Contributions of left frontal and temporal cortex to sentence comprehension: Evidence from simultaneous TMS-EEG

Leon O. H. Kroczek[1,2]*, Thomas C. Gunter[1]*, Anna U. Rysop[3], Angela D. Friederici[1] & Gesa Hartwigsen[3]

https://doi.org/10.1016/j.cortex.2019.01.010

[1] Department of Neuropsychology, Max Planck Institute for Human Cognitive and Brain Sciences Leipzig, Germany

[2]Department of Psychology, University of Regensburg, Regensburg, Germany

[3] Research Group "Modulation of Language Networks", Department of Neuropsychology, Max Planck Institute for Human Cognitive and Brain Sciences Leipzig, Germany

*these authors contributed equally to the manuscript.

Author contributions: G.H. and T.G. designed research; A.R. & L.K. supervised data collection; L.K. analyzed data; T.G., G.H., L.K., and A.F. wrote the paper; A.R. commented the paper.

Competing financial interests: The authors declare no conflict of interest.

Word count: Abstract: 240 words, Introduction: 1426 words, Discussion: 1941 words

Running title: Role of left IFG and STG in sentence comprehension

Key words: syntax, semantic, N400, prediction, virtual lesion

Address for correspondence:

Thomas C. Gunter
Department of Neuropsychology
Max Planck Institute for
Human Cognitive and Brain Sciences
D-04103 Leipzig
Germany
Phone: +49 /(0)3 41/ 99 40 115
Fax: +49 /(0)3 41 / 99 40 2260
Email: gunter@cbs.mpg.de

Gesa Hartwigsen
Department of Neuropsychology
Max Planck Institute for
Human Cognitive and Brain Sciences
D-04103 Leipzig
Germany
Phone: +49 /(0)3 41/ 99 40 162
Fax: +49 /(0)3 41 / 99 40 2260
Email: hartwigsen@cbs.mpg.de

Abstract

Sentence comprehension requires the rapid analysis of semantic and syntactic information. These processes are supported by a left hemispheric dominant fronto-temporal network, including left posterior inferior frontal gyrus (pIFG) and posterior superior temporal gyrus/sulcus (pSTG/STS). Previous electroencephalography (EEG) studies have associated semantic expectancy within a sentence with a modulation of the N400 and syntactic gender violations with increases in the LAN and P600. Here, we combined focal perturbations of neural activity by means of short bursts of transcranial magnetic stimulation (TMS) with simultaneous EEG recordings to probe the functional relevance of pIFG and pSTG/STS for sentence comprehension. We applied 10 Hz TMS bursts of three pulses at verb onset during auditory presentation of short sentences. Verb-based semantic expectancy and article-based syntactic gender requirement were manipulated for the sentence final noun. We did not find any TMS effect at the noun. However, TMS had a short-lasting impact at the mid-sentence verb that differed for the two stimulation sites. Specifically, TMS over pIFG elicited a frontal positivity in the first 200 ms post verb onset whereas TMS over pSTG/STS was limited to a parietal negativity at 200-400 ms post verb onset. This indicates that during verb processing in sentential context, frontal brain areas play an earlier role than temporal areas in predicting the upcoming noun. The short-living perturbation effects at the mid-sentence verb suggest a high degree of online compensation within the language system since the sentence final noun processing was unaffected.

1. Introduction

Successful communication depends on the rapid comprehension of sentences. Sentence comprehension develops over time in a relatively specific left hemisphere dominant fronto-temporal brain network (Friederici, 2012; Maess, Mamashli, Obleser, Helle, & Friederici, 2016; Obleser & Kotz, 2010). Across this time course, both the semantic (i.e., meaning related) and syntactic (i.e., structural) content of the sentence is constantly analyzed and specific predictions about the next words are generated based on prior knowledge and contextual information (Bar, 2007; Bendixen, Schroger, & Winkler, 2009; Griffiths & Tenenbaum, 2011; Kroczek & Gunter, 2017; Kuperberg & Jaeger, 2015; Rao & Ballard, 1999). To investigate the processing of the semantic and syntactic content, most of the previous studies examined how well words are integrated at particular positions in a sentence (cf. Friederici, 2017; Kutas & Federmeier, 2011; Van Petten & Luka, 2012).

With respect to the brain regions associated with semantic and syntactic aspects of sentence processing, previous functional neuroimaging studies have shown that both the left inferior frontal gyrus (IFG) (BA44, BA45) and posterior superior temporal gyrus / sulcus (pSTG/STS) contribute to successful sentence comprehension (e.g. Obleser and Kotz, 2010). Specifically, the left anterior IFG (aIFG, BA45) was discussed to be involved in semantic processes (Hagoort, 2005; Price, 2010; Goucha & Friederici, 2015). Aside from left aIFG, left angular gyrus was also assigned a key role in semantic processing, both at the word and sentence level (e.g. Hartwigsen et al., 2016; Obleser et al., 2007; Obleser and Kotz, 2010). Moreover, variation of the semantic expectancy of a sentence key noun was – among other regions – associated with left pSTG/STS and adjacent posterior middle temporal gyrus (Baumgaertner, Weiller, & Buchel, 2002; Hartwigsen et al., 2017; Lau, Phillips, & Poeppel, 2008; Obleser & Kotz, 2010). Morpho-syntactic processing, on the other hand, was specifically associated with left posterior IFG (pIFG, BA44) (Hammer, Goebel, Schwarzbach, Munte, & Jansma, 2007). For instance, increased activity in pIFG was reported for the processing of syntactic gender violations in determiner phrases such as '*das Baum*' (the$_{[neuter]}$ tree$_{[masculine]}$) instead of the correct '*der Baum*' (the$_{[masculine]}$ tree$_{[masculine]}$) (Heim, van Ermingen, Huber, & Amunts, 2010).

Regarding the time-course of semantic and syntactic aspects of sentence processing, numerous previous electroencephalography (EEG) studies have investigated different event-related potential components (ERPs). Specifically, it was demonstrated that morpho-syntactic violations such as violations of article-noun congruency evoke a left-anterior negativity (LAN) around 300-400 ms after word presentation and an additional late positive component starting around 600 ms after violation onset (P600) (see Friederici, 2017). Variations of the semantic expectancy are associated with a centro-parietal negativity around 400 ms (N400) that is usually larger when unexpected relative to expected nouns need to be integrated into a sentence (Gunter, Friederici & Schriefers, 2000; Kutas & Federmeier, 2011). Importantly, it should be noted that the N400 might represent a downstream effect of the prediction made on the preceding verb (e.g. Stites & Federmeier, 2015). Indeed, a recent MEG-study found effects of semantic predictability at the main verb of the sentence (Maess et al., 2016). Specifically, a reversed N400m effect, the magnetic pendant of the N400, was reported for the verb, with highly predictive verbs eliciting a stronger N400m relative to verbs with a lower predictability. This effect was taken to reflect a pre-activation of possible nouns based on the selectional restrictions of the verb.

Notwithstanding their crucial role in understanding cognition, electrophysiology and functional neuroimaging are correlational in nature. The causal relevance of brain regions and the respective ERP-components related to sentence comprehension therefore remain unclear. Causal non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) can help to resolve this issue. While an abundant literature on sentence processing used event-related potentials to disentangle semantic and syntactic processing during sentence comprehension, to the best of our knowledge, no study directly probed the functional relevance of different brain regions for these processes and related this to ERP-components like the N400 or P600. The present study therefore represents the first attempt to unravel the causal contribution of inferior frontal and posterior temporal regions to sentence comprehension by combining focal perturbation of neural activity induced by TMS with EEG measurement in a simultaneous fashion.

In particular, the use of very short TMS bursts that were applied “online” (i.e., during task processing) allowed us to address the duration of the after-effect of such perturbations on sentence comprehension. In contrast to the long-lasting plastic changes in task-related activity induced by repetitive TMS protocols that are given before task processing (i.e., “offline”; Siebner & Rothwell, 2003), online TMS bursts should affect neural processing for a very short time period of several hundreds of milliseconds only (Siebner, Hartwigsen, Kassuba, & Rothwell, 2009). However, the exact duration of such interventions on cognitive functions is unknown. One important advantage of the online approach is that the direct and focal perturbation of a brain region is too short for functional reorganization to occur. Online TMS should thus reveal direct structure-function relationships (Hartwigsen, 2015).

In the present study, we relied on a well-established sentence comprehension paradigm from a previous study that manipulated semantic expectancy and morpho-syntactic processing by varying both the semantic fit between the verb and the noun and the syntactic fit between noun and its article (Gunter et al., 2000). In that study, a dissociation between semantic and syntactic processing was reflected in different

ERP-components, with a larger N400 for nouns with a lower semantic verb expectancy and a larger LAN and P600 for morpho-syntactic violations. Building upon these results, we combined a similar paradigm with online TMS during EEG recording. Please note that our syntactic manipulation is based on the comparison of a sentence with a syntactic gender violation relative to a well-formed sentence. In contrast, the semantic manipulation in our stimuli contrasts two well-formed sentences that simply differ in the degree of the expectancy of the final sentence noun. In contrast to the previous study, however, we here employed shorter 4-word sentences (i.e. pronoun-verb-article-noun) that were presented acoustically. To capture a potential behavioral impact of the TMS induced perturbation that is usually quantified in terms of decreased response accuracy or increased response speed (Hartwigsen, 2015), a lexical decision task was included. Motivated by a previous study that used similar sentences and found effects already at the mid-sentence verb position in addition to the sentence-final noun position (Maess et al., 2016), the present study applied TMS over pIFG and pSTG/STS at verb onset. This allowed for testing whether the perturbation effect would only impact processing during the stimulated period (i.e., processing of the verb) or outlast verb presentation and also impact integration of the final noun into a sentence. Thus, a main purpose of our study was to investigate predictions based on the verb. Consequently, TMS was applied at the verb position because strong predictions on the upcoming semantic information are generated there.

Based on the above-discussed studies, we expected to find a dissociation of TMS effects on semantic and syntactic aspects of sentence comprehension. In particular, TMS over left pIFG should selectively affect the morpho-syntactic aspect of sentence processing if the disruptive effect would outlast the verb position and interfere with the syntactic expectations generated by the article. At the noun position, this would lead to a reduction in the amplitude of the LAN and/or P600 and potentially also a decrease in the behavioral difference between correct and incorrect syntactic gender. In contrast, TMS over pSTG/STS should selectively affect semantic processing and therefore modulate the amplitude of the N400 either at the verb and/or its noun-argument. Consequently, we expected an EEG effect at the verb and/or a reduction of the N400 amplitude at the noun, as TMS might interfere with the build-up of semantic expectancies based on the verb. This might also decrease the behavioral difference between highly expected and less expected sentence nouns. Our design further allowed us to distinguish between two alternative hypotheses on the duration of the TMS effect. The first hypothesis was that the effect would outlast the duration of the stimulation and therefore affect the processing of the sentence final noun. As an alternative hypothesis, the effect might be short-lived and only influence verb processing.

Our results show that the effects of TMS were short-lasting and selectively affected verb processing. Consequently, we cannot draw any conclusions on the causal role of frontal and posterior temporal brain regions in semantic and morpho-syntactic processing at the final sentence noun. From a psycho-linguistic perspective, this result is important since it suggests that the language network is highly dynamic and adaptive and remains undisturbed in its final computations when sentence processing is locally perturbed by TMS.

2. Materials and Methods

2.1. Participants

Twenty-four healthy native German speakers participated in this study (mean age = 26.88 years, SD = 3.19; age range 25–34 years, 12 females). All participants were right handed (mean laterality quotient = 95.92, SD=6.72; according to the Edinburgh handedness inventory; Oldfield, 1971) and had normal or corrected-to-normal vision, and no hearing deficits. Prior to the experiment, all participants had a medical briefing for TMS. Exclusion criteria for participation were early bilingualism, a history of psychiatric or neurological disease as well as contra-indications against TMS. Participants gave written informed consent, received 10 €/h compensation, and were informed about their right to quit the study without any disadvantage. The study met the prerequisites of the guidelines of the Declaration of Helsinki and was approved by the Ethics committee of the University of Leipzig (118/16-ek). The study was conducted according to the approved guidelines.

