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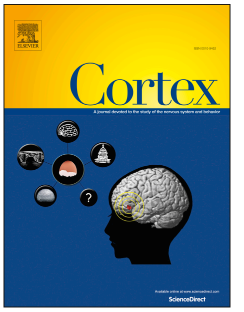

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Repetitive transcranial magnetic stimulation over left angular gyrus modulates the predictability gain in degraded speech comprehension

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Abstract

Increased neural activity in left angular gyrus (AG) accompanies successful comprehension of acoustically degraded but highly predictable sentences, as previous functional imaging studies have shown. However, it remains unclear whether the left AG is causally relevant for the comprehension of degraded speech. Here, we applied transient virtual lesions to either the left AG or superior parietal lobe (SPL, as a control area) with repetitive transcranial magnetic stimulation (rTMS) while healthy volunteers listened to and repeated sentences with high- vs. low-predictable endings and different noise vocoding levels. We expected that rTMS of AG should selectively modulate the predictability gain (i.e., the comprehension benefit from sentences with high-predictable endings) at a medium degradation level. We found that rTMS of AG indeed reduced the predictability gain at a medium degradation level of 4-band noise vocoding (relative to control rTMS of SPL). In contrast, the behavioral perturbation induced by rTMS changed with increased signal quality. Hence, at 8-band noise vocoding, rTMS over AG vs. SPL decreased the number of correctly repeated keywords for sentences with low-predictable endings. Together, these results show that the degree of the rTMS interference depended jointly on signal quality and predictability. Our results provide the first causal evidence that the left AG is a critical node for facilitating speech comprehension in challenging listening conditions.

1. Introduction

Humans can comprehend speech very robustly, often despite severe degradation in adverse listening situations or in chronically impaired hearing conditions (e.g., with cochlear implants; Pisoni, 2000). In recent years, much progress on the functional neuroanatomy of the networks involved in this feature has been made (e.g., Scott, 2000; Davis and Johnsrude, 2003; for review see Rauschecker and Scott, 2009), and the involvement of brain areas outside primary auditory cortex (e.g. superior temporal cortex), has been convincingly demonstrated (for review see Price, 2010; Peelle, 2012). In particular, a series of studies have implied the left angular gyrus (situated in inferior parietal cortex; for recent review see Seghier, 2013) to serve a critical, if ill-understood, function in achieving speech comprehension (Obleser et al., 2007; Obleser and Kotz, 2010; Bonner et al., 2012; Clos et al., 2012; Erb et al., 2013; Golestani et al., 2013).

For instance, Obleser et al. (2007) demonstrated that semantic predictability of degraded speech (e.g., “She cooked him a hearty meal”) not only allowed for a substantial gain in speech comprehension (i.e., a *predictability gain*), but also increased task-related activity in a network of left-hemispheric, heteromodal brain areas. Within this network, the left angular gyrus exhibited the maximal effect. Additionally, the effective connectivity of left angular gyrus with the other areas appeared particularly increased when comprehension was likely to succeed (i.e., in degraded but highly predictable speech). Moreover, patient studies implied a general relevance of the angular gyrus for sentence comprehension (Dronkers, 2004) and imaging data demonstrated an engagement of the angular gyrus when healthy subjects had to recover meaning in (pseudo-)word comprehension (Raettig and Kotz, 2008). Hence, it is not a question of *whether* but rather of *how* the angular gyrus comes to support speech comprehension.

The above cited evidence supports a view where angular gyrus has access to higher-level semantic and/or combinatorial knowledge (i.e., semantic memory) and is especially geared to draw on this knowledge when in need of enhancing or even superseding the degraded perceptual evidence (Binder et al., 2009). In sum, the reported studies show that semantic processing as the cognitive act of accessing stored knowledge about the world (Binder et al., 2009) engages, among others, the left angular gyrus.

It is in line with such a framework that high semantic predictability most effectively improves speech comprehension at intermediate levels of degradation (e.g., Pichora-Fuller, 1995; Stickney and Assmann, 2001). If, on the one hand, the amount of acoustic–phonetic evidence is too sparse (e.g., with 1-band vocoding, see Davis et al., 2011; Strauss et al., 2013), semantic predictability cannot facilitate comprehension to substantial degrees, as no semantic cues can be reliably extracted. If, on the other hand, speech comprehension without context is already at ceiling under ideal listening conditions, there is obviously nothing to gain in terms of predictability. Most interestingly for the present study, angular gyrus activation has been found to match this behavioral pattern well (Obleser et al., 2007). Thus, intermediate levels of degradation both yield most behavioral dynamic range for gains from semantic predictability, and most neural dynamic range for angular gyrus involvement (for review see Price, 2010, Obleser, 2014).

However, it remains unclear whether left angular gyrus involvement truly reflects a *necessary* neurocomputational stage that *precedes* comprehension, or whether its activation in functional imaging studies rather reflects an epiphenomenal *outcome* of successful comprehension. Therefore, the present study used repetitive transcranial magnetic stimulation (rTMS) to interrupt normal angular gyrus functioning while listeners tried to comprehend degraded sentences (e.g. noise-vocoded speech; Shannon et al., 2005; Erb et al., 2013).

We employed the *k*-factor (Boothroyd & Nitrouer, 1988) as a measure that directly expresses the predictability gain that results from context. To quote its inventors, the *k*-factor "expresses the effect of context as the ratio of the logarithms of the error probabilities for the context and no-context situations" (p. 102). *k* is dimensionless and, critically, has the desirable features of being independent of overall level of performance, the degree, or the type of degradation (see below for details).

Our main hypothesis was that the behavioral gain in comprehension that listeners draw from degraded, yet predictable speech (i.e., the predictability gain) necessitates angular gyrus involvement. Accordingly, an rTMS-induced interference should abolish or reduce the behavioral predictability gain (see Figure 1D). We here demonstrate that this is the case, and specifically that rTMS reduces the predictability gain at a medium degradation level of 4-band noise vocoded speech but rather disrupts sentences with low-predictable endings when the intelligibility of the sentence increases. Together, our results demonstrate a finely tuned interplay of angular gyrus' functional integrity, degradation severity, and the resulting predictability gain.

2. Material and Methods

2.1. Subjects

Fifteen native German speakers (4 females, age range: 20-31 years, mean age: 24.8 years) with no history of psychiatric, neurological or hearing disorders participated in the study. All subjects were right-handed (mean laterality index 0.97 ± 0.09 SD, according to the Edinburgh Handedness Inventory; Oldfield, 1971) and experienced with TMS but naïve to noise vocoded speech. Participants were paid 8 € per hour. Written informed consent was obtained before the experiments. 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.

2.2. Experimental procedures

This study used a 2 × 5 × 2 within-subject factorial design including the factors (1) semantic content (high- vs. low-predictability), (2) quality of the audio signal (noise vocoding level: 2-, 4-, 8-, 16- and 32-band noise vocoded) and (3) rTMS site (angular gyrus (AG) vs. superior parietal lobule (SPL), with the latter serving as control site). Participants underwent two sessions during which rTMS was either applied to the angular gyrus or superior parietal lobule in counterbalanced order. Both sessions were performed at least 14 days apart to prevent carry-over effects from the rTMS procedures and avoid learning effects with the stimulus material. The same set of 200 sentences was presented auditorily in both sessions with a different randomization and vocoding level within each session.

