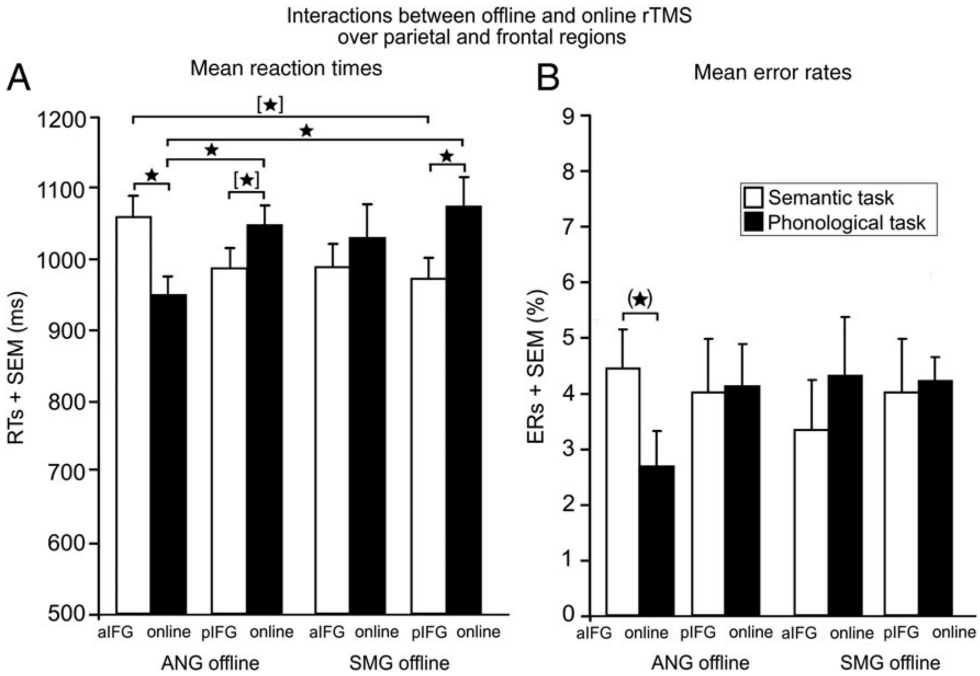

Figure 5. Interactions between offline and online rTMS. (*A*) The significant three-way interaction between task, offline rTMS and online rTMS on mean reaction times (RTs). *P < 0.05; two-tailed; corrected for multiple comparisons with the Bonferroni–Holm correction; [*]P < 0.05, at threshold with the Bonferroni–Holm correction. (*B*) The significant three-way interaction between task, offline and online rTMS on mean error rates (ERs). (*)P < 0.05, two-tailed, does not survive the Bonferroni–Holm correction. a/pIFG, anterior/posterior inferior frontal gyrus; ANG, angular gyrus; SMG, supramarginal gyrus; SEM, standard error of the mean.

introduced as powerful alternatives to conventional ANOVAs (see Jaeger 2008). In a complementary analysis, we applied a mixed model with a binary logistic function to the error data. Since the results from this analysis were very similar to those obtained from the conventional ANOVA, we are confident that the latter can be regarded as valid.

Discussion

This study addressed the functional relevance of parietal and frontal nodes in the left hemisphere during phonological and semantic word decisions by means of a condition-and-perturb rTMS approach. We found causal evidence for 2 segregated functional-anatomic networks subserving phonological versus semantic decisions in the healthy brain (Fig. 6).

Our findings are consistent with the notion that an intact left aIFG led to correct semantic decisions conditional on functional integrity of left ANG. Notably, unifocal rTMS over either left ANG or aIFG (combined with sham rTMS or rTMS of a non-semantic area) did not significantly delay semantic decisions. This is consistent with the hypothesis that the respective other, non-lesioned area might either be sufficient to sustain semantic decisions on its own or have compensated for the rTMS-induced perturbation. In contrast, a “double lesion” induced by combined rTMS of both ANG and aIFG significantly affected the speed and (albeit to a lesser degree) accuracy of semantic relative to phonological decisions. Offline conditioning caused a dysfunction of ANG, which increased the functional relevance of aIFG as the possibly uniquely remaining site capable of proper processing of semantic decisions (Fig. 6A). Alternatively, offline conditioning may have sensitized aIFG to the disruptive effect of online rTMS. In any case, the “lesion effect” caused by acute disruption of neural processing in aIFG was not sufficient to impair semantic