2.2. Experimental Design and Stimuli

This study used a 2x2 factorial within-subject design with the factors semantic expectancy (high vs. low cloze probability) and syntactic gender (correct vs. incorrect). We included a total of 160 experimental items consisting of shortened German sentences taken from our previous study (Gunter et al., 2000). The four word sentences (i.e. pronoun-verb-article-noun) had either a low (< 25%; mean 15.3%; see Taylor, 1953) or a high cloze probability (>56%; mean: 74.2%) for their sentence final noun. Put differently, verbs in high cloze sentences can be regarded as highly predictive whereas verbs in low cloze sentences are low predictive. Overall, there were 40 experimental sentences per condition (cf. Table 1). In these experimental sentences, the masculine gender article (“den”) was morpho-syntactically incorrect whereas the neuter article (“das”) was correct. To avoid any morpho-syntactic expectation driven by the article, we added 160 filler items of a middle cloze probability in which the matching between gender article and noun was reversed (i.e., “das" was incorrect and “den" was incorrect). Since participants had to carry out a lexical decision task on the sentence final noun, half of the stimuli had to end with a pseudoword. For each of the experimental and filler conditions, corresponding pseudowords were created using WordGen software (WinWordGen, Version 1.0; Duyck et al. 2004). Pseudowords had the same number of syllables as the sentence final nouns and were phono-tactically legal. Since we were interested in the predictive role of the two verb classes, number of syllables, word frequency and word duration (see below) was controlled. There was no significant difference in number of syllables for the high (mean= 1.7; SD= 0.791) and the low (mean= 2.025; SD= 0.832) predictive verbs (t(78) = -1.791, p= 0.08). As in the Maess et al. (2016) study, there was a significant difference in frequency class between high predictive (mean frequency class= 14.4, SD= 3.794) and low predictive verbs (mean frequency class= 11.2, SD= 3.490) as measured by the Wortschatz database (http://wortschatz.uni-leipzig.de/; t(78) = 3.865, p=0.0002). This difference corresponds to a ratio of only 1:8. Please note, that Halgren et al (2002) showed only a minor influence of word frequency for the N400 when comparing words with a mean frequency of 15 with 336 per million, which corresponds to a much higher ratio of approximately 1:23. We therefore suggest that word frequency differences in our 40 stimulus pairs will be of less importance compared to their predictiveness. This claim was substantiated by an additional analysis of the pilot-data using a subset of 19 pairs of stimuli which fell within the same word frequency class and evoked n equivalent response as the complete set of 40 stimulus pairs (see below and Figure SI 1 & 2 in the supplementary material).

Table 1: Example of the four types of experimental sentences used in both experiments

	Correct syntactic gender	**Incorrect syntactic gender**
High cloze %	Sie bereist das Land. *She travels the*$_{neuter}$ *land*$_{neuter}$.	Sie bereist den Land. *She travels the*$_{masc}$ *land*$_{neuter}$.
Low cloze %	Sie befährt das Land. *She drives the*$_{neuter}$ *land*$_{neuter}$.	Sie befährt den Land. *She drives the*$_{masc}$ *land*$_{neuter}$.

In contrast to the original Gunter et al. (2000) study, the present stimulus material was presented acoustically. During the audio recording of the material (sampling rate 44.1 kHz, Audacity 2.0), a professional male native speaker uttered the sentence material with normal speed and without a specific emphasis of the words. Sound files were processed using Adobe Audition 3.0. A 50 ms silence period was inserted at the beginning and the end of each sentence and a 20 ms silence period was inserted at the onset of the noun. The amplitude of the acoustic material was normalized using the root mean square. Sentences had an average length of 1633 ms (SD = 169 ms) with verb onset at 221 ms, article onset at approx. 861 ms, and noun onset at 1118 ms. The mean verb length was 640 ms (SD = 116), the mean article length was 257 ms (SD = 25 ms), and the mean noun length was 514 ms (SD = 116 ms). There was no significant difference in article duration between correct and incorrect syntactic gender (F(1,156) = 2.52, p = .114). Likewise, there were no significant differences in the temporal distance between verb onset and noun onset between experimental conditions (semantic expectancy: F(1,156) = 0.744, p = 0.390, syntactic gender: F(1,156) = 0.051, p = 0.821, interaction: F(1,156) = 0.063, p = .803).

To avoid acoustic expectancies and cues for a particular sentence final noun, sentences of the incorrect and pseudoword conditions were created by cross-splicing correct sentences. To this end, the speaker always uttered correct sentences (i.e., morpho-syntactically correct versions using both the article “der” and “den” and sentences ending with a pseudoword). In a next step, the noun/pseudoword was stripped from the sentence and then recombined into new sentences that were morpho-syntactically correct or incorrect or ended with a pseudoword. This led to a total of 160 experimental sentences (40 per condition), 160 filler sentences and 960 pseudoword sentences. Sixteen additional sentences that did not occur in the experimental stimulus set were created for a practice block before the experiment.

2.3. Procedure

Each participant underwent three experimental sessions that varied in TMS site (i.e., pIFG, pSTG/STS or sham TMS as control condition, see below). Order of stimulation sites was counterbalanced across participants. A randomized stimulus list was created for each participant and session. Sentences were presented via headphones and stimulus presentation was controlled by the software ‘Presentation’ (Neurobehavioral Systems, Inc., Albany, CA, USA). A fixation cross was displayed on the screen throughout the experiment. The duration between stimulus presentation was jittered (range = 1205 - 1395 ms). During the experiment, subjects had to perform a lexical decision task. Reaction times were measured with the onset of the critical noun/pseudoword. Responses exceeding 2000 ms were counted as misses. Response key assignment was counterbalanced across subjects. To prevent TMS-specific carry-over and habituation effects or memory effects due to repetition of stimuli, experimental sessions were separated by one week. In total, 640 trials were presented per session. A single session lasted approximately 2.5 to 3.5 hours. A different set of pseudowords was used in each session to preserve the novelty of the pseudowords for the lexical decision task.

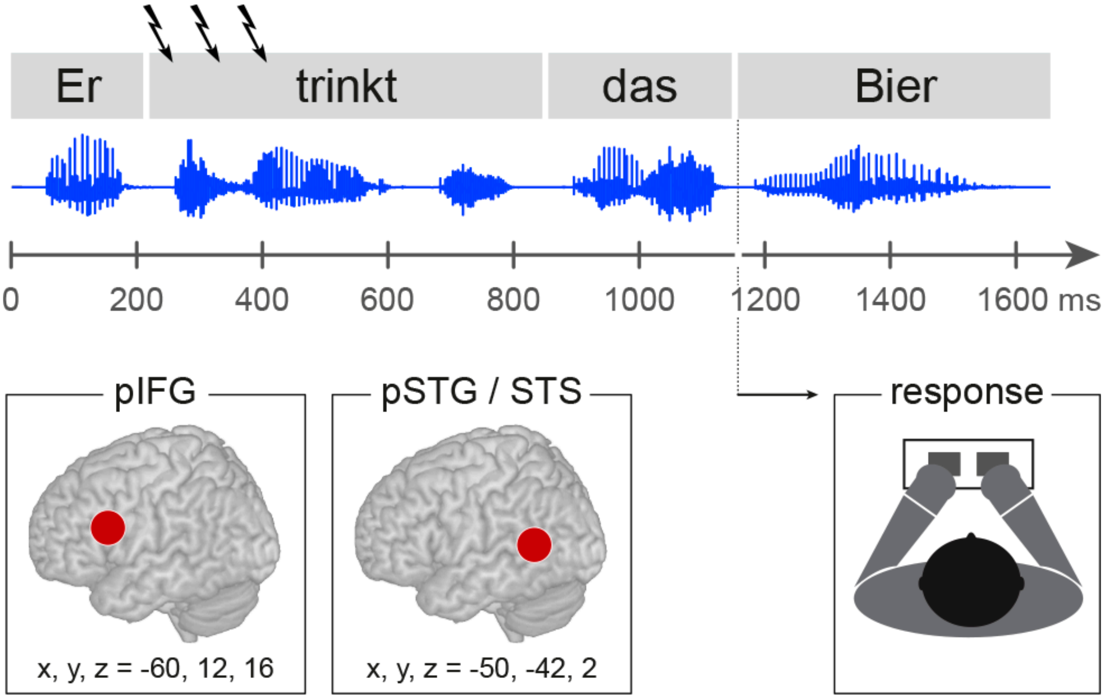


Figure 1. Experimental design. Participants listened to acoustically presented sentences and performed a lexical decision task on the final sentence noun. A 3-pulse burst of effective or sham TMS at 10 Hz was applied with verb onset over either pIFG or pSTG/STS in separate sessions. Mean coordinates for both stimulation sites are given in MNI space.

2.4. Transcranial Magnetic Stimulation (TMS)

We used neuronavigated TMS (Localite, St. Augustin, Germany) based on co-registered individual T1-weighted MRI images to navigate the TMS coil and maintain its exact location and orientation throughout all sessions. As a prerequisite for stereotactical coil placement, individual structural T1-weighted scans were acquired in an extra session or taken from the institute's participant database (MPRAGE sequence in sagittal orientation, voxel size = 1 x 1 x 1.5 mm; TR = 1.3 s, TE = 3.36 ms; whole brain). TMS was performed using the mean Montreal Neurological Institute (MNI) coordinates for left pIFG (x, y, z= -60, 12, 16) and pSTG/STS (x, y, z= -50, -42, 2) from a previous fMRI study that used similar material (Obleser & Kotz 2010). Using these stereotactic coordinates, individual stimulation sites were determined by calculating the inverse of the normalization transformation and transforming the coordinates from standard to individual space for each subject. During each experimental session, subjects were co-registered to their individual structural brain image. TMS intensity was set to 90% of individual resting motor threshold of the left primary motor hand area (Hartwigsen et al., 2010). The individual resting motor threshold (RMT) was determined in the first session and held constant across sessions as in our previous studies (e.g. Hartwigsen et al., 2016; Kuhnke et al., 2017). This procedure guaranteed that differences in the effects of both TMS sites were not confounded by different stimulation intensities. RMT was defined as the lowest stimulation intensity producing a visible motor evoked potential of approximately 50 µV (peak-to-peak amplitude) in the relaxed first dorsal interosseus muscle with single pulse TMS given over the motor hot spot. Stimulation intensity was corrected for the scalp-to-cortex distance between the motor cortex and the two stimulation sites following a simple linear correction approach (Stokes et al., 2005). For the primary motor cortex, we used the mean stereotactic coordinates from a meta-analysis (Mayka et al., 2006) as a starting point and applied the same algorithms as described above. Mean corrected stimulation intensity was 47% (SD = 7.78%) total stimulator output for the pIFG condition and 53% (SD = 7.31%) for the pSTG/STS condition.

During the experiment, an online TMS burst of three pulses with a frequency of 10 Hz was applied in each trial. TMS was given at verb onset and controlled via ‘Presentation’ (Neurobehavioral Systems, Inc., Albany, CA, USA). For pIFG TMS, the coil was oriented 45° to the sagittal plane, with the second phase of the biphasic pulse inducing a posterior-to-anterior current flow (Hartwigsen et al., 2010). Due to anatomical restrictions, coil placement for pSTG/STS required rotation of the coil at an angle of 225°. Consequently, the current flow was inversed. The position of the TMS coil was monitored during the whole experiment and adjusted if necessary. For the ineffective sham condition, an additional coil was placed over the first coil at a 90° angle. Only the second coil was charged. This montage created similar acoustic sensations compared to the effective condition without actively stimulating the brain. Overall TMS application and stimulation intensities were well within the published safety guidelines (Rossi et al. 2009). TMS was applied using a Magpro X100 stimulator (MagVenture, Farum, Denkmark) and figure-of-eight-shaped coils (C-B60; outer diameter 7.5 cm).

2.5. EEG recording

EEG was recorded using 59 Ag/AgCl electrodes located according to sites defined in the extended 10-20 system of the American Clinical Neurophysiology Society (2006) and embedded in a cap (EC80, EasyCap GmbH, Germany). Sternum served as ground. The EEG was amplified using two PORTI-32/MREFA amplifiers (TMS-international, dynamic range 22 Bits) and digitized on-line at 2000 Hz. Impedances were kept below 5 kΩ. During data acquisition, the EEG was referenced against the vertex (Cz) electrode; a linked mastoid reference was calculated off-line. The electro-oculogram (EOG) was measured horizontally as well as vertically. To minimize TMS induced electromagnetic artifacts, electrode leads were placed orthogonal to the current flow in the TMS coil and fixated with an elastic net (cf. Sekiguchi et al. 2011).