Prior to the experiment, subjects had a training of 10 trials that were not included in the main experiment (Figure 1A). Across the whole procedure, participants were seated comfortably in an upright position facing a 15” LCD monitor at a distance of approximately 100 cm depicting either a fixation cross or a green traffic light (Figure 1B). Neuronavigated TMS (Brainsight 2, Rogue Research, Montreal) was used for stereotactical coil placement over the left AG or SPL (Figure 1C). To prevent head movements, the subject’s head was fixated bilaterally with the TMS coil (mounted on an adjustable arm) on the left side and another arm with a head rest (Manfrotto 244, Cassola, Italy) on the right side. Note that after positioning, the coil remained fixed across the whole procedure with its position being visualized on the screen of the neuronavigation software. If necessary, the position of the coil was corrected by modifying the adjustable arms’ alignment. Subsequently, the experiment started and subjects were asked to listen to and repeat binaurally presented noise vocoded sentences. During each trial, a green traffic light appeared on the screen at keyword onset (i.e., simultaneous with the acoustic onset of the sentence-final word), indicating that the sentence should be repeated as quickly and as accurately as possible. At the same time, a short burst of 5 stimuli of 10 Hz rTMS was applied over either the AG or SPL (Figure 1B), leading to a total of 1000 rTMS pulses in each session. Given the variable sentence length and the randomized presentation of the stimuli, the inter-stimulus interval could not be anticipated. Applying online rTMS bursts with keyword onset was conceived to maximally interfere with the integration of the final keyword into the sentence context. It should thus selectively affect the behavioral predictability gain of high-predictability sentences, particularly so at a medium degradation level. Note that online rTMS is thought to acutely interfere with task processing for the duration of the stimulation period (i.e., 500 ms in our study; Hartwigsen & Siebner, 2012). Stimuli were applied via in-ear headphones (SE215, Shure, Niles, IL) providing approximately 30 db anti-noise shield against the rTMS evoked noise.

A dynamic microphone (F-V220, Sony, Tokyo) in combination with an internal PCI sound card (SB X-Fi, Creative Technology Ltd., Jurong East) was used to record responses for 5 seconds during each trial. Stimulus presentation and response recording was controlled via presentation software (Neurobehavioral Systems; Albany, CA, version 16). After 100 trials, a short break of about 10 min was included. Participants did not receive any feedback about the accuracy of their responses. The whole experiment had a duration of about 90 minutes.

2.3. Stimulus material

The stimulus set consisted of 200 spoken sentences of the German SPIN (speech intelligibility in noise) set (Erb et al., 2012; Kalikow et al., 1977). Each sentence included 4–9 words (mean 6.3 ± 0.95 SD) and 8–12 syllables (mean 10 ± 0.83 SD) and had a duration of 1574–2737 ms (mean 2109 ± 217.5 SD). The last word of each sentence served as keyword. Sentences were structured such that it was either easy to predict the final word (high-predictability condition, e.g. "The storm broke the sailboat's mast.") or unlikely to predict the final word (low-predictability condition, e.g. "The old man thinks about the mast."). Keywords comprised 1–2 syllables (mean

1.55 ± 0.5 SD) and had a duration of 248–670 ms (mean 459 ± 81.9 SD). In total, this study utilized 100 different keywords yielding 200 sentences (100 high-predictability vs. 100 low-predictability sentences).

Sentences were spoken by a professional female speaker and recorded in a soundproof chamber onto a PC using an A/D converter at 44.1 kHz and 16 bit resolution. Sentence audio files were cut at zero-crossings, down-sampled off-line to 22.05 kHz, and normalized with respect to average root-mean-squared amplitude. Each sentence was noise-vocoded (Shannon et al., 1995) using Greenwood's cochlear formula (Greenwood, 1990) in Matlab 7.11 (The Mathworks, Inc., Natick, MA). For full details of the noise-vocoding algorithm see Erb et al. (2012). In short, noise vocoding reduced the spectral information in the signal to varying, arbitrary degrees (depending on the number of bands used) while the slow temporal cues of the amplitude envelope remain intact (Rosen, 1992). The intelligibility of the stimulus increases with increasing numbers of bands, and this manipulation has been widely used in neuroimaging studies of speech comprehension (e.g., Davis et al., 2003; Scott, 2006; Obleser et al., 2007; Erb et al., 2013).

Previous studies (e.g., Obleser et al., 2007; Obleser and Kotz, 2010; McGettigan et al., 2012) have demonstrated that the degradation levels where listeners would draw the most benefit from semantic cues (i.e., the most predictability gain) were in the range of 4- to 8-band noise vocoding. To cover these levels within our noise vocoded stimuli, we created 5 versions of each sentence (2-, 4-, 8-, 16- and 32-band noise vocoded).

For each session, different trial sets were constructed via stratified block randomization such that each noise vocoding band was represented by 40 sentences (20 high-predictability vs. 20 low-predictability sentences) in each session, leading to 200 sentences (or, trials per session) for the whole study.

2.4. Repetitive Transcranial Magnetic Stimulation (rTMS)

Neuronavigated rTMS was performed by using the mean Montreal Neurological Institute (MNI) coordinates determined from two previous studies (i.e., angular gyrus: x, y, z= -46, -60, 34 mm (Obleser et al., 2007); superior parietal lobule: x, y, z= -34, -42, 70 mm (Blair et al., 2012); Figure 1C). Before the experiment, a high-resolution MRI scan of the whole brain was acquired for each subject using an MPRAGE sequence in sagittal orientation (voxel size= 1x1x1.5 mm; TR=1.3 s, TE= 3.46 ms). Individual rTMS sites were determined by calculating the inverse of the normalisation transformation and transforming these coordinates from standard to individual space for each subject in Matlab 7.7 (for a similar procedure, see Hartwigsen et al., 2010a, Hartwigsen et al., 2010b; Hartwigsen et al., 2012). To this end, individual T1-weighted images were segmented using the standard tissue probability maps provided in the Statistical Parametric Mapping software (SPM8; http://www.fil.ion.ucl.ac.uk/spm/) implemented in MATLAB 7.7 (Mathworks) (Friston et al., 1995)). Afterward, the resulting image was normalized and resampled to 1 x 1 x 1 mm^3 voxels.

Note that MRI-guided, neuro-navigated stimulation yields a high spatial accuracy in the range of a few millimetres (Sparing et al., 2008) and represents the method of choice for exact placement and monitoring of the coil throughout the TMS experiment (see Hartwigsen et al., 2010c).

We chose left superior parietal cortex as control site since it did not show any significant upregulation whatsoever during fMRI in our previous studies that used comparable stimulus material (Obleser et al., 2007; Obleser and Kotz, 2010). Previous neuroimaging studies suggested that left superior parietal lobe is mainly involved in tasks that require visuo-spatial processing and (visuo-) spatial attention (Bushara et al., 1999; Cai et al., 2013). Moreover, Braun et al. (2001) demonstrated stronger activation of this area during signing than speaking.

Other studies proposed that left superior parietal cortex might play a key role as multisensory integration hub during auditory and visual processing (e.g. Molholm et al., 2006). In sum, there is no evidence for a functional contribution of this area to degraded speech comprehension on the sentence level.

Note that we refrained from including sham rTMS or vertex stimulation as additional control site for the following reasons: First, we would argue that vertex is not suited as control site in our design since the rTMS-induced sensory input between vertex stimulation and rTMS over our lateralized region of interest are not comparable. Therefore, we chose two active sites that are comparable with respect to the side effects of the rTMS procedure (i.e., unpleasantness of the stimulation, auditory and sensory effects). Secondly, sham stimulation is not a well-suited control for online rTMS as the absence of the anticipated somatosensory stimulus of actual rTMS may induce oddball effects.