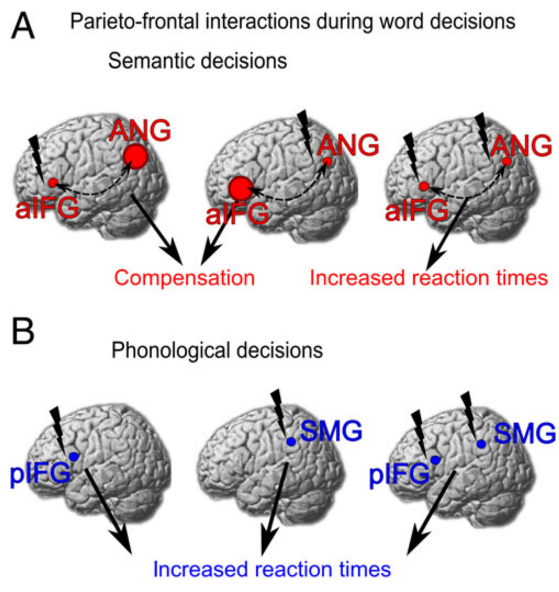

Figure 6. Schematic illustration of parieto-frontal contributions to phonological and semantic word decisions. (*A*) rTMS over either left aIFG or ANG alone does not significantly affect semantic decisions (left and middle panel) because the respective other non-lesioned region can compensate for the rTMS-induced lesion effect as indicated by the large circles. Only combined rTMS over both areas affects reaction times (and to a lesser degree also error rates) (right panel). (*B*) rTMS over either left pIFG or SMG disrupts phonological decisions (left and middle panel) without any additive effect for combined TMS over both regions (right panel).

decisions because intact neural processing in ANG was still sufficient to maintain a normal level of task activation. The impairment of local processing in ANG may have prevented effective compensation of acutely disrupted semantic processing in aIFG and hence impaired semantic processing. Therefore, the observed lesion effect after combined rTMS of ANG and aIFG can be explained by a summation effect of the "lesion effects" induced by both rTMS protocols. These results provide the first causal evidence that both ANG and aIFG jointly contribute to semantic decisions and indicate that the functional significance of one area within this network is critically enhanced when the functional integrity of the other is compromised. Similar findings have been reported for parietal-premotor networks during action reprograming (Hartwigsen et al. 2012). Other studies demonstrated that online rTMS over a homologous cortical site can unmask the offline lesion effect by blocking compensatory processes (Sack et al. 2005). Therefore, it was suggested that the weight of the relative contribution of an area within a network can rapidly change, indicating a general flexibility of brain networks in terms of distributed processing (Hartwigsen et al. 2012).

Our finding of an acute compensation of a unifocal lesion effect during semantic processing fits previous observations that rTMS over either region alone did not affect semantic decisions (Hartwigsen, Baumgaertner et al. 2010; Hartwigsen, Price et al. 2010). However, this interpretation seems to be in discordance with other studies that reported delayed semantic processing after unifocal rTMS over aIFG (Devlin et al. 2003; Gough et al. 2005). These diverging observations may be reconciled by considering methodological details: Indeed, previous studies have used stimulation intensities considerably higher than those used in our study. It is thus conceivable that the potential for an acute compensation of the virtual lesion effect between our parieto-frontal areas might be restricted to a moderate focal dysfunction evoked with rTMS at low stimulation intensities.