Before the ERP-analyses, TMS and participant-induced artifacts were removed using the FIELDTRIP toolbox (Version: 20170601, Oosterveld et al., 2011): After segmenting the continuous EEG-data into smaller segments of 3000 ms, the actual TMS induced electromagnetic artefact of each biphasic TMS burst was removed and then interpolated from 2 ms pre pulse to 50 ms post pulse using cubic interpolation. This procedure removes the strong but short-lived step- and ringing-artifacts caused by the stimulation as well as artifacts related to the cranial muscles (cf, Herring, Thut, Jensen & Bergmann, 2015). To remove artifacts related to eye-blinks and eye-movements, an Independent Component Analysis (ICA) was performed on a separate subset of the data that consisted of 1300 ms long segments time-locked to the noun/pseudoword (and thus without the TMS pulse). To increase reliability of the ICA algorithm, this training data had been high-pass filtered with a cut-off of 1 Hz (Winkler et al., 2015). On the basis of this training set, components related to eye-blinks, eye-movements or muscle activity were identified and then removed from the original, unfiltered data segments. The remaining components were then back-projected using the ICA's transformation matrix resulting in a dataset, which was cleaned from TMS- and eye-related artifacts. Additionally, channels with amplitudes exceeding a range of 200 µV in more than 20% of all trials were removed and then interpolated using spline interpolation (max 10 channel, mean = 0.82, SD = 1.79). In a next step, the EEG was resampled with a new sampling rate of 500 Hz and then high-pass filtered with a cut-off of 0.1 Hz (Tanner et al., 2015) as well as low-pass filtered with a cut-off of 30 Hz.

Finally, trials exceeding a range of 150 µV were removed (resulting in a mean of 620 trials, SD = 37; there were no significant differences in the amount of artifact free trials between conditions: all p > .05). A 10 Hz low-pass filter was used for visualization purposes only.

In the ERP analyses, single subject averages were calculated for high and low predictive verbs as well as the four stimulus categories of the sentence final nouns (syntax x semantic). The epochs lasted from 200 ms prior to the onset of the critical word to 1000 ms afterwards. A 200 ms pre-stimulus baseline was applied between -200 and 0 for the noun. To avoid any impact of the TMS pulses on the baseline of the verb, it was computed between -250 and -50 preceding verb onset.

The analysis of the noun was conducted on averaged data of four ROIs in order to investigate the topographical distribution of relevant effects: anterior left (AF3, F5, F3, FC5, FC3, FC1), anterior right (AF4, F6, F4, FC6, FC4, FC2), posterior left (CP5, CP3, CP1, P5, P3, PO3) and posterior right (CP6, CP4, CP2, P6, P4, PO4). Based on previous findings (Gunter et al., 2000, Friederici, 2011), the analysis was performed in time-windows of interest between 300 – 500 ms (LAN, N400) and 600 – 900 ms (P600).

On the basis of the pilot and a previous study (Maess et al., 2016), we used a frontal (AF3, AFZ, AF4, F3, FZ, F4) and a posterior ROI (P3, PZ, P4, PO3, POZ, PO4) to analyze the data of the verb and created 5 latency windows of 200 ms each (from 0-200 to 800-1000 ms). Correction for multiple comparisons was applied after Holm (1979).

2.6. Statistical analysis

Behavioral data was analyzed separately for response speed and accuracy using a repeated measures ANOVA with the factors *semantic expectancy* (high vs. low cloze probability), *syntactic gender* (correct vs. incorrect) and *TMS* (sham, pIFG and pSTG/STS). Reaction times were analyzed only for trials with a correct response.

In the ERP analysis, a repeated measures ANOVA using *semantic expectancy* (high vs. low cloze probability), *syntactic gender* (correct vs. incorrect) and *TMS* (sham, pIFG and pSTG/STS), *laterality* (left vs. right) and *anteriority* (anterior vs. posterior) as within-subject factors was calculated for the noun position for time-windows of interest. For the verb position, only *verb prediction* (high vs. low predictive verbs), *TMS* (sham, pIFG and pSTG/STS) and *ROI (anterior vs. posterior)* were included as within-subject variables. P-values were corrected for violations of sphericity (Greenhouse & Geisser, 1959).

2.7. Pilot Experiment

There were two major changes in the experimental design compared to our previous study (Gunter et al., 2000). In the present study sentences were presented acoustically and participants had to perform a lexical decision task. Therefore, a pilot study with 24 participants who did not participate in the main experiment was conducted without TMS to test whether the adapted experimental design would show similar ERP effects as in the original study. In short, the pilot experiment replicated the previous findings, that is, a N400 effect at the sentence final noun for semantic expectancy, as well as a LAN and P600 effect for syntactic gender violations. Furthermore, there was a trend towards an interaction of semantic and syntactic factors in the P600 (see supplementary material). The scalp-distribution of the LAN-effect was much more posterior compared to the original Gunter et al. (2000) study. Variability in the LAN distribution (from left anterior to almost N400-like) has been observed and described in more recent studies (see for instance Molinaro, Barber, and Carreiras, 2011, Tanner, 2014). It is still unclear what this variability reflects. Since the present experiment was neither designed nor intended to explore such differences in the scalp distribution of the LAN, we refrain from commenting on the LAN-N400 debate and refer the interested reader to the respective literature (cf. Molinaro, Barber, Caffarra, & Carreiras, 2015 and Tanner, 2014, 2018).

The results are summarized in Figure 2. In addition, the pilot data was used to characterize effects of predictability at the verb position. In line with the findings of Maess et al. (2016), high predictive verbs elicited an increased negativity compared low predictive words between 400 - 700 ms that was pronounced on posterior electrodes. To ensure that this effect was not simply driven by differences in lexical frequencies an additional analysis was conducted on a subset of 19 high and 19 low predictive verbs that were exactly matched for lexical frequency. A comparable signal to noise ratio as in the analysis of the full item set was achieved by additionally entering pseudoword sentences into the analysis (note that pseudowords were only presented at the noun position). Importantly, high predictive verbs elicited an increased negativity compared to low predictive verbs between 400 and 600 ms, even when verbs were exactly matched for lexical frequency (see supplementary material SI 1 & 2). The results of the pilot study and the study by Maess et al. (2016) were used to guide the analysis in the main experiment. In particular, the objective was to investigate whether any of the main effects reported here would be modulated by TMS.

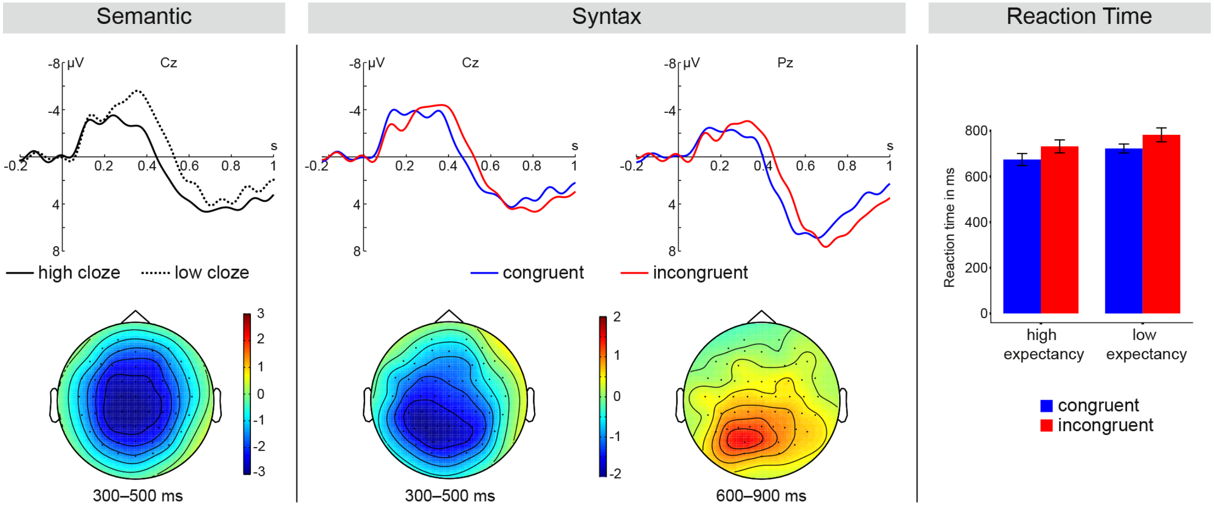


Figure 2. Results from the pilot study. ERP and behavioral effects on the noun and verb position of the pilot study.

3. Results

3.1. Behavioral data

A main effect of semantic expectancy showed that responses for high cloze sentence endings were faster than for low cloze sentences [$F(1,23) = 164.564$; $p < .001$, $\eta_p^2 = 0.877$]. A significant main effect of syntactic gender indicated that responses for correct sentences were faster than for incorrect ones [$F(1,23) = 71.613$; $p < .001$, $\eta_p^2 = 0.757$]. There were no significant interactions with TMS (all $p > 0.05$).

Analysis of response accuracies revealed only a main effect of semantic expectancy with increased accuracy for high cloze (94.41 % correct) compared to low cloze (91.58 % correct) nouns [$F(1,23) = 27.262$; $p < .001$, $\eta_p^2 = 0.542$]. Figure 3 provides an overview of the behavioral results (see also Figure SI 3).

3.2. EEG results

3.2.1. Sentence final noun

The analysis on the sentence final noun revealed significant main effects of semantic expectancy (N400) and syntactic gender (LAN & P600). However, none of these effects showed an interaction with TMS. Analysis in the early time window of 300 - 500 ms revealed a main effect of semantic expectancy [$F(1,23) = 66.024$; $p < .001$, $\eta_p^2 = 0.742$] and an interaction of semantic expectancy x anteriority [$F(1,23) = 55.200$; $p < .001$, $\eta_p^2 = 0.706$]. Low cloze sentences elicited a greater negativity than high cloze sentences (N400). A post-hoc t-test revealed that this effect was larger at posterior electrodes compared to anterior electrodes [$t(23) = 7.430$, $p < .001$]. Furthermore, analysis in the early window showed a main effect of syntactic gender [$F(1,23) = 21.188$, $p < .001$, $\eta_p^2 = 0.480$] and an interaction of syntactic gender x laterality [$F(1,23) = 9.558$, $p = .005$, $\eta_p^2 = 0.293$]. Syntactic gender violations elicited a greater negativity than correct nouns (LAN) with a left-lateralized topographical distribution [left vs. right: $t(23) = -3.091$, $p = .005$]. Analysis in the late time window of 600 - 900 ms revealed a main effect of syntactic gender [$F(1,23) = 7.363$, $p = .012$, $\eta_p^2 = 0.243$] and an interaction of syntactic gender x laterality x anteriority [$F(1,23) = 5.341$, $p = .03$, $\eta_p^2 = 0.188$]. A step-down analysis revealed an increased positivity for syntactic gender violations (P600) in posterior [$F(1,23) = 9.286$, $p = .006$, $\eta_p^2 = 0.288$] but not anterior ROIs [$F(1,23) = 3.652$, $p = .069$]. Additionally, a main effect of semantic expectancy [$F(1,23) = 12.222$, $p = .002$, $\eta_p^2 = 0.347$] and an interaction of semantic expectancy x laterality [$F(1,23) = 17.726$, $p < .001$, $\eta_p^2 = 0.435$] was found. Similar to the early window, low cloze sentences elicited a greater negativity than high cloze sentences. This effect was right-lateralized [left vs. right: $t(23) = 4.210$, $p < .001$]. Figure 3 provides an overview of the results (see also Figure SI 2).