We used a figure-of-eight-shaped coil (MC-CB-60; outer diameter 7.5 cm) connected to a MagPro X100 stimulator (MagVenture 4.3.20, Medtronic, Fridley, MN) in all conditions. The coil was positioned tangentially to the head with the handle pointing parallel to the sagittal plane, and the second phase of the biphasic pulse inducing a posterior to anterior current flow (Hartwigsen et al., 2010b). Stimulation intensity was set to 90% of individual resting motor threshold of the left primary motor hand area (Hartwigsen et al., 2010a). The resting motor threshold was defined as the lowest stimulus intensity producing a visible motor evoked potential of approximately 150–200 µV (peak-to-peak amplitude) in the relaxed first dorsal interosseus muscle in 10 consecutive stimuli with single pulse TMS given over the motor hot spot at rest without any pre-contraction. The motor hot spot was determined functionally by estimating its position approximately 1 cm anterior and 4-5 cm lateral from the vertex (see Kaelin-Lang, 2007) and starting with a fixed intensity of approximately 50% total stimulator output. The coil position was then moved until the optimal motor hotspot was located and stimulation intensity was gradually adjusted during the individual motor threshold determination. The rTMS protocol was within the published safety limits (Rossi et al., 2009).

2.5. Data analysis

All data were analyzed using custom Matlab (version 7.11, Mathworks) scripts and SPSS software (Version 21, IBM). Response recordings were evaluated off-line with a fixed scheme by the experimenter. For each trial, we scored the percentage of correctly repeated words per sentence (including the sentence-final keyword; herewith referred to as *ratio of correctly repeated words per sentence*), the failure or success to correctly repeat sentence-final keyword (*keywords correct*) and the speech onset time (*SOT*). The assessment of correct answers was performed liberally with respect to order, declination, conjugation and tense. Homonyms or synonyms were counted as errors.

To elucidate the amount of context dependency of sentence or keyword comprehension, we utilized the k-factor as described by Boothroyd and Nittrouer (1988). By computing the ratio of the logarithmic error probabilities to correctly comprehend sentences with high-predictable endings to those with low-predictable endings, the k-factor directly expresses the predictability gain $k = \log(1 - p_h)/\log(1 - p_l)$, where p_h is the probability of recognition for a speech unit in context [high-predictability] and p_l is the probability of recognition without context [low-predictability]). For more information on the precise calculation of *k* for the present data, the reader is referred to the *supplementary information Methods* section. Note that, as a ratio, the k-factor reflects the absence of a particular predictability when k = 1. A decrease in error probability with increasing context results in an increasing k-factor. Importantly, the k-factor is particularly robust against ceiling effects and should thus be more appropriate than the simple difference between high-predictable and low-predictable sentences.

Since rTMS was always applied at keyword onset (see above for details), the analysis of the total ratio of correctly repeated words per sentence might appear less intuitive than only analyzing the sentence-final keyword. However, we would argue that the total ratio of correctly repeated words is particularly suited to express the complete process of word–into–(sentence–)context integration which has been associated with angular gyrus integrity in previous fMRI studies (e.g. Binder et al., 2009; Obleser et al., 2007; Obleser and Kotz, 2010). Hence, the ratio of correctly repeated words might serve as a complementary, more fine-grained measure in our analyses. We will thus report full analysis of both measures below (and results will confirm a very high correlation of both, further providing evidence for the integrative function of angular gyrus).

Speech onset time was defined as time from keyword onset until articulation onset and was extracted manually using Cubase SX 3.1 (Steinberg Media Technologies, Hamburg, Germany). In case of self-corrections by the subjects, we always counted the last articulation. Assessments of the speech onset time was performed by two independent raters with an inter-rater reliability of $r = 0.99$.

We computed two-way repeated-measures ANOVAs to separately investigate the effects of rTMS on the k-factor for the ratio of correctly repeated words per sentence, keywords correct, and speech onset time. Kolmogorov-Smirnov tests gave no indication of a violation of the normality assumption.

Note that the primary aim of this study was the investigation of the disruptive effects of angular gyrus rTMS on sentences with a medium degradation level (i.e., 4-bands and 8-bands noise vocoding levels, see above). Based on an inspection of the raw data (see Figure 2A & 3A), we excluded all noise vocoding levels where behaviour was at floor or ceiling (i.e., 2-bands, 16-bands and 32-bands) from further analysis since this might distort the analyses. Note that the k-factor returned values of approximately 1 for 16- and 32-band noise vocoding level for both measures and rTMS sites, indicating that there was no predictability gain with these bands.

Hence, our 2×2 ANOVA models included the within-subject factors *noise vocoding* level (4-band vs. 8-band noise vocoded) and *rTMS site* (AG vs. SPL). The Greenhouse-Geisser correction was used to correct for non-sphericity where appropriate (i.e., Mauchly's criterion significant). Conditional on significant F-values, post-hoc paired t-tests further explored differences among conditions.

Initial p-values < $\alpha = 0.05$ (two-tailed) were considered significant for all comparisons. To adjust for possibly inflated type I error in multiple comparisons, the Bonferroni-Holm correction was applied to all post-hoc t-tests. We further report a convenient measure of effect size, r (e.g. Rosenthal, 1991) for all effects of interest to facilitate comparison across studies, with r being [0;1]-bound. By convention, r >.3 describes medium and r >.5 describes large effects (Cohen, 1988).

3. Results

3.1. Ratio of correctly repeated words per sentence

As outlined in the Methods section, we employed two different dependent measures. Both measures were based on the k-factor that directly expresses the predictability gain. The first measure, the *ratio of correctly repeated words per sentence* was intended to assess the effect that rTMS over AG might have on the process of forming the predictive context from the content words *preceding* the rTMS pulse and the keyword, respectively. Note that the ratio of correctly repeated words per sentence served as a complementary measure to the keywords correct score.

In line with our hypothesis, the two-way interaction between noise vocoding level and rTMS site was significant for the ratio of correctly repeated words per sentence ($F_{1,14} = 8.99$, $p = 0.01$, effect size $r = 0.62$; Figure 2). Accordingly, post-hoc paired t-tests revealed a higher k-factor for the ratio of correctly repeated words per sentence at 4-bands after rTMS of SPL as compared with rTMS of AG ($t_{15} = 2.46$; $p = 0.028$, $r = 0.53$; despite being at threshold when employing the Bonferroni-Holm correction for multiple comparisons). This finding indicates that rTMS of AG reduced the predictability gain for high-predictable vs. low-predictable sentences at a medium degradation level of 4-bands (see Figure 2B-D). Note that the rTMS-induced suppression of the predictability gain decreased the k-factor to a value close to 1, indicating that there was almost no predictability gain at all after AG rTMS.

In contrast, this effect changed with increasing quality of the speech signal: At 8-bands, we found a trend towards a *higher* k-factor after rTMS over AG vs. rTMS over SPL ($t_{15} = 1.80$; $p = 0.09$, effect size $r = 0.42$).

The 2x2 ANOVA on the ratio of correctly repeated words per sentence did not reveal significant main effects of noise vocoding level ($p = 0.17$) or rTMS site ($p = 0.56$).

3.2. Keywords correct

Our second dependent measure *keywords correct* assessed correct scores only of the sentence-final keyword, during which the rTMS pulses were applied and which constitutes the classic measure of accuracy in sentences with high vs. low predictabilities (e.g. Kalikow et al., 1977).

In line with our main hypothesis and the results from the ratio of correctly repeated words per sentence measure described above, rTMS of AG also significantly modulated the predictability gain as evidenced by a significant two-way interaction between noise vocoding level and rTMS ($F_{1,14}$ = 5.32, p = 0.037, r = 0.52). Post-hoc paired t-tests did not show any evidence for a significantly altered k-factor after rTMS over AG vs. SPL at a noise vocoding level of 4-bands (p = 0.2). However, with 8-bands, we again found a significantly higher k-factor after rTMS over AG vs. SPL (t_{15} = 2.88; p = 0.012, r = 0.60; significant after Bonferroni-Holm correction). In contrast, no notable predictability gain had been present with rTMS over SPL (control site), as obvious by a k-factor around 1 (see Figure 3B).

Together, the results from the ratio of correctly repeated words per sentence and keywords correct indicate that rTMS over AG reduced the predictability gain for sentences with a medium degradation level of 4-bands but selectively affected the more challenging low-predictable sentences with increased intelligibility at 8-bands (please refer to the *supplementary information Results* section 3.2. for details).