With respect to the precise role of left aIFG and ANG in semantic decisions, it was argued that ANG is engaged in all aspects of semantic processing that require concept retrieval and conceptual integration (Binder et al. 2009) and provides semantic constraints during language comprehension (Price 2010). Left aIFG, on the other hand, has been associated with executive semantic processes (Wagner et al. 2001; Heim et al. 2009). Specifically, Martin and Allen (2008) proposed that the semantic store for the maintenance of semantic information in short-term memory is located in the left aIFG (see also [Jonides et al. 1998; Martin and He 2004; Hamilton et al. 2009]). This area was associated with various semantic processing facets including the retrieval of semantic information as well as semantic selection, the maintenance of semantic information and inhibition in verbal working memory tasks (Jonides et al. 1998; Badre and Wagner 2004; Martin and Cheng 2006). This converges with a recent meta-analysis suggesting that executive control over semantic processing is underpinned by a distributed neural network including the left aIFG and ANG (Noonan et al. 2013). Within this network, the aIFG was associated with top-down control, that is, the controlled retrieval and selection of semantic knowledge (Whitney et al. 2012). Accordingly, another study (Whitney et al. 2011) reported that rTMS of the aIFG selectively disrupted executively demanding semantic judgments while leaving semantic decisions based on strong automatic associations unaffected. The ventral part of the left ANG (overlapping our rTMS site), on the other hand, was associated with more automatic, stimulus-driven semantic processing, irrespective of the executive control demands (Noonan et al. 2013; Humphreys and Lambon Ralph 2015). In line with these observations, Kohler et al. (2004) found that rTMS over the aIFG but not over the inferior parietal cortex/ANG modulated semantic word encoding, a process that also draws on executive control demands.

Together, the previous studies suggest a key contribution of both aIFG and ANG to semantic processing, with the ventral ANG being more engaged in automatic, bottom-up processing and the aIFG being more related to top-down control during executively demanding semantic tasks. Our results contribute by demonstrating complementary semantic processing abilities in both areas with semantic word decisions. However, this also indicates a certain degree of redundancy in the parieto-frontal semantic network, at least for cognitively less-demanding tasks. Indeed, we might speculate that the observed compensatory potential between both regions with our data is restricted to semantic tasks with relatively low executive demands, that is, semantic judgments on highly frequent nouns that simply rely on "basic" semantic computations (retrieval of a specific semantic category). In contrast, with increasing control demands, we would predict that the left ANG is not capable to compensate for a disruption of the aIFG. This would be supported by the findings of Gardner et al. (2012) who reported that patients with lesions of the posterior temporal/inferior parietal cortex were less impaired in tasks drawing on executive control processes than patients with lesions of the frontal cortex.

The present study replicated previous findings in healthy volunteers that unifocal rTMS over either left SMG or pIFG disrupted phonological but not semantic decisions (Gough et al. 2005; Romero et al. 2006; Hartwigsen, Price et al. 2010; Grabski et al. 2013), providing further support for the notion that both regions contribute to efficient phonological decisions. Our results extend these studies by showing that the lesion effect over either region cannot be further enhanced by rTMS over both areas. Hence, we did not find support for the hypothesis that targeting both SMG and pIFG with rTMS would increase the disruption of phonological decisions when compared with the application of each rTMS protocol alone. Indeed, the effect of combined stimulation of both areas on phonological decisions matched that induced by rTMS over either area alone (combined with rTMS over a semantic area). Thus, the present study did not find any evidence that disruption of 1 phonological region triggered some degree of acute compensation by the other area (Fig. 6*B*). This critical new result also extends our previous findings that dual-site rTMS over homologous areas in the parietal or frontal cortex did not further increase the disruptive effect induced by unifocal rTMS over either area alone (Hartwigsen, Baumgaertner et al. 2010; Hartwigsen, Price et al. 2010).

Our results show that a single rTMS intervention targeting 1 of the phonological nodes was already sufficient to disrupt phonological decisions at the systems level. Two explanations may account for this observation: Possibly, each region made a unique and essential contribution. Therefore, a focal lesion effect could not be compensated by the non-targeted phonological area. Alternatively, it is conceivable that rTMS-induced excitation may have spread to the interconnected phonological node and unifocal rTMS had already induced a "double lesion" impairing neural processing not only in the targeted area but also in the remote phonological area. Effects by TMS induced in remote anatomically connected areas are well described in the motor system (Bestmann et al. 2003; Siebner et al. 2003; Stefan et al. 2008), although it is less clear whether physiological remote effects are capable to interfere with behavior (Cai et al. 2012).