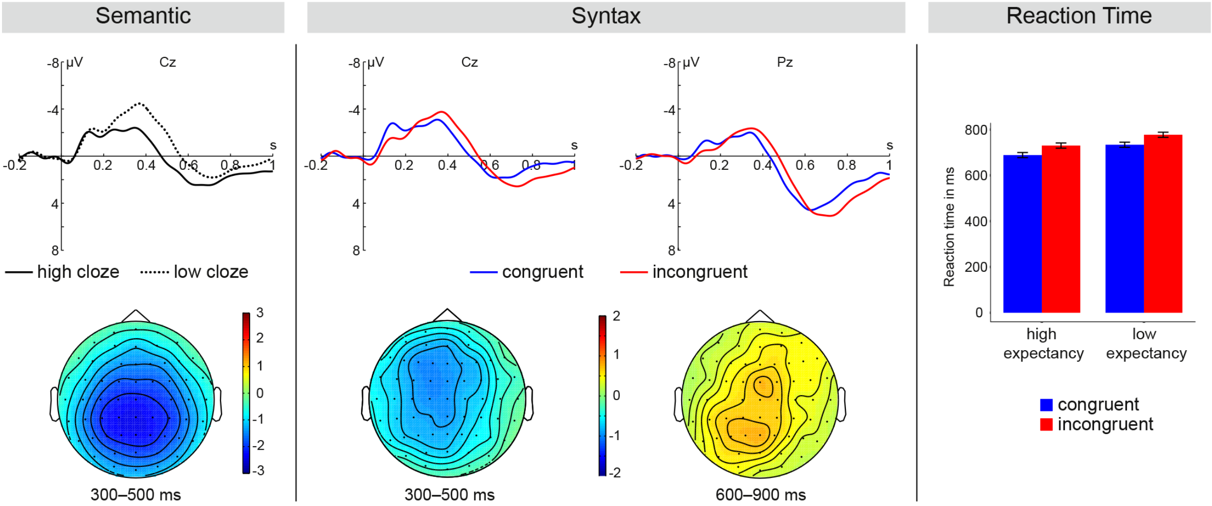


Figure 3. Effects of TMS on the noun. ERP effects at the noun position. Results are averaged across TMS conditions, as there was no interaction with stimulation site.

3.2.2. Verb position

The analysis for the verb position revealed a three-way interaction of TMS, verb prediction and ROI in all time windows [Holm corrected for multiple comparisons; 0-200 ms: $F(2,46) = 4.596$, $p = .034$, $\eta_p^2 = 0.167$; 200-400 ms: $F(2,46) = 5.071$, $p = .034$, $\eta_p^2 = 0.181$; 400-600 ms: $F(2,46) = 6.127$, $p = .022$, $\eta_p^2 = 0.210$; 600-800 ms: $F(2,46) = 6.115$, $p = .034$, $\eta_p^2 = 0.210$; 800-1000 ms: $F(2,46) = 3.366$, $p = .043$, $\eta_p^2 = 0.128$]. A step-down analysis for the frontal ROI revealed a significant interaction of verb prediction and TMS between 0 and 200 ms [$F(2,46) = 6.149$, $p = .021$, $\eta_p^2 = 0.211$]. A further step-down analysis of TMS in this time window revealed a main effect of verb prediction for pIFG TMS [$F(1,23) = 16.997$, $p < .001$, $\eta_p^2 = 0.425$], but not at the other TMS conditions [sham: F(1,23) = 0.272, p = .607; pSTG/STS: F(1,23) = 0.032, p = .861]. This early effect of predictability was due to a more positive response (i.e. a less negative response) to high predictive verbs compared to low predictive verbs.

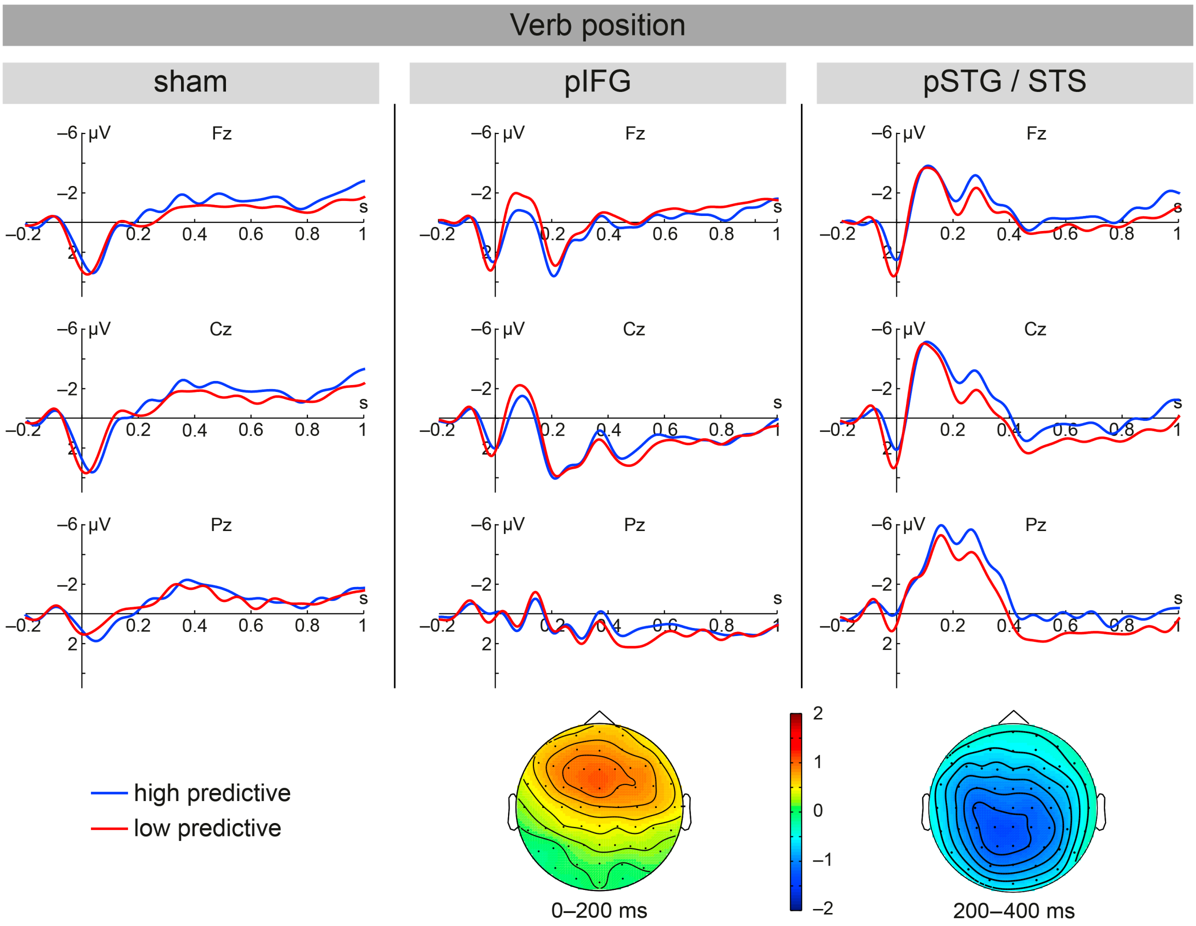


Figure 4. Effects of the different TMS conditions on verb processing. ERP effects of predictability at the verb position in the main experiment. ERPs are shown for all stimulation sites (sham, pIFG, pSTG/STS).

A step down analysis for the posterior ROI showed significant interactions of verb prediction and TMS between 200 and 400 ms [F(2,46) = 5.526, p = .035, η_p^2 = 0.194]. The ROI results were further confirmed by an independent cluster-based permutation test (cf. supplementary material).

A further step-down analyses on the basis of TMS in the 200-400 ms time window revealed main effects of verb prediction for pSTG/STS TMS [F(1,23) = 25.245, p < .001, η_p^2 = 0.523]. There was no effect for the other TMS conditions [sham: F(1,23) = 0.002, p = .962; pIFG: F(1,23) = 1.125; p = .300]. Indeed, pSTG/STS TMS led to a larger difference between high and low predictive verbs than pIFG TMS with high predictive verbs eliciting a greater negativity than low predictive verbs (see Figure 5).

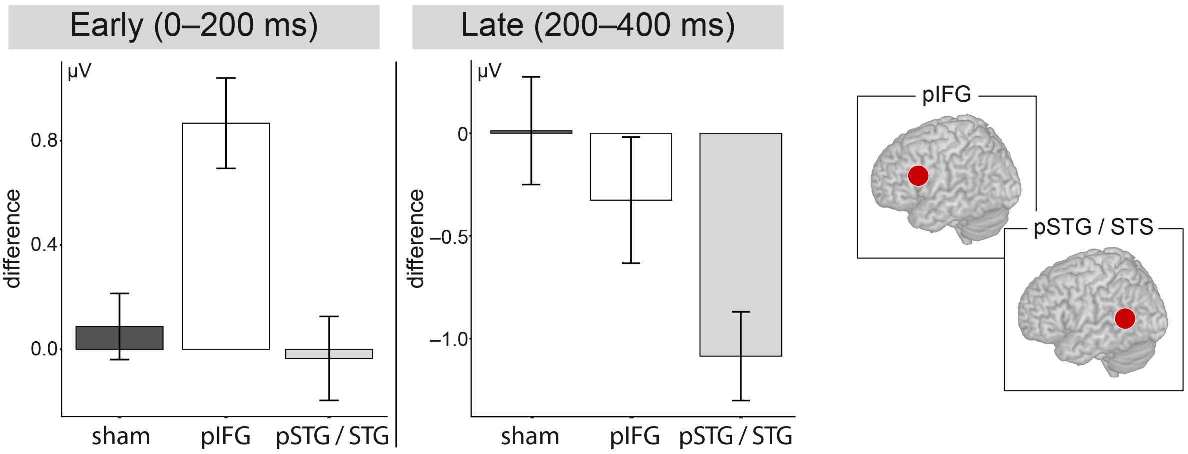


Figure 5. Early and late TMS effects on the verb. Difference of high predictive and low predictive verbs at the frontal and posterior ROI. Error bars reflect the SEM.

4. Discussion

This study used a simultaneous “online” combination of TMS and EEG to elucidate the role of the left inferior frontal and posterior temporal cortex in sentence comprehension. Our main finding was that TMS over both regions differentially affected verb processing but did not impact either the ERP or behavior at the sentence final noun. This finding can be interpreted in two different ways. First, it may suggest that the left inferior frontal and posterior temporal cortex do not play a significant role in the processing of the relation between the verb and its noun-argument. A second alternative explanation is that our TMS protocol only had a short-lived effect, which was restricted to the verb position and compensated downstream the sentence. This would indicate that prediction based on the sentence's verb was still possible to some degree, either because the TMS induced perturbation did not completely disrupt verb processing, and/or other regions of the semantic system may have compensated for the disruption. We would argue that the second alternative explanation based on compensation is much more likely, because the first explanation would contrast with most language-related fMRI and TMS studies discussed earlier.

Processing verb-noun relations in the language network

In our study, no modulatory effects of TMS were observed for the sentence final noun when TMS was applied at the mid-sentence verb, neither for the ERPs nor the behavioral responses of the lexical decision task. This is surprising given that the lexical decision on the noun revealed a strong influence of the verb-based semantic expectancy and the syntactic gender violation as reflected in overall longer response time for low relative to high cloze endings and for incorrect vs. correct syntactic gender. Likewise, significant main effects of syntactic gender (LAN and P600) and semantic expectancy (N400) in the ERP responses at the sentence final noun showed that our paradigm was sensitive to the experimental manipulations and nicely replicated the previous EEG study using a visual version of our material (Gunter et al., 2000). Additionally, we observed a significant difference between high and low predictive verbs, which in a previous MEG study was suggested to reflect a pre-activation of possible nouns based on the selectional restrictions of the verb (Maess et al., 2016). Importantly, verb processing was modulated significantly by TMS without, however, impacting processing of the sentence final noun. These data are in contrast to psycholinguistic views based on reaction time experiments varying the predictability of the verb-noun relation without measuring at both the verb and the noun position. Most of these views (Federmeier, Wlotko, De Ochoa-Dewald, & Kutas, 2007; Grisoni, Miller, & Pulvermuller, 2017; Kutas & Fedemeier, 2011; Lau et al., 2008) assume that the verb plays a crucial role in predicting the sentence final noun. Accordingly, one would have expected that the observed disruption of verb processing in our study should affect the processing of the upcoming noun.