Additionally, a significant main effect of noise vocoding level ($F_{1,14}$ = 10.86; p = 0.005, r = 0.66) pointed towards an overall decrease in the k-factor at 8-bands, independent of the rTMS site. This is consistent with an overall largest predictability effect at 4-bands (for similar results of predictability in German simple sentences see Obleser & Kotz, 2010).

Finally, we found the expected strong correlation between the ratio of correctly repeated words per sentence and keyword correct (computed across all sentences using the Pearson correlation coefficient, r = 0.98, p<0.001), indicating that both measures converged and that the effect of the rTMS intervention expresses to equal extent in slightly different measures of comprehension performance.

Please refer to the *supplementary information Results* section for the results of the speech onset time which did not exhibit any interaction of rTMS and noise vocoding level.

4. Discussion

This study addressed the functional relevance of intact left angular gyrus function for the comprehension of degraded speech. The data provide the first causal evidence that the left AG has a key role in facilitating speech comprehension at the sentence level under compromised signal quality. Hence, disruptive rTMS of AG decreased the comprehension gain that listeners could draw from high sentence predictability at a medium degradation level of 4-band noise vocoding. This was evidenced by a significant reduction in the k-factor for the ratio of correctly repeated words within a sentence at 4-bands after rTMS of AG. Of note, the rTMS-induced interference effects observed here were both functionally and anatomically specific: Repetitive TMS over AG selectively reduced the gain listeners could draw from predictable context compared to rTMS over the control site SPL. Interestingly, the modulatory effect of AG rTMS changed with increasing quality of the speech signal. Angular gyrus rTMS, but not superior parietal rTMS, selectively reduced the number of correctly repeated keywords for sentences with *low-predictable* endings at 8-bands (see below for a detailed discussion). Note that this effect was observed for both the percentage of correctly repeated keywords and (albeit to a lesser degree) the overall percentage of correctly repeated words in a sentence, indicating a robust virtual lesion effect.

Our findings provide further support for the notion that the left AG is engaged in higher-level semantic processes that require concept retrieval and/or conceptual integration (Binder et al., 2009; Seghier, 2013) with increased contribution under perceptually degraded listening conditions (Obleser et al., 2007). This also matches previous patient studies demonstrating that lesions of the left AG are associated with difficulties in processing complex sentences (Dronkers et al. 2004), leading to the suggestion that this region may play a role in integrating semantic information into context (Lau et al. 2008).

4.1. Contributions of left angular gyrus to degraded speech comprehension

The rTMS-induced shift in the k-factor between 4-band and 8-bands observed in our study allows us to further disentangle the contribution of left AG to speech comprehension at the sentence level. At a medium degradation level (i.e., with 4-band noise vocoding), the left AG has a key role in comprehending highly predictable content. In other words, with intermediate signal quality, the influence of context provided by semantic predictability proved effective in improving performance (Obleser et al., 2007). A second novel finding of our study was that rTMS increased the overall difference between sentences with high-predictable and low-predictable endings at 8-band noise vocoding. Of note, the observed changes in the k-factor resulted from a decrease in the number of correctly repeated words with *low-predictable* endings as obvious from Figure 2A and 3A. Indeed, complementary analyses (see *supplementary information Results,* section 3.2. for details) showed that the number of correctly repeated keywords was significantly decreased with angular gyrus rTMS relative to rTMS over SPL for sentences with low-predictable but not high-predictable endings at 8-band noise vocoding. This might indicate that, with increasing quality of the speech signal, left AG appears to be more engaged in a general aspect of semantic processing, i.e., the identification of the correct ending of a sentence. Hence, there was only a very small behavioral benefit of the semantic context with 8-band noise vocoding since behavior in the high-predictable condition had almost reached ceiling (cf. Figure 2A & 3A). Accordingly, with more intelligible listening conditions, rTMS of AG decreased the percentage of correctly repeated keywords in sentences with the more challenging *low-predictable* endings, which presumably reflects an increase in task-difficulty.

Flanking analyses did not reveal any disruptive effects of rTMS on the most intelligible conditions (i.e., at 16- or 32-band noise vocoding; see *supplementary information Results*). This shows the robustness of the semantic network under near-normal listening conditions and might provide further support for our conclusion that left AG plays a key role for degraded speech comprehension under adverse listening conditions. Indeed, our findings suggest that with the most intelligible conditions, the behavioral effects had reached a ceiling for both high-predictable and low-predictable sentences. Together, these findings suggest that left AG is causally relevant for different aspects of speech comprehension, with its exact contribution depending on the level of perceptual degradation.

The current data imply that critical involvement of the AG is restricted to challenging listening conditions. Concomitantly, a previous study with comparable stimuli in English reported increased neural activity of the AG in response to degraded but highly predictable speech (Obleser et al., 2007). Importantly, the observed increase in activity was restricted to effortful yet successful speech comprehension and returned to baseline when the sentences were both highly predictable and readily intelligible; excluding the possibility that this simply resulted from success in comprehension. Accordingly, it was suggested that the level of activation in the AG reflects the amount of semantic information that can be successfully retrieved from a given input (Binder and Desai 2011). This notion is further supported by previous imaging studies stressing the role of the AG as a multimodal integration hub when a task reaches a certain difficulty level (Price, 2010; Turken and Dronkers, 2011; Seghier, 2013).

The observed absence of any disruptive rTMS effect on the most intelligible conditions in our study is well in line with a previous study that did not find any disruptive effect of rTMS over AG on semantic decisions under unhampered listening conditions (Hartwigsen et al., 2010a). Alternatively, other brain regions within a larger semantic network might have compensated the disruptive effect of rTMS over AG under the most intelligible listening conditions, indicating a certain degree of redundant processing (e.g. Price and Friston, 2002) in the semantic system.

One might argue that rTMS of AG might have interfered with verbal working memory rather than degraded speech comprehension per se; the overt repetition of auditorily presented sentences engaged in our study does draw on verbal working memory. Indeed, some previous imaging studies suggested that the left AG is part of a distributed working memory loop for semantics (Vigneau et al., 2006; Buchsbaum and D'Esposito 2008), a system recruited during speech comprehension and production (Jacquemot and Scott 2006). However, while the present task doubtlessly engages working memory processes, we believe that this explanation is unlikely for several reasons. First, an rTMS protocol primarily interfering with working memory should have affected both high-predictability and low-predictability sentences at a medium degradation level. Second, one would have even expected a stronger virtual-lesion effect with increasing working memory demands, i.e., with low-predictability. However, the raw data (Figure 2A & 3A) suggest that rTMS selectively interfered with high-predictable but not low-predictable sentences at 4-bands while this effect was reversed with increasing signal quality. We believe that the shift in the k-factor between 4-bands and 8-bands observed with rTMS over AG points towards a finely attuned contribution of degraded speech comprehension through left AG, which takes into account both the intelligibility of the speech signal and the sentence's predictability.

Our findings would thus be more congruent with the notion of Obleser and Kotz (2010) that left inferior parietal cortex might serve as a mediating structure that facilitates speech comprehension when signal intelligibility is compromised.

4.2. A functional–anatomical parcellation of left angular gyrus

At least three previous meta-analyses have reported consistent AG activation in a variety of different speech and language tasks (e.g. Vigneau et al., 2006; Binder et al., 2009; Price, 2010). Accordingly, the left AG has been to consist of multiple subdivisions that are characterized by specific functional and connectivity patterns (Seghier, 2013). Interestingly, our rTMS site (i.e., x, y, z = –46, –60, 34, as based on Obleser et al., 2007) corresponds well to the ventral part of the left AG identified across previous imaging studies by Seghier (2013; i.e., x, y, z = –42, –69, 31). This area was suggested to provide semantic constraints based on prior knowledge of the world and the experimental context during speech comprehension (Price, 2010). Such constraints may help to facilitate meaning extraction from ambiguous sentences as suggested by Clos et al. (2012).