However, the precise role of left SMG and pIFG in phonological decisions remains unclear. Both areas may be directly involved in phonological processing (e.g., subvocal articulation) or may contribute to executive processing that is particularly important for phonological decisions. Several previous TMS studies suggested a contribution of pIFG and/or SMG to phonological working memory. For instance, Kirschen et al. (2006) demonstrated that rTMS over a region in the inferior parietal lobe closely located to our SMG area significantly modulated phonological short-term memory. In that study, rTMS was applied during rehearsal of phonologically similar or dissimilar pseudowords. Relative to sham rTMS, rTMS over SMG selectively enhanced the retrieval of phonologically similar items, probably by reducing the phonological confusion with these items. Specifically, the authors suggested that the rTMS-induced disruption of the phonological store in the inferior parietal lobe inhibited the formation of item–item associations, thereby improving the ability to differentiate between phonologically similar items. Another study (Nixon et al. 2004) reported impairments in phonological working memory after disruption of left pIFG. In that study, rTMS was applied over either pIFG or aIFG during a delayed phonological matching task either in the delay phase or in the decision phase. rTMS selectively increased phonological errors when applied over pIFG during the delay phase. Accordingly, the authors suggested a role of the left pIFG in the maintenance of phonological representations, probably via subvocal auditory rehearsal. Likewise, Kahn et al. (2005) found that single pulse TMS over the pIFG during phonological encoding affected subsequent memory performance, providing evidence for a role of this area in effective episodic encoding. This further converges with an rTMS study by Romero et al. (2006) who demonstrated a contribution of the pIFG and SMG to phonological judgments as well as short-term retention of verbal material.

Together, the previous studies and our data support the notion of a unique and essential contribution of left SMG und pIFG to phonological decisions. This corresponds with Baddeley's (1992) parieto-frontal "phonological loop" model for temporary short-term memory. Based on the results of patient and neuroimaging studies, it was argued that left SMG was associated with the short-term storage of information, whereas subvocal rehearsal appears to be associated with Broca's area and the premotor cortex (Baddeley 2003a,b). Although our task did not require the generation of any spoken output, counting syllables requires both the short-term storage and the subvocal rehearsal of the presented auditory information. We would thus argue that the disruption of 1 of these processes is already sufficient to impair phonological decisions.

A recent lesion-symptom mapping study on patients with chronic post-stroke aphasia reported that errors on the phonematic structure of spontaneous speech were related to damage of left SMG whereas impairments on the semantic structure were associated with damage of a larger network including left temporo-parietal, temporal and frontal regions (Henseler et al. 2014). This is in agreement with our findings of a greater resilience of the semantic relative to the phonological network against a focal perturbation of a single area.

It needs to be borne in mind that the tasks employed in our study were both meta-linguistic in nature. However, previous imaging studies reported neural activation for these tasks in parieto-frontal networks comparable with those obtained from studies using more natural phonological or semantic tasks such as pseudoword or word reading or rhyming (Vigneau et al. 2006). Hence, we are confident that our tasks indeed require phonological and semantic processing.

Given the variable effects of rTMS reported in previous studies (e.g., (Hamada et al. 2013) and the limited sample size of our study ($n = 17$), future research, in particular involving larger sample sizes, is needed to confirm and further explore the results observed in this study. Particularly, this research might explore whether the stronger robustness of the semantic system is restricted to low rTMS intensities and low executive task demands.

In sum, our results provide novel evidence for a functional-anatomic segregation of parieto-frontal networks for phonological and semantic decisions. The greater robustness of the semantic network against a unifocal rTMS lesion suggests that efficient and accurate semantic decisions may be possible with either an intact ANG or aIFG. Alternatively, this might indicate that left ANG is not as directly connected with aIFG as is left SMG with pIFG, rendering the conditioning of ANG less detrimental to the semantic network than the conditioning of SMG to the phonological network. This may demonstrate that the ability of the semantic system to acutely compensate for a transient virtual lesion can be effectively blocked by offline rTMS to another critical node within the same intra-hemispheric network. This might be of relevance for the inherent potential of the language system for compensation or recovery after stroke.

We conclude that the condition-and-perturb approach provides a powerful tool to assess the capacity of different language networks to acutely compensate for focal dysfunctions.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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Notes

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