The apparent discrepancy between these previous studies and the absence of a modulatory TMS effect on the noun in our study is most likely explained by rapid compensation within the semantic network, potentially by a stronger contribution of other semantic key nodes, such as the left angular gyrus or anterior temporal lobe (e.g. Binder, Desai, Graves, & Conant, 2009; Davey et al., 2016; Jung and Lambon Ralph, 2016). In other words, if a particular node of a specific network is disrupted, other areas may be stronger engaged, which still enables 'normal' performance (see Hartwigsen, 2018). For instance, previous studies on the word level have shown that TMS over the IFG does not necessarily delay semantic processing performance if left angular gyrus remains intact (Hartwigsen et al., 2010; 2016). Such findings indicate a high degree of compensation and flexible adaptation during language processing (see Hartwigsen, 2018). In this context, it is important to note that it is unlikely that the TMS induced perturbation completely "silences" the targeted region but rather modulates the signal-to-noise ratio in the stimulated area (e.g. Ruzzoli, Marzi and Miniussi, 2010; Schwarzkopf, Silvanto and Rees, 2011). Consequently, concerning the results reported in the studies cited above (Hartwigsen et al., 2010, 2016), one may also argue that activity in the IFG was not completely down-regulated and the remaining activity may have contributed to maintain task function. Following this explanation, one may assume that some robustness of the semantic system helped to maintain information in the semantic network in our study, enabling processing of the noun and leaving the responses at the noun position unaffected.

Notably, despite the null effect at the level of the noun, the present data show a striking difference of how the two TMS sites modulated the verb prediction effect in a sentence. TMS over pIFG led to an early frontal positivity whereas TMS over pSTG/STS led to a later parietally distributed modulation. Both regions were also found to be activated in the MEG study by Maess et al. (2016), with a stronger contribution of the IFG to the mid-sentence verb than to the sentence final noun. The parietal effect in our study had a more negative waveform for the high predictive verb, which is congruent with the N400m-effect discussed by Maess et al. (2016) also resulting from a stronger effect for highly predictive verbs. The time course of the EEG effects in the present study suggests that the pIFG plays a role in the early stages of the verb-based prediction process whereas the influence of the pSTG/STS emerges later. While both high and low cloze sentences engage semantic processing, verbs in the high cloze condition will generate stronger (or more specific) predictions about the upcoming noun. The observed TMS-induced difference in the electrophysiological response for the high and low cloze conditions at the verb shows that TMS interacted with the verb-based semantic processes, potentially by selectively modulating the conditions with stronger semantic predictions. Such a condition-specific effect is not unexpected since TMS effects strongly depend on the given context-induced activity or brain state (“state dependency”, e.g. Silvanto, Muggelton & Walsh, 2008; Silvanto & Cattaneo, 2017). Consequently, the TMS-induced differences in the electrophysiological response to high and low cloze conditions most likely reflect a modulation of the amount of semantic prediction that was induced by the respective condition. This further suggests that the electrophysiological response might be more sensitive to the TMS-induced modulation than the behavioural response, at least if an implicit task is used as in our study.

Frontal-temporal interactions during sentence processing

In this context, it is important to note that previous studies on visual and verbal memory showed that sustained activation of representations in posterior temporal cortices is under frontal top-down control (Fiebach, Rissman, & D'Esposito, 2006; Tomita, Ohbayashi, Nakahara, Hasegawa, & Miyashita, 1999; see also Sreenivasan, Curtis, & D'Esposito, 2014). In a similar way, one could speculate that in the present experiment, pIFG exerts top-down control on pSTG/STS during verb processing to constrain predictions about the upcoming noun reflected by the earlier TMS sensitivity of this area. This notion is compatible with the hypothesis that the IFG is responsible for the generation and/or maintenance of predictions while the pSTS is associated with cortical representations of predicted elements (see also Cope et al., 2017 for a discussion of the causal top-down influence of the frontal cortex to predictive processing in speech perception in the temporal cortex). In any case, it seems safe to conclude that pIFG and pSTG/STS closely interact during language comprehension, as has been shown for syntactic processing (e.g. den Ouden et al., 2012). This functional interaction is likely mediated by direct and indirect anatomical fiber connections between the two areas. A direct connection is mediated via a dorsal pathway which connects pSTG/STS with pIFG (BA44) via the superior longitudinal fasciculus / arcuate fasciculus (Friederici, 2017). An indirect fiber tract connects pIFG and pSTG/STS via the anterior insula (Catani et al., 2012; Xu et al., 2015), a brain area that was associated with cognitive control and attentional processes during language comprehension (Tang et al., 2012, Zaccarella & Friederici, 2015a&b; Mestres-Missé et al., 2012). This connection might be bi-directional in nature (Augustine, 1996). The exact role of these connections during sentence processing is still debated (Friederici, 2009; Saur et al., 2008; Skeide, Brauer & Friederici, 2016). While sentence processing is likely driven by both bottom-up and top-down interactions between temporal and frontal regions (Friederici, 2012, 2017; Bouton et al., 2018), top-down processing might occur earlier in the pIFG and might influence the pSTG/STS. This information transfer from pIFG is mediated via the dorsal fiber tracks connecting pIFG and the temporal cortex. Note, however, that the assumed interplay between both regions needs further evidence from future studies.

TMS-protocols and language processing

Although the exact duration of the impact of online TMS on cognitive processing is not known, it is usually assumed that the effect of short bursts should last for several hundred milliseconds (Pascual-Leone et al., 2000; Walsh and Cowey, 2000; Siebner et al., 2009; Fuggetta et al., 2008). In particular, high-frequency online TMS bursts typically affect cortical activity at the stimulated area for a period outlasting the stimulation for about half the duration of the stimulation train (Rotenberg et al., 2014). We applied short TMS bursts of 3 pulses at a frequency of 10 Hz, which might affect processing for a total duration of approximately 300-450 ms counted from the first pulse onwards. Please note that although the mean verb-length of 640 ms is outside of this effective TMS window, the word recognition point (Marslen-Wilson & Welsh, 1978) will typically be inside of it. At this point in time, the word has been recognized and activated. Consequently, we would argue that despite the relatively short TMS window, it is reasonable to assume that TMS impacted verb processing, as reflected in the significant effects found in the electrophysiological measures.

It should be noted that previous behavioral TMS studies used a variety of different protocols to explore different language processes. Some studies applied a single pulse before a target word (Canetto et al., 2009) or at the sentence final noun (Franzmeier, 2012), whereas others used paired pulses (Sakai et al., 2002) or longer bursts of 4 to 5 pulses (e.g. Devlin et al., 2003; Gough et al., 2005; Hartwigsen et al., 2010; 2016; Kuhnke et al., 2017). The few existing studies that combined TMS and EEG during language processing employed 5 pulse bursts at 10 Hz (Fuggetta et al., 2009; Kuipers et al., 2013). For instance, in a visual verb-verb priming study, Kuipers et al. (2013) applied 5 pulses with prime onset over the left primary motor cortex. The target verb was presented 400 ms after the last pulse and showed an enhanced N400 component for hand-related verbs. In the present experiment, we refrained from a longer stimulation period to reduce the impact of the TMS pulses on the EEG signal quality and we aimed at restricting our TMS perturbation to the verb on psycholinguistic grounds. Our results suggest that future studies might use longer stimulation periods or apply TMS during the sentence final word if the main interest lies in the investigation of word integration processes.

Conclusion

The present study highlights the importance of left posterior inferior frontal gyrus and posterior superior temporal gyrus / sulcus in language comprehension. Our results suggest the following conclusions. The strong modulatory effect of TMS over pIFG in frontal regions occurred earlier in time and was relatively short-lasting. This effect was followed by a modulation of posterior regions approximately 200 ms later, indicating that the contribution of both regions to the build-up of semantic predictions changes over time. Notably, these effects were short-lived and selectively influenced the processing of the verb. This suggests a high degree of compensatory flexibility during language comprehension.

Data policy

Anonymized data (in accordance with the Ethics agreement) and analysis scripts are available on request.

Acknowledgements

We are indebted to Christian Obermeier who was involved in the early phase of this experiment. We thank Ina Koch, Maike Herrmann, Ole Numssen, Tilo Zotschew for help with the data acquisition, Sven Gutekunst for technical assistance as well as Kerstin Flake for her assistance with Figure preparation. This work was supported by the Max Planck Society.

References

Augustine, J. R. (1996). Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Research Reviews*, *22*(3), 229–244. http://doi.org/10.1016/S0165-0173(96)00011-2.

Bar, M. (2007). The proactive brain: using analogies and associations to generate predictions. *Trends Cogn Sci*, *11*(7), 280-289. doi: 10.1016/j.tics.2007.05.005

Barber, H & Carreiras, M. (2005). Grammatical Gender and Number Agreement in Spanish: An ERP Comparison. *Journal of Cognitive Neuroscience*, 17(1),137–153, https://doi.org/10.1162/0898929052880101

Baumgaertner, A., Weiller, C., & Buchel, C. (2002). Event-related fMRI reveals cortical sites involved in contextual sentence integration. *Neuroimage*, *16*(3), 736-745. https://doi.org/10.1006/nimg.2002.1134

Bendixen, A., Schroger, E., & Winkler, I. (2009). I heard that coming: event-related potential evidence for stimulus-driven prediction in the auditory system. *J Neurosci*, *29*(26), 8447-8451. doi: 10.1523/JNEUROSCI.1493-09.2009

Bergmann, T.O., Karabanov, A., Hartwigsen, G., Thielscher, A., & Siebner, H.R. (2016). Combining non-invasive transcranial brain stimulation with neuroimaging and electrophysiology: Current approaches and future perspectives. *NeuroImage*, *140*, 4–19. Doi:10.1016/j.neuroimage.2016.02.012

Binder, J. R., Desai, R. H., Graves, W. W., & Conant, L. L. (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cereb Cortex, 19(12), 2767-2796. doi: 10.1093/cercor/bhp055

Bouton, S., Chambon, V., Tyrand, R., Guggisberg, A. G., Seeck, M., Karkar, S., . . . Giraud, A. L. (2018). Focal versus distributed temporal cortex activity for speech sound category assignment. *Proc Natl Acad Sci U S A*, *115*(6), 1299-1308. doi: 10.1073/pnas.1714279115

Catani M., Dell'acqua F., Vergani F., Malik F., Hodge H., Roy P., Valabregue R., Thiebaut de Schotten M. (2012). Short frontal lobe connections of the human brain. *Cortex*, *48*(2), 273–291. DOI: 10.3109/02688697.2014.889810

Cattaneo, Z., Devlin, J. T., Vecchi, T., & Silvanto, J. (2009). Dissociable neural representations of grammatical gender in Broca's area investigated by the combination of satiation and TMS. *NeuroImage*, *47*(2), 700–704. Doi: 10.1016/j.neuroimage.2009.04.097

Cope, Thomas E., Sohoglu, E., Sedley, W., et al. (2017). Evidence for causal top-down frontal contributions to predictive processes in speech perception, *Nature Communications*, *8*(1), 2154. doi: 10.1038/s41467-017-01958-7

Curtis CE, D'Esposito M. (2003). Persistent activity in the prefrontal cortex during working memory. *Trends Cogn Sci*, *7*(9), 415-423. https://doi.org/10.1016/s1364-6613(03)00197-9

Davey, J., Cornelissen, P. L., Thompson, H. E., Sonkusare, S., Hallam, G., Smallwood, J., & Jefferies, E. (2015). Automatic and Controlled Semantic Retrieval: TMS Reveals Distinct Contributions of Posterior Middle Temporal Gyrus and Angular Gyrus. J Neurosci, 35(46), 15230-15239. doi: 10.1523/JNEUROSCI.4705-14.2015

den Ouden, D.-B., Saur, D., Mader, W., Schelter, B., Lukic, S., Wali, E., Timmer, J., & Thompson, C.K. (2012). Network modulation during complex syntactic processing. *NeuroImage*, *59*(1), 815–823. https://doi.org/10.1016/j.neuroimage.2011.07.057