In contrast to the ventral part of the AG targeted in the present study, a more dorsal part of the AG (x, y, z = –35, –64, 45) identified across different studies by Seghier (2013) was associated with bottom-up processes during semantic search (Price, 2010; Seghier et al., 2010), fact retrieval (e.g., Ischebeck et al., 2009), and the automatic allocation of attention to memory (Cabeza et al., 2008; Ciaramelli et al., 2008).

Recently, Sehm et al. (2013) applied anodal transcranial direct current stimulation over left AG while subjects trained to discriminate between acoustically degraded and undegraded written minimal (e.g. $\text{Tisch}_{\text{acoustic}}$ – $\text{Fisch}_{\text{written}}$) and identical word pairs ($\text{Tisch}_{\text{acoustic}}$ – $\text{Tisch}_{\text{written}}$). Most relevant to the present results, anodal (i.e., facilitatory) transcranial direct current stimulation induced a response bias towards reporting identity of acoustically degraded and written words. Participants were thus more likely to judge both pairs of stimuli as identical. Thus, facilitation of AG activity arguably promotes an enhanced perceptual fusion of degraded auditory with undegraded written input. This further corroborates the notion of a supramodal role of the left AG in perceptual decision making (Kuhn et al., 2011).

Previous patient studies demonstrated that damage to the left AG is associated with a wide range of deficits, including speech comprehension (Dronkers et al., 2004), spatial disorientation and agraphia (e.g., Ardila and others 2000; Corbett and others 2009). This suggests that multiple processes depend on the functional or structural integrity of the AG (Seghier 2013). However, the above cited lesion studies do not allow for a more fine-grained functional-anatomic subdivision of processes in the left AG. It is important to emphasize that virtual lesions induced by rTMS are far more focal, and of course more transient, than stroke-induced lesions. Rather than leading to a total loss of task-function, rTMS induces mild functional disruption of the stimulated area (see Hartwigsen and Siebner, 2012). Moreover, an important advantage of rTMS-induced lesions relative to studies of structural lesions is that there is insufficient time for functional reorganization to occur when online rTMS is given during a task and thus, the acute “lesion” effect should not be confounded by chronic processes mediating functional recovery locally and at the systems level (see Hartwigsen and Siebner, 2012). Hence, rTMS allows for a precise functional–anatomical subdivision of heterogeneous areas (e.g., Gough et al., 2005; Hartwigsen et al., 2010b).

With respect to the existing models of speech perception, the role of left AG is currently clearly underspecified. For instance, recent models on the functional neuroanatomy of language favour an organization along two processing streams: a ventral stream that is responsible for mapping sound onto meaning and a dorsal stream that is involved in mapping sound onto articulation (Hickok and Poeppel, 2004, 2007; Rauschecker and Scott, 2009). However, these dual-stream models allow little explicit predictions on the role of left AG. The dorsal route has been suggested to include a temporo-parietal area that might match left supramarginal gyrus and was associated with audio-motor transformation during (pseudo-)word repetition (Hickok and Poeppel, 2007). In contrast, Rauschecker and Scott argued that left AG activation is not driven by acoustic processing of speech but is rather recruited when higher-order linguistic factors improve speech comprehension (see also Obleser et al., 2007). In line with our results, these authors suggested that AG is associated with more heteromodal, linguistic factors in speech comprehension (rather than acoustic or phonetic processing).

4.3. Conclusions

The present study highlights the importance of the left angular gyrus in successfully comprehending speech in adverse listening conditions. The angular gyrus is here demonstrated to be a critical node for facilitating speech comprehension at the sentence level under compromised signal quality. The results of our study may help specifying mechanistic neural models of speech comprehension in adverse listening situations and will prove useful in applying this knowledge to more effective treatments of chronically impaired hearing conditions.

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Figure Legends

Figure 1

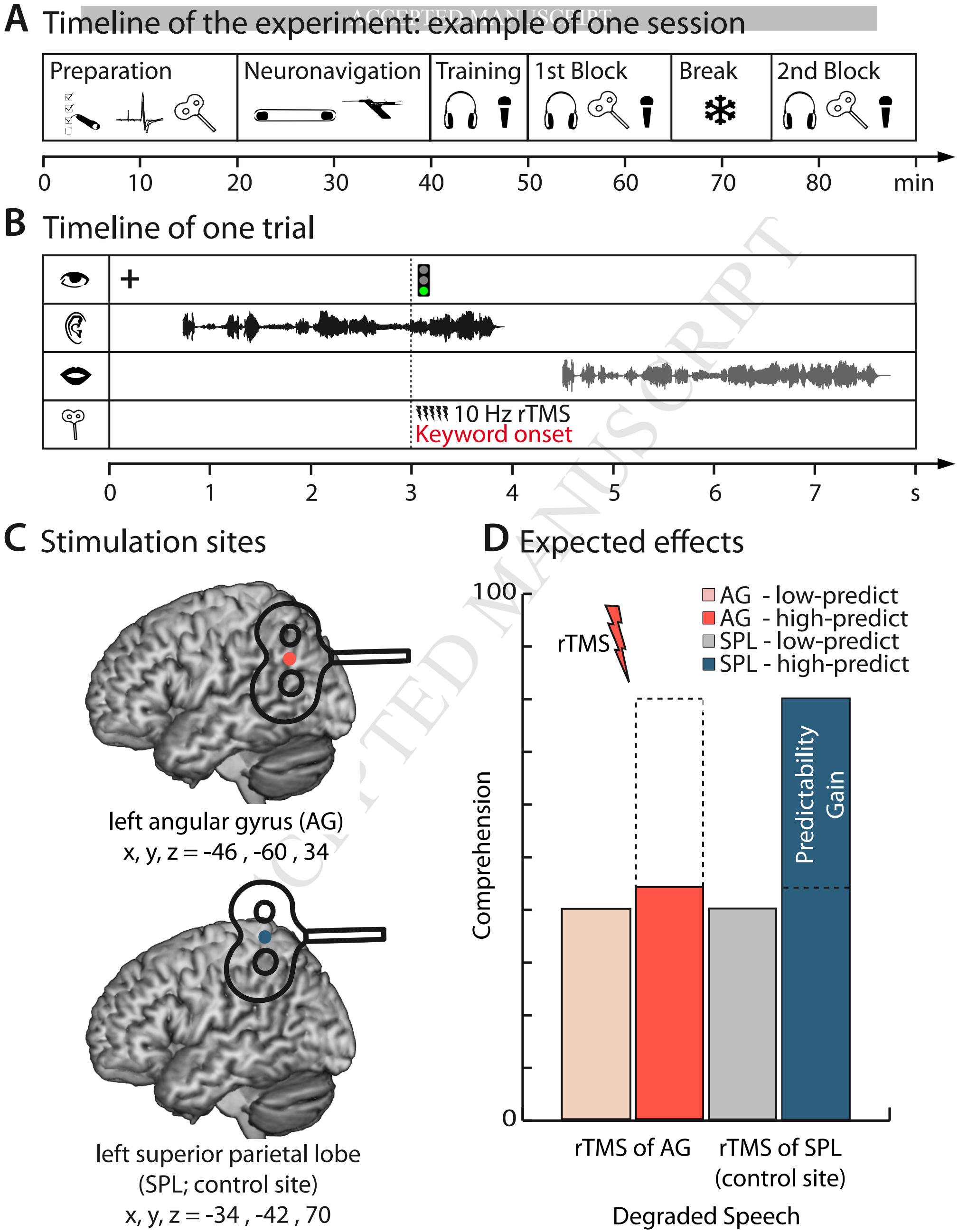
Experimental design. **A** The experiment consisted of two sessions that were performed at least 14 days apart in counterbalanced order. After a training session, individual resting motor threshold was determined and neuronavigated repetitive transcranial magnetic stimulation (rTMS) was applied over either the left angular gyrus or superior parietal lobule (control site). **B** Subjects were asked to listen to and repeat the noise vocoded sentence as quickly and as accurately as possible when the green traffic light appeared. rTMS was applied at keyword onset during each trial. The subject's responses were recorded for 5 s with a microphone. Afterwards, a fixation cross indicated the next trial. **C** rTMS sites for the left angular gyrus (x, y, z = -46, -60, 34 mm within MNI space) and left superior parietal lobule (x, y, z = -34, -42, 70 mm within MNI space; control site) were based on mean stereotactic coordinates from two recent studies (Obleser et al., 2007; Blair et al., 2012). **D** Expected effects of rTMS over angular gyrus: Relative to rTMS over left superior parietal lobe, rTMS over left angular gyrus should significantly decrease the predictability gain for high-predictability sentences at a medium degradation level.