Devlin, J. T., Matthews, P. M., & Rushworth, M. F. (2003). Semantic processing in the left inferior prefrontal cortex: A combined functional magnetic resonance imaging and transcranial magnetic stimulation study. *Journal of Cognitive Neuroscience*, *15*(1), 71–84. https://doi.org/10.1162/089892903321107837

Duyck, W., Desmet, T., Verbeke, L. P. C., & Brysbaert, M. (2004). WordGen: A tool for word selection and nonword generation in Dutch, English, German, and French. *Behavior Research Methods*, *36*(3), 488–499. https://doi.org/10.3758/bf03195595

Federmeier, K.D., Wlotko, E.W., De Ochoa-Dewald, E., & Kutas, M. (2007). Multiple effects of sentential constraint on word processing. *Brain Research*, *1146*, 75-84. Doi: 10.1016/j.brainres.2006.06.101

Fiebach CJ, Rissman J, D'Esposito M. 2006. Modulation of inferotemporal cortex activation during verbal working memory maintenance. *Neuron*. *51*(2), 251-261. https://doi.org/10.1016/j.neuron.2006.06.007

Franzmeier, I., Hutton, S. B., & Ferstl, E. C. (2012). The role of the temporal lobe in contextual sentence integration: A single pulse TMS study. *Cognitive Neuroscience*, *3*(1), 1–7. http://doi.org/10.1080/17588928.2011.556248

Fuggetta, G., Rizzo, S., Pobric, G., Lavidor, M., & Walsh, V. (2009). Functional representation of living and nonliving domains across the cerebral hemispheres: A combined event-related potential/transcranial magnetic stimulation study. *Journal of Cognitive Neuroscience*, *21*(2), 403–414. https://doi.org/10.1162/jocn.2008.21030

Friederici, A.D. (2009). Pathways to language: Fiber tracts in the human brain. *Trends in Cognitive Sciences*, *13*(4), 175-181. https://doi.org/10.1016/j.tics.2009.01.001

Friederici, A. D. (2011). The brain basis of language processing: from structure to function. *Physiol Rev, 91*, 1357-1392. https://doi.org/10.1152/physrev.00006.2011

Friederici, A. D. (2012). The cortical language circuit: from auditory perception to sentence comprehension. *Trends Cogn Sci*, *16*(5), 262-268. doi: 10.1016/j.tics.2012.04.001

Friederici, A.D. (2017). Language in our brain. Cambridge, MA: The MIT Press.

Goucha, T., & Friederici, A. D. (2015). The language skeleton after dissecting meaning: A functional segregation within Broca's Area. *Neuroimage, 114*, 294-302. doi: 10.1016/j.neuroimage.2015.04.011

Gough, P. M., Nobre, A. C., & Devlin, J. T. (2005). Dissociating linguistic processes in the left inferior frontal cortex with transcranial magnetic stimulation. *Journal of Neuroscience*, *25*(35), 8010–8016. https://doi.org/10.1523/jneurosci.2307-05.2005

Griffiths, T. L., & Tenenbaum, J. B. (2011). Predicting the future as Bayesian inference: people combine prior knowledge with observations when estimating duration and extent. *J Exp Psychol Gen*, *140*(4), 725-743. doi: 10.1037/a0024899

Greenhouse, S. W., & Geisser, S. (1959). On methods in the analysis of profile data. *Psychometrika*, *24*, 95–112.

Grisoni, L., Miller, T.M., & Pulvermuller, F. (2017). Neural Correlates of Semantic Prediction and Resolution in Sentence Processing. *Journal of Neuroscience*, *37*(18), 4848-4858. doi: 10.1523/JNEUROSCI.2800-16.2017

Gunter, T. C., Friederici, A. D., & Schriefers, H. (2000). Syntactic gender and semantic expectancy: ERPs reveal early autonomy and late interaction. *J Cogn Neurosci*, *12*(4), 556-568.

Hagoort, P. (2005). On Broca, brain, and binding: a new framework. Trends Cogn Sci, 9(9), 416-423. http://dx.doi.org/10.1016/j.tics.2005.07.004.

Halgren, E., Dhond, R. P., Christensen, N., Van Petten, C., Marinkovic, K.,Lewine, J. D., et al. (2002). N400-like magnetoencephalography responses modulated by semantic context, word frequency and lexical class in sentences. *Neuroimage, 17*, 1101–1116. doi: 10.1006/nimg.2002.1268

Hammer, A., Goebel, R., Schwarzbach, J., Munte, T. F., & Jansma, B. M. (2007). When sex meets syntactic gender on a neural basis during pronoun processing. *Brain Res*, *1146*, 185-198. doi: 10.1016/j.brainres.2006.06.110

Hartwigsen, G. (2018). Flexible Redistribution in Cognitive Networks. *Trends Cogn Sci, 22*(8), 687-698. doi: 10.1016/j.tics.2018.05.008

Hartwigsen, G. (2015). The neurophysiology of language: Insights from non-invasive brain stimulation in the healthy human brain. *Brain Lang*, *148*, 81-94. doi: 10.1016/j.bandl.2014.10.007

Hartwigsen, G., Henseler, I., Stockert, A., Wawrzyniak, M., Wendt, C., Klingbeil, J., . . . Saur, D. (2017). Integration demands modulate effective connectivity in a fronto-temporal network for contextual sentence integration. *Neuroimage*, *147*, 812-824. doi: 10.1016/j.neuroimage.2016.08.026

Hartwigsen, G., Price, C. J., Baumgaertner, A., Geiss, G., Koehnke, M., Ulmer, S., & Siebner, H. R. (2010). The right posterior inferior frontal gyrus contributes to phonological word decisions in the healthy brain: Evidence from dual-site TMS. *Neuropsychologia*, *48*(10), 3155-3163. doi:0.1016/j.neuropsychologia.2010.06.032

Hartwigsen, G., Weigel, A., Schuschan, P., Siebner, H. R., Weise, D., Classen, J., & Saur, D. (2016). Dissociating Parieto-Frontal Networks for Phonological and Semantic Word Decisions: A Condition-and-Perturb TMS Study. *Cerebral Cortex*, *26*, 2590–2601. http://doi.org/10.1093/cercor/bhv092

Heim, S., van Ermingen, M., Huber, W., & Amunts, K. (2010). Left cytoarchitectonic BA 44 processes syntactic gender violations in determiner phrases. *Hum Brain Mapp*, *31*(10), 1532-1541. doi: 10.1002/hbm.20957

Herring, J. D., Thut, G., Jensen, O., & Bergmann, T. O. (2015). Attention Modulates TMS-Locked Alpha Oscillations in the Visual Cortex. *The Journal of Neuroscience*, *35*(43), 14435-14447. https://doi.org/10.1523/jneurosci.1833-15.2015

Holm, S. (1979). A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics*, 65-70.

Jung, J., & Lambon Ralph, M. A. (2016). Mapping the Dynamic Network Interactions Underpinning Cognition: A cTBS-fMRI Study of the Flexible Adaptive Neural System for Semantics. Cereb Cortex, 26(8), 3580-3590. doi: 10.1093/cercor/bhw149

Kroczek, L. O. H., & Gunter, T. C. (2017). Communicative predictions can overrule linguistic priors. *Scientific Reports*, *7*(1), 17581. Doi: 10.1038/s41598-017-17907-9

Kuhnke, P., Meyer, L., Friederici, A.D., & Hartwigsen, G. (2017). Left posterior inferior frontal gyrus is causally involved in reordering during sentence processing. *NeuroImage*, *148*, 254-263. Doi: 10.1016/j.neuroimage.2017.01.013

Kuipers, J.R., van Koningsbruggen, M., & Thierry, G. (2013). Semantic priming in the motor cortex: evidence from combined repetitive transcranial magnetic stimulation and event-related potential. *Neuroreport*, *24*(12), 646–51. Doi: 10.1097/WNR.0b013e3283631467

Kuperberg, G. R. & Jaeger, T. F. (2015). What do we mean by prediction in language comprehension? *Lang. Cogn. Neurosci. 3798*, 1–70. https://doi.org/10.1080/23273798.2015.1102299

Kutas, M, & Federmeier, K.D. (2011). Thirty Years and Counting: Finding Meaning in the N400 Component of the Event-Related Brain Potential (ERP). *Annu. Rev. Psychol*, *62*, 621-647, doi: 10.1146/annurev.psych.093008.131123

Lau, E. F., Phillips, C., & Poeppel, D. (2008). A cortical network for semantics: (de)constructing the N400. *Nat Rev Neurosci*, *9*(12), 920-933. doi: 10.1038/nrn2532

Maess, B., Mamashli, F., Obleser, J., Helle, L., & Friederici, A. D. (2016). Prediction Signatures in the Brain: Semantic Pre-Activation during Language Comprehension. *Front Hum Neurosci*, *10*, 591. doi: 10.3389/fnhum.2016.00591

Marslen-Wilson, W.D. & Welsh, A. (1978). Processing Interactions and Lexical Access During Word Recognition in Continuous Speech. *Cognitive Psychology*, *10*(1), 29-63. https://doi.org/10.1016/0010-0285(78)90018-x

Mestres-Missé, A., Turner, R., and Friederici, A. D. (2012). An anterior-posterior gradient of cognitive control within the dorsomedial striatum. *Neuroimage*, *62*(1), 41–7. https://doi.org/10.1016/j.neuroimage.2012.05.021

Molinaro, N., Barber, H. A., & Carreiras, M. (2011). Grammatical agreement processing in reading: ERP findings and future directions. *Cortex*, 47(8), 908–930. https://doi.org/10.1016/j.cortex.2011.02.019

Molinaro, N., Barber, H. A., Caffarra, S., & Carreiras, M. (2015). On the left anterior negativity (LAN): The case of Morphosyntactic agreement: A Reply to Tanner et al. *Cortex*, 66,156-159. http://dx.doi.org/10.1016/j.cortex.2014.06.009

Obleser, J., & Kotz, S. A. (2010). Expectancy constraints in degraded speech modulate the language comprehension network. *Cerebral Cortex*, *20*(3), 633-640. doi: 10.1093/cercor/bhp128

Obleser, J., Wise, R. J., Alex Dresner, M., & Scott, S. K. (2007). Functional integration across brain regions improves speech perception under adverse listening conditions. *Journal of Neuroscience* *27*(9), 2283-2289. doi: 10.1523/JNEUROSCI.4663-06.2007

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, *9*(1), 97-113. https://doi.org/10.1016/0028-3932(71)90067-4

Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J.M. (2011). “FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data,” *Computational Intelligence and Neuroscience*, *2011*, 1. doi:10.1155/2011/156869

Pascual-Leone, A., Walsh, V., & Rothwell, J. (2000). Transcranial magnetic stimulation in cognitive neuroscience – virtual lesion, chronometry, and functional connectivity. *Current Opinion in Neurobiology*, *10*(2), 232–237. https://doi.org/10.1016/s0959-4388(00)00081-7

Price, C. J. (2010). The anatomy of language: a review of 100 fMRI studies published in 2009. *Ann NY Acad Sci 1191*, 62–88. http://dx.doi.org/10.1111/j.1749-6632.2010.05444.x.

Rao, R. P., & Ballard, D. H. (1999). Predictive coding in the visual cortex: a functional interpretation of some extra-classical receptive-field effects. *Nat Neurosci*, *2*(1), 79-87. doi: 10.1038/4580

Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*, *120*(12), 2008–2039. https://doi.org/10.1016/j.clinph.2009.08.016

Rotenberg, A., Horvath, J. C., & Pascual-Leone, A. (Eds.) (2014). *Neuromethods: Transcranial Magnetic Stimulation*. New York: Springer. https://doi.org/10.1007/978-1-4939-0879-0

Ruzzoli, M., Marzi, C. A., & Miniussi, C. (2010). The neural mechanisms of the effects of transcranial magnetic stimulation on perception. *Journal of Neurophysiology,103(6),* 2982–2989. https://doi.org/10.1152/jn.01096.2009

Sakai, K. L., Noguchi, Y., Takeuchi, T., & Watanabe, E. (2002). Selective Priming of Syntactic Processing by Event-Related Transcranial Magnetic Stimulation of Broca ' s Area, *Neuron*, *35*, 1177–1182. https://doi.org/10.1016/s0896-6273(02)00873-5

Saur, D., Kreher, B.W., Schnell, S., Kümmerer, D., Kellmeyer, P., Vry, M.-S., Umarova, R., Musso, M., Glauche, V., Abel, S., Huber, W., Rijntjes, M., Hennig, J., & Weiller, C. (2008). Ventral and dorsal pathways for language. *Proceedings of the National Academy of Sciences*, *105*(46), 18035–18040. https://doi.org/10.1073/pnas.0805234105

Schwarzkopf, D. S., Silvanto, J., & Rees, G. (2011). Stochastic resonance effects reveal the neural mechanisms of transcranial magnetic stimulation. *J Neurosci, 31*(9), 3143-3147. doi: 10.1523/JNEUROSCI.4863-10.2011

Sekiguchi, H., Takeuchi, S., Kadota, H., Kohno, Y., Nakajima, Y. (2011). TMS-induced artifacts on EEG can be reduced by rearrangement of the electrode's lead wire before recording. *Clinical Neurophysiology*, *122*(5), 984-990. https://doi.org/10.1016/j.clinph.2010.09.004.

Siebner, H. R., Hartwigsen, G., Kassuba, T., & Rothwell, J. C. (2009). How does transcranial magnetic stimulation modify neuronal activity in the brain? Implications for studies of cognition. *Cortex*, *45*(9), 1035-1042. https://doi.org/10.1016/j.cortex.2009.02.007

Siebner, H. R., & Rothwell, J. (2003). Transcranial magnetic stimulation: new insights into representational cortical plasticity. *Exp Brain Res*, *148*(1), 1-16. doi: 10.1007/s00221-002-1234-2

Silvanto, J., & Cattaneo, Z. (2017). Common framework for "virtual lesion" and state-dependent TMS: The facilitatory/suppressive range model of online TMS effects on behavior. *Brain Cogn, 119*, 32-38. doi: 10.1016/j.bandc.2017.09.007

Silvanto, J., Muggleton, N., & Walsh, V. (2008). State-dependency in brain stimulation studies of perception and cognition. *Trends Cogn Sci, 12*(12), 447-454. doi: 10.1016/j.tics.2008.09.004

Skeide, M., Brauer, J., & Friederici, A.D. (2016). Brain functional and structural predictors of language performance. *Cerebral Cortex*, *26*(5), 2127–2139. https://doi.org/10.1093/cercor/bhv042

Sreenivasan, K.K, Curtis, C.E.,D'Esposito, M. (2014). Revisiting the role of persistent neural activity during working memory. *Trends Cogn Sci*., *18*(2), 82–89. doi: 10.1016/j.tics.2013.12.001

Stokes, M. G., Chambers, C. D., Gould, I. C., Henderson, T. R., Janko, N. E., Allen, N. B., & Mattingley, J. B. (2005). Simple metric for scaling motor threshold based on scalp-cortex distance: application to studies using transcranial magnetic stimulation. *J Neurophysiol*, *94*(6), 4520-4527. https://doi.org/10.1152/jn.00067.2005

Tang, Y. Y., Rothbart, M. K., and Posner, M. I. (2012). Neural correlates of establishing, maintaining, and switching brain states. *Trends Cogn Sci*, *16*(6), 330–7. https://doi.org/10.1016/j.tics.2012.05.001

Tanner, D. (2018, May 13). Robust neurocognitive individual differences in grammatical agreement processing: A latent variable approach. https://doi.org/10.31234/osf.io/njgt6

Tanner, D., & van Hell, J. G. (2014). ERPs reveal individual differences in morphosyntactic processing. *Neuropsychologia,* 56, 289-301. https://doi.org/10.1016/j.neuropsychologia.2014.02.002

Tanner, D. , Morgan-Short, K. and Luck, S. J. (2015). How inappropriate high-pass filters can produce artifactual effects and incorrect conclusions in ERP studies of language and cognition. *Psychophysiol*, *52*, 997-1009. doi:10.1111/psyp.12437

Taylor, W. L. (1953). "Cloze" procedure: A new tool for measuring readability. *Journalism Quarterly*, *30*, 415-417. https://doi.org/10.1177/107769905303000401

Tomita H, Ohbayashi M, Nakahara K, Hasegawa I, Miyashita Y. (1999). Top-down signal from prefrontal cortex in executive control of memory retrieval. *Nature*, *401*, 699-703. https://doi.org/10.1038/44372

Van Petten, C., & Luka, B. J. (2012). Prediction during language comprehension: Benefits, costs, and ERP components. *International Journal of Psychophysiology*, *83*(2), 176-190. https://doi.org/10.1016/j.ijpsycho.2011.09.015

Walsh, V., & Cowey, A. (2000). Transcranial magnetic stimulation and cognitive neuroscience. *Nature Reviews Neuroscience*. *1*(1), 73–79. https://doi.org/10.1038/35036239

Winkler, I., Debener, S., Müller, K.-R., & Tangermann, M. (2015). *On the influence of high-pass filtering on ICA-based artifact reduction in EEG-ERP*. Paper presented at the 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society. https://doi.org/10.1109/EMBC.2015.7319296

Xu, J., Wang, J, Fan, L., Zhang, W., Qingmoa, H., & Jiang, T. (2015). Tractography-based Parcellation of the Human Middle Temporal Gyrus. *Scientific Reports, 5*, 18883, doi:10.1038/srep18883.

Zaccarella, E., & Friederici, A.D. (2015a). Merge in the Human Brain: A Sub-Region Based Functional Investigation in the Left Pars Opercularis. *Frontiers in Psychology*, *6*, 01818, DOI: 10.3389/fpsyg.2015.01818

Zaccarella, E., & Friederici, A. D. (2015b). Language Reflections of word processing in the insular cortex: A sub-regional parcellation based functional assessment. *Brain and Language*, *142*, 1–7. http://doi.org/10.1016/j.bandl.2014.12.006

Supplementary Material:

Contributions of left frontal and temporal cortex to sentence comprehension: Evidence from simultaneous TMS-EEG

Statistics for the Pilot experiment

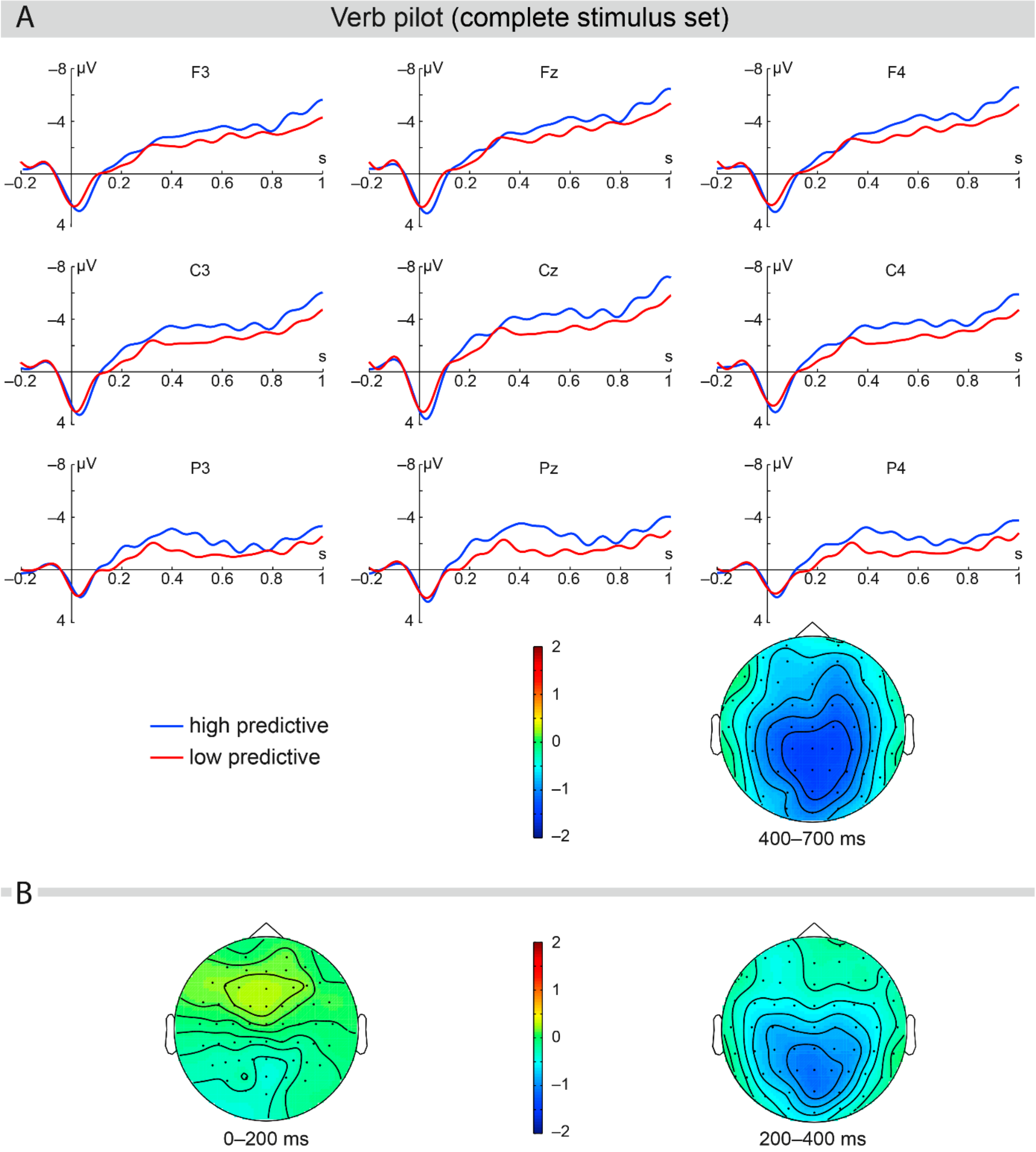
Noun

In the early window of 300 – 500 ms there was broadly distributed main effect for semantic expectancy, with low cloze sentences showing an increased negativity compared to high cloze sentences [$F(1,23) = 31.67$, $p < .001$, $\eta_p^2 = 0.579$]. Furthermore, a main effect of syntactic gender with an increased negativity for incorrect vs. correct sentences was observed [$F(1,23) = 20.94$, $p < .001$, $\eta_p^2 = 0.477$]. This effect had a left-posterior topographical distribution [syntactic gender x laterality: $F(1,23) = 6.49$, $p = .018$, $\eta_p^2 = 0.220$, syntactic gender x anteriority: $F(1,23) = 8.27$, $p = .008$, $\eta_p^2 = 0.265$]. In the late time-window of 600 – 900 ms there was a main effect of syntactic gender [$F(1,23) = 4.628$, $p = .042$, $\eta_p^2 = 0.168$] and an interaction of syntax x anteriority [$F(1,23) = 6.284$, $p = .020$, $\eta_p^2 = 0.215$]. A step-down analysis revealed that syntactic gender violations elicited a more positive ERP than correct sentences in posterior ROIs [$F(1,23) = 6.875$, $p = .015$, $\eta_p^2 = 0.230$] but not in anterior ROIs [$F(1,23) = 1.221$, $p = .280$]. There was also a main effect of semantic expectancy [$F(1,23) = 5.147$, $p = .033$, $\eta_p^2 = 0.183$] and an interaction of semantics x anteriority [$F(1,23) = 15.998$, $p < .001$, $\eta_p^2 = 0.410$]. A step-down analysis revealed an increased negativity for low cloze sentences compared to high cloze sentences in anterior ROIs [$F(1,23) = 13.980$, $p = .001$, $\eta_p^2 = 0.378$] but not posterior ROIs [$F(1,23) = 0.515$, $p = .48$]. Finally, in the late time-window there was also a trend towards an interaction between semantic expectancy and syntactic gender [F(1,23) = 4.248, p = .051, η_p^2 = 0.156]. Further analyses demonstrated, that P600 effect for syntactic gender violation was only observed in high cloze sentences [F(1,23) = 11.519, p = .002, η_p^2 = 0.334], but not in low cloze sentences [F(1,23) = 0.158, p = .694].

In summary, despite the changes of the experimental design the pilot study showed an almost exact replication of the findings reported in Gunter et al., (2000). Differences to the original study were only observed in the topographical distribution of the early effect of syntactic gender as well as in a long-lasting negativity in response to low cloze sentences.