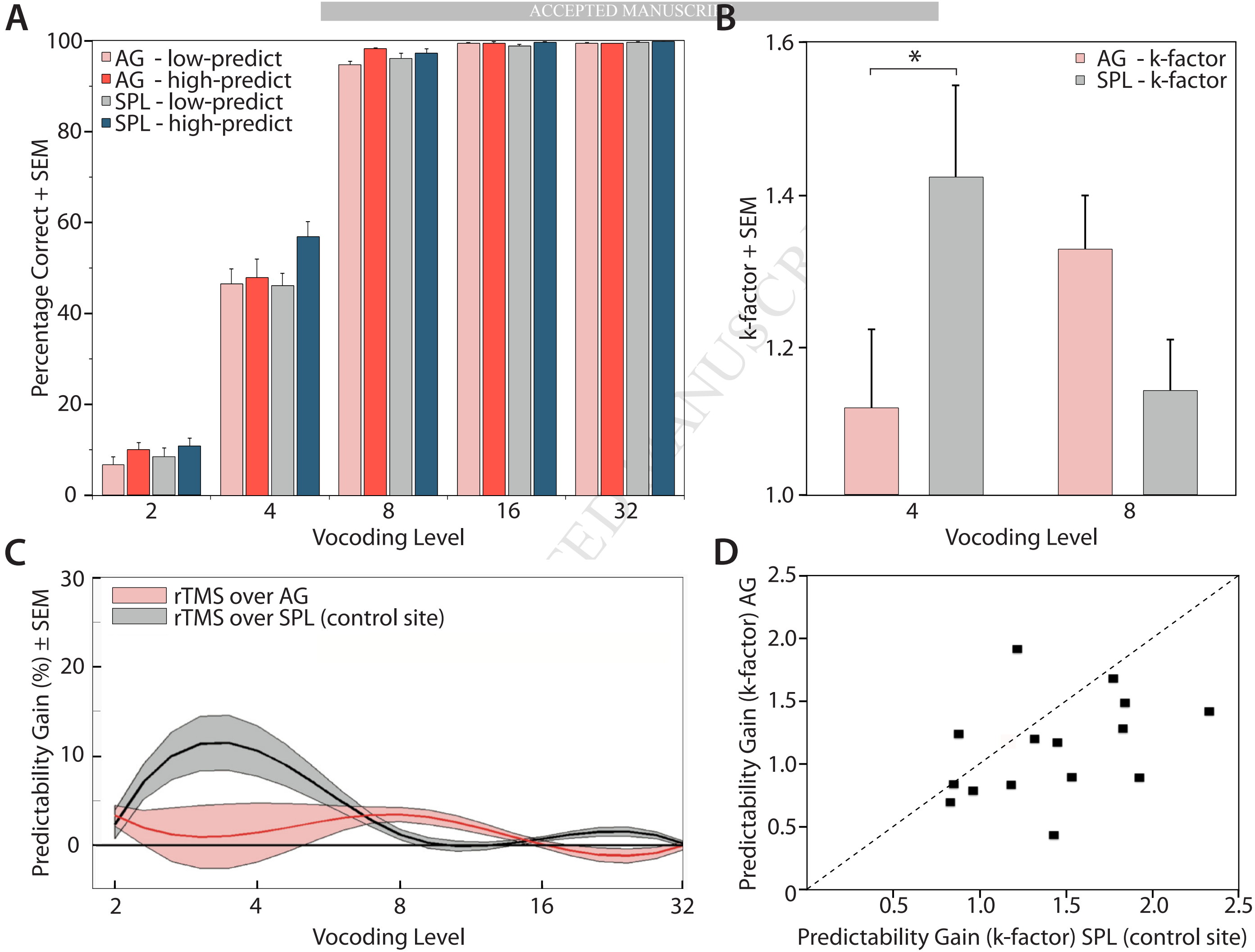
Figure 2

Results for the ratio of correctly repeated words per sentence. **A** Raw data for the percentage of correctly repeated words as a function of semantic content (high-predictability vs. low-predictability sentences), noise vocoding level and rTMS site. **B** Predictability gain (expressed by the k-factor) for the 4-band and 8-band condition as a function of rTMS site. **C** Predictability gain (based on the difference between high-predictable and low-predictable sentences in the raw data) as a function of noise vocoding level for rTMS over angular gyrus (AG, red ± SEM) vs. superior parietal lobe (SPL, blue ± SEM; control site) for the percentage of correctly repeated words. Curves were modeled using cubic spline data interpolation in Matlab 7.11. **D** Individual predictability gain (expressed by the k-factor) as a function of rTMS site. Note that we only display significant effects in the 4-band condition here. * $p < 0.05$; two-tailed. Error bars represent one-fold standard error of the mean.

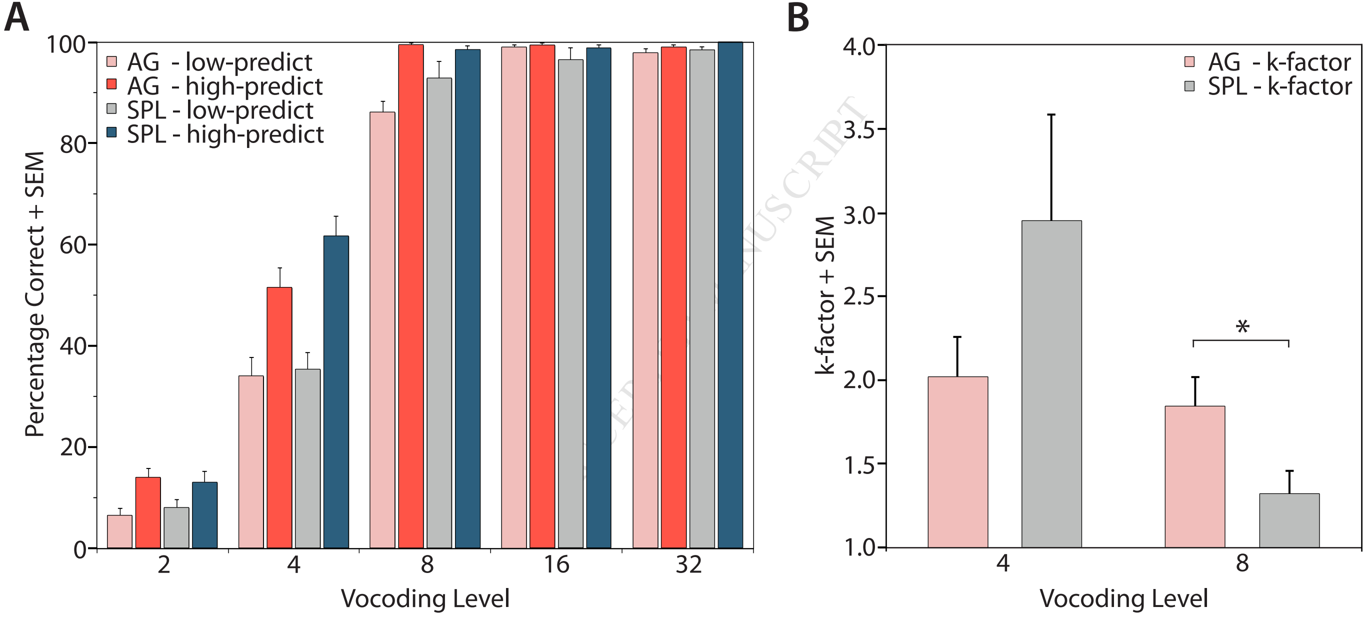
Figure 3

Results for the accuracy of the final sentence keyword comprehension. **A** Raw data for the percentage of correctly repeated keywords as a function of semantic content (high-predictability vs. low-predictability sentences), noise vocoding level and rTMS site. **B** Percentage of correctly repeated keywords (expressed by the k-factor) for the 4-band and 8-band condition as a function of rTMS site. See text for details.


A Timeline of the experiment: example of one session
Preparation
Neuronavigation
Training
1st Block
Break
2nd Block
0
10
20
30
40
50
60
70
80
min
B Timeline of one trial
+
10 Hz rTMS
Keyword onset
0
1
2
3
4
5
6
7
s
C Stimulation sites
left angular gyrus (AG)
x, y, z = -46 , -60 , 34
left superior parietal lobe
(SPL; control site)
x, y, z = -34 , -42 , 70
D Expected effects
100
0
Comprehension
rTMS
AG - low-predict
AG - high-predict
SPL - low-predict
SPL - high-predict
Predictability Gain
rTMS of AG
rTMS of SPL
(control site)
Degraded Speech



A
AG - low-predict
AG - high-predict
SPL - low-predict
SPL - high-predict
Percentage Correct + SEM
100
80
60
40
20
0
2
4
8
16
32
Vocoding Level
B
*
AG - k-factor
SPL - k-factor
k-factor + SEM
1.6
1.4
1.2
1.0
4
8
Vocoding Level
C
rTMS over AG
rTMS over SPL (control site)
Predictability Gain (%) ± SEM
30
20
10
0
2
4
8
16
32
Vocoding Level
D
Predictability Gain (k-factor) AG
2.5
2.0
1.5
1.0
0.5
0
0.5
1.0
1.5
2.0
2.5
Predictability Gain (k-factor) SPL (control site)


A
100
80
60
40
20
0
AG - low-predict
AG - high-predict
SPL - low-predict
SPL - high-predict
Percentage Correct + SEM
2
4
8
16
32
Vocoding Level
B
4.0
3.5
3.0
2.5
2.0
1.5
1.0
AG - k-factor
SPL - k-factor
k-factor + SEM
*
4
8
Vocoding Level

Supplementary Information

2. Materials and Methods

2.5. Data analysis

Following Boothroyd and Nittrour (1988), we calculated the k factor as follows:

$$k_{jc} = (ln(1 - p(correct|pred = \ high)_{jc}) / \, ln\big(1 - p(correct|pred = low)_{jc}\big)$$

k_{jc} denotes the k factor in a particular participant j and in a particular condition c (e.g. 4 band noise vocoding and angular gyrus TMS). The ratio of correctly repeated keywords to total number of keywords in high-predictable sentences, averaged across trials, is denoted by p(correct|pred = high) and can take values between 0 and 1. Likewise, the ratio of correctly repeated keywords in low-predictable sentences is calculated and averaged across trials for p(correct|pred = low). As the natural logarithm ln is not defined or yields divisions by 0 for values of 0 and 1, respectively, we used an established correction formula for cells of individual averaged trial data where no errors [p(correct) = 1] or only errors [p(correct)= 0] had occurred. The correction, established in signal detection theory (MacMillan and Creelman, 2005), sets p(correct)=1 to p(correct)=1–1/(2N), where N is the number of trials that entered the averaging (N=20 in the present case). Likewise, p(correct)=0 was corrected to p(correct)=1/2N.

3. Results

To complement the analyses based on the k-factor and assess potential effects of rTMS over AG on other noise vocoding levels, the raw-data for keywords correct were transformed to Rationalized Arcsine Units (RAU; Studebaker, 1985), which linearizes proportional data and approximates normal distribution and thus allows performing parametric statistics on these proportional data. Note that this enabled us to include the most intelligible conditions where a k-factor around 1 had indicated the absence of any predictability effect. For the ratio of correctly repeated words per sentence, we used the raw data instead as the words within a sentence were not independent from each other, which might violate the assumptions for the application of the RAU transformation (Sherbecoe and Studebaker (2004).

Three-way repeated-measures ANOVAs were then used to separately investigate the effects of rTMS on the ratio of correctly repeated words per sentence and keywords correct since Kolmogorov-Smirnov tests had indicated that all data were distributed normally. The Greenhouse-Geisser correction was used to correct for non-sphericity where appropriate (i.e., Mauchly's criterion significant). The 2 × 5 × 2 ANOVA models included the within-subject factors *semantic content* (high- vs. low-predictability), *noise vocoding level* (2, 4-, 8-, 16- and 32-band noise vocoded) and *rTMS site* (AG vs. SPL).

3.1. Complementary analyses on the ratio of correctly repeated words per sentence

For the ratio of correctly repeated words per sentence on the raw data, we found a significant three-way interaction between semantic content, noise vocoding level and rTMS site ($F_{4,56}$ = 6.32, p = 0.01, G–G epsilon = 0.41). We followed this up by running two separate two-way ANOVAs, for the two rTMS sites, respectively. It turned out that rTMS over AG abolished the critical semantic content by noise vocoding level interaction altogether ($F_{4,56}$ = 1.04, p =0.40, G–G epsilon = 0.37). In contrast, rTMS over the control site in SPL left it unchanged from what would be expected from the speech-degradation, non-TMS literature ($F_{4,56}$ = 8.53, p < 0.001, G–G epsilon = 0.42).

Supporting our main analyses based on the k-factor, the semantic content by rTMS site interaction reached significance at 4-bands ($F_{1,14}$ = 6.68, p = 0.02) and 8-bands ($F_{1,14}$ = 5.56, p = 0.03), but not at any other band (all p > 0.2).

The following effects did not interact with rTMS site: As expected, we found that overall, higher signal quality was associated with an increase in the ratio of correctly repeated words per sentence, with a pronounced ceiling effect at 16-band noise vocoding (main effect of noise vocoding level $F_{4,56}$ = 1359.03; $p < 0.0001$, G–G epsilon = 0.34). Finally, a main effect of semantic content ($F_{1,14}$ = 19.01; $p<0.001$) indicated that across all conditions, the ratio of correctly repeated words was higher for sentences with high-predictable than low-predictable endings.

3.2. Complementary analyses on keywords correct

In line with the results for the ratio of correctly repeated words per sentence described above, the three-way interaction between semantic content, noise vocoding level and rTMS site was highly significant for the keywords correct measure ($F_{4,56}$ = 5.6, p = 0.001). When applying the breakdown into two two-way ANOVAs by rTMS site, notably, rTMS over AG did not abolish the known semantic content by noise vocoding level on the sentence-final keyword altogether ($F_{4,56}$ = 10.4, $p < 0.001$). As expected, this interaction was also highly significant after rTMS over the control site in left SPL ($F_{4,56}$ = 8.06; $p < 0.001$; G-G epsilon = 0.37).

Breaking down the three-way interaction by noise vocoding level, rather, confirmed the effect observed with the *k*-factor (Figure 3): rTMS over AG reduced the predictability gain at 4-band noise vocoding level compared with rTMS at the control site ($F_{1,14}$ = 4.6, p = 0.05), but also *shifted* the effect to a less severe 8-band noise vocoding level. At 8-bands, the rTMS by semantic content interaction now reached significance ($F_{1,14}$ = 10.76, p = 0.005), because rTMS over AG *increased* the magnitude of the predictability gain at this less severe degradation level.

To further explore the direction of the observed rTMS-induced modulation with 8-band noise vocoding, the ANOVA was followed-up with Bonferroni-Holm corrected post-hoc paired t-tests. These analyses revealed that the interaction resulted from a significant decrease in the number of correctly repeated keywords for sentences with low-predictable endings after rTMS of AG as compared to rTMS of SPL (t_{14} = 2.86, p = 0.013, r = 0.61). In contrast, there was no significant difference in the number of correctly repeated keywords after rTMS over AG vs. SPL for high-predictable sentences (t_{14} = 0.77, p = 0.45, r = 0.2).

The main effect of noise vocoding level was again significant ($F_{4,56}$ = 732.36; p < 0.001), as was the effect of predictability (main effect of semantic content: $F_{1,14}$ = 104.71; p < 0.001). A significant interaction between noise vocoding level and semantic content ($F_{4,56}$ = 11.91; p < 0.001) indicated that the benefit of the semantic content critically depended on the vocoding level.

3.3. Speech onset time (SOT)

Speech onset time (SOT) was analyzed as a reaction-time–analogue measure. The three-way repeated measures ANOVA again included the factors *noise vocoding level* (2-, 4- ,8-, 12-, 16- and 32-band noise-vocoded), *semantic content* (high- vs. low-predictable endings) and *rTMS site* (AG vs. SPL).

We did not find any significant effects of rTMS on SOT (all p>0.13). A main effect of noise vocoding level ($F_{4,48}$ = 107.79; p < 0.001; G-G epsilon = 0.9; supplementary Figure 2) indicated that more severe vocoding levels led to increased SOT, however, this did not interact with rTMS site. Additionally, we found a main effect of semantic content ($F_{1,12}$ = 55.61; p < 0.001; G-G epsilon = 0.82), showing that high-predictability sentences were repeated faster than low-predictability sentences. The predictability gain was also influenced by the noise vocoding level ($F_{4,48}$ =6.47; p<0.001; G-G epsilon = 0.35) but this did not interact with rTMS site. Hence, the difference between high-predictability and low-predictability sentences was significant only for

$\geq$8-band sentences (8-band: t_{14}=8.52; p<0.001; 16-band: t_{14}=10.96; p<0.001; 32-band: t_{14}=8.16; p<0.001; Bonferroni-Holm corrected) but was absent when the speech signal quality decreased (2-band: t_{14}=0.35; p=0.73; 4-band: t_{14}=1.69; p=0.11).

Finally, we tested for a potential influence of the number of syllables presented in a sentence (ranging from 8–12) on task performance. Specifically, one might expect that speech onset times increase with an increasing number of syllables presented in a sentence, while the percentage of correctly repeated words per sentence or correctly repeated final words (keywords correct) might decrease. This might indicate an increase in working memory load or task difficulty for more complex sentences. However, there was no significant correlation for either dependent measure (all p > 0.13).

References

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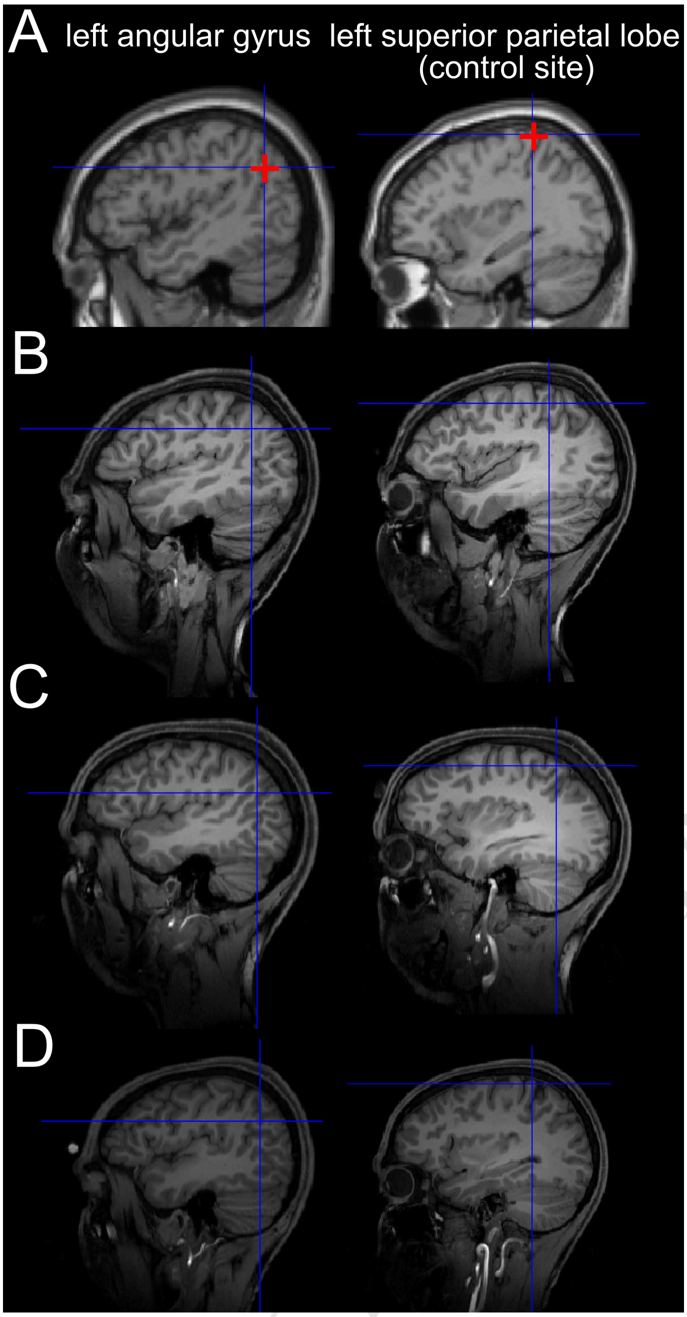
Figure Legends

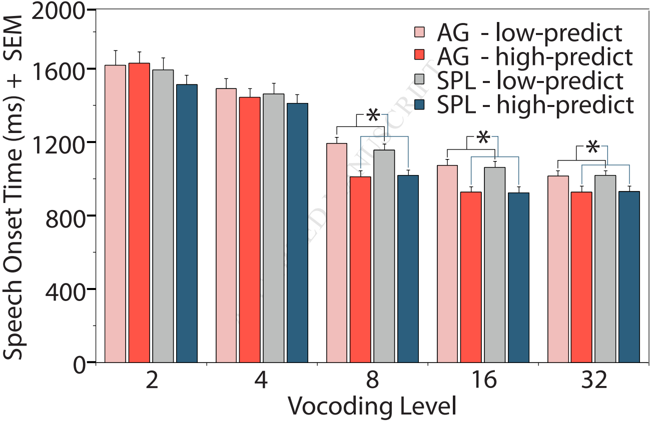
Supplementary Figure 1

A. Mean group coordinates for our rTMS sites in standard space (visualized on the single subject T1 template provided in the SPM 8 software). **B, C, D.** Individual coordinates for the respective sites in native space for three representative subjects.

Supplementary Figure 2

Speech onset time as a function of semantic content (high-predictability vs. low-predictability sentences), noise vocoding level and rTMS site. AG, angular gyrus; SPL, superior parietal lobe; control site. *p < 0.05. Error bars represent one-fold standard error of the mean.


A
left angular gyrus
left superior parietal lobe (control site)
B
C
D



Speech Onset Time (ms) + SEM
2000
1600
1200
800
400
0
AG - low-predict
AG - high-predict
SPL - low-predict
SPL - high-predict
*
*
*
2
4
8
16
32
Vocoding Level