Verb

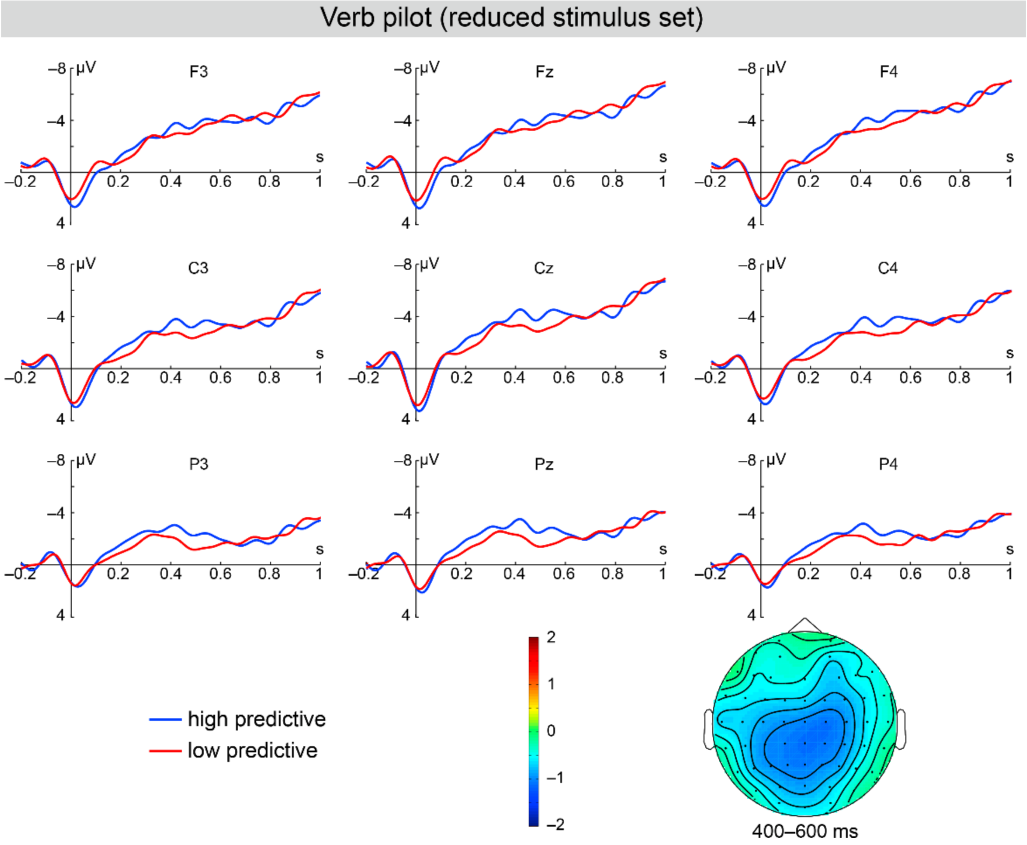
ERPs elicited by the verb were analyzed in 100 ms steps. There was a significant main effect of verb predictability between 400 - 700 ms [F(1,23) = 7.650, p = .011, η_p^2 = 0.250] with a posterior distribution (see Figure SI 1 A & B).



SI Figure 1A & B. Results from the pilot study. Figure A shows ERP effects on the verb for the pilot experiment. Figure B shows the topographical distribution of the predictability effect for time windows that were found to be modulated in the TMS experiment.

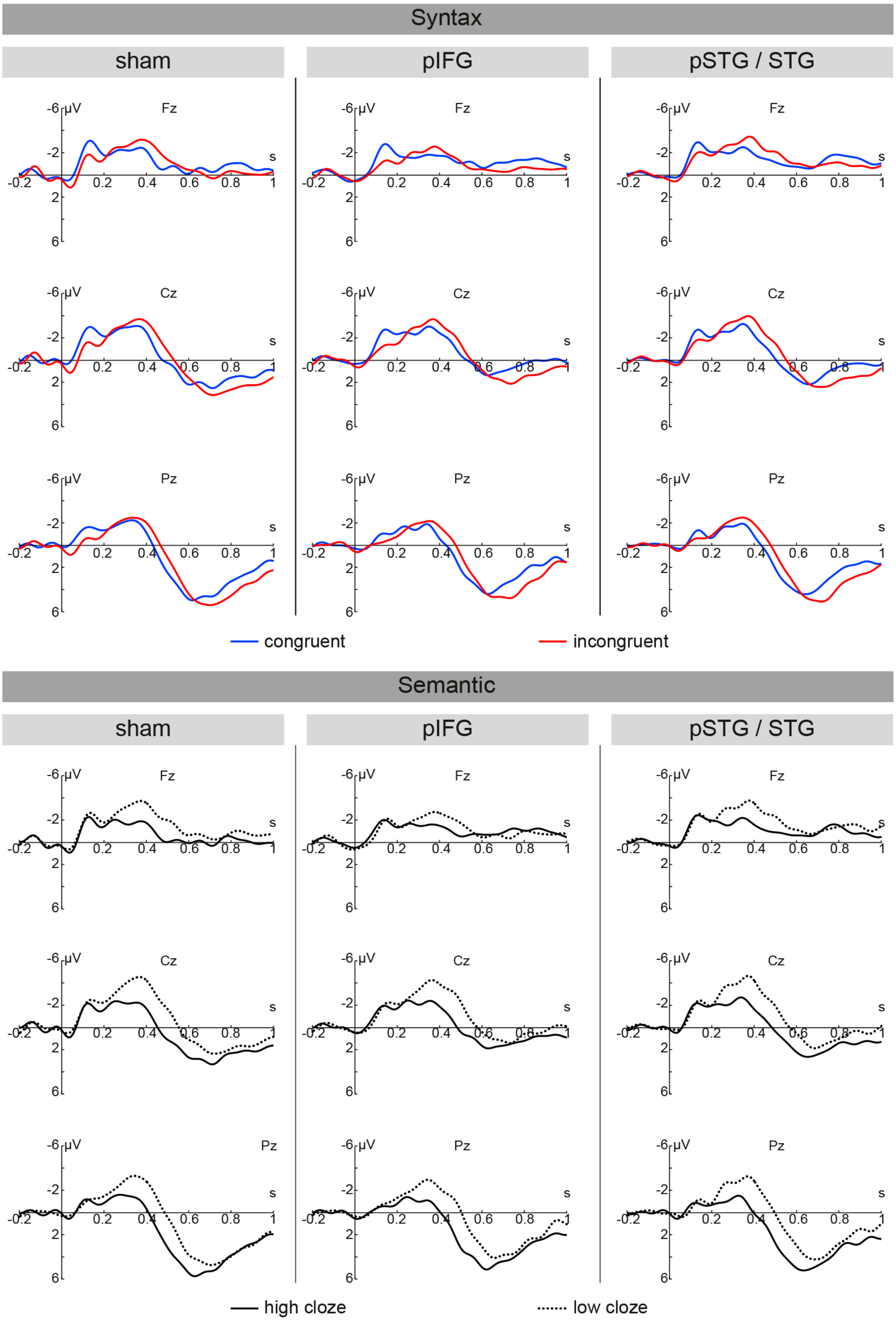
Controlling lexical frequency of the verbs:

An additional analysis was performed on a subset of items in order to test whether the effect was still present when lexical frequency of the verbs was controlled. Within the original stimulus set, there were 19 high and 19 low predictive items that exactly matched for their lexical frequency. To achieve a similar signal-to-noise ratio between the subset analysis with 19 items and the original analysis with 40 items per condition, we added the pseudoword trials of these 19 items into the subset analysis. Please note that pseudoword items did only differ from the experimental items at the noun position but were identical at the verb position. The statistical analysis of this matched subset of trials revealed a main effect of verb predictability between 400 – 600 ms [$F(1,23) = 9.232$, $p = .006$, $\eta_p^2 = 0.286$] with high predictive verbs eliciting a stronger negativity relative to low predictive verbs (see Figure SI 2). This subset analysis demonstrates that the effect of verb predictability as found in the original analysis was not driven by lexical frequency of the verbs.



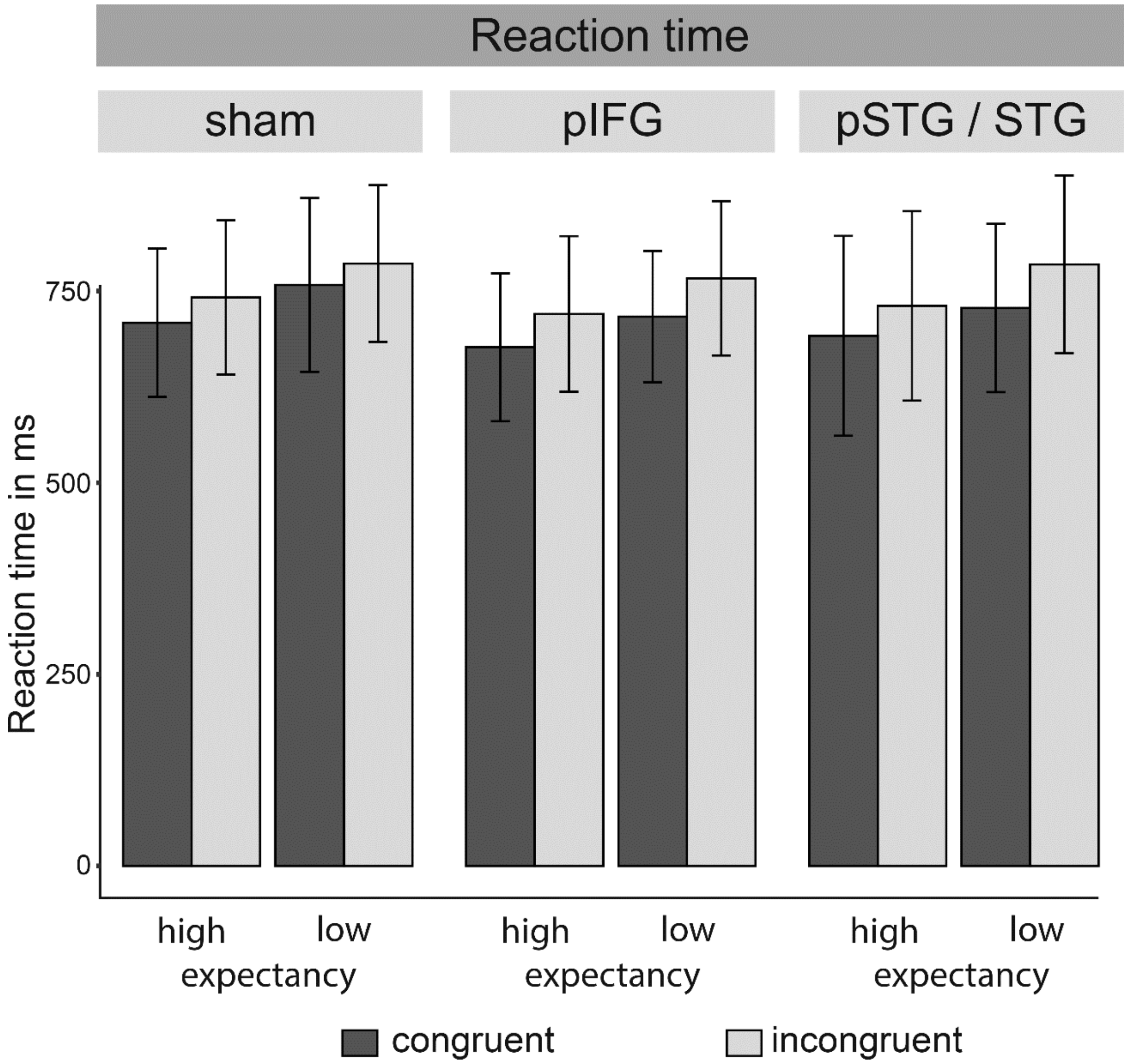
SI Figure 2. Results from the pilot study. ERP effects on the verb for the pilot experiment for the reduced stimulus set of 19 frequency matched item pairs and the topographical distribution of the significant predictability effect

ERP Effects of TMS on the noun



SI Figure 3. Effects of TMS on the noun. Results on the noun position for the syntactic and semantic conditions displayed for all three TMS conditions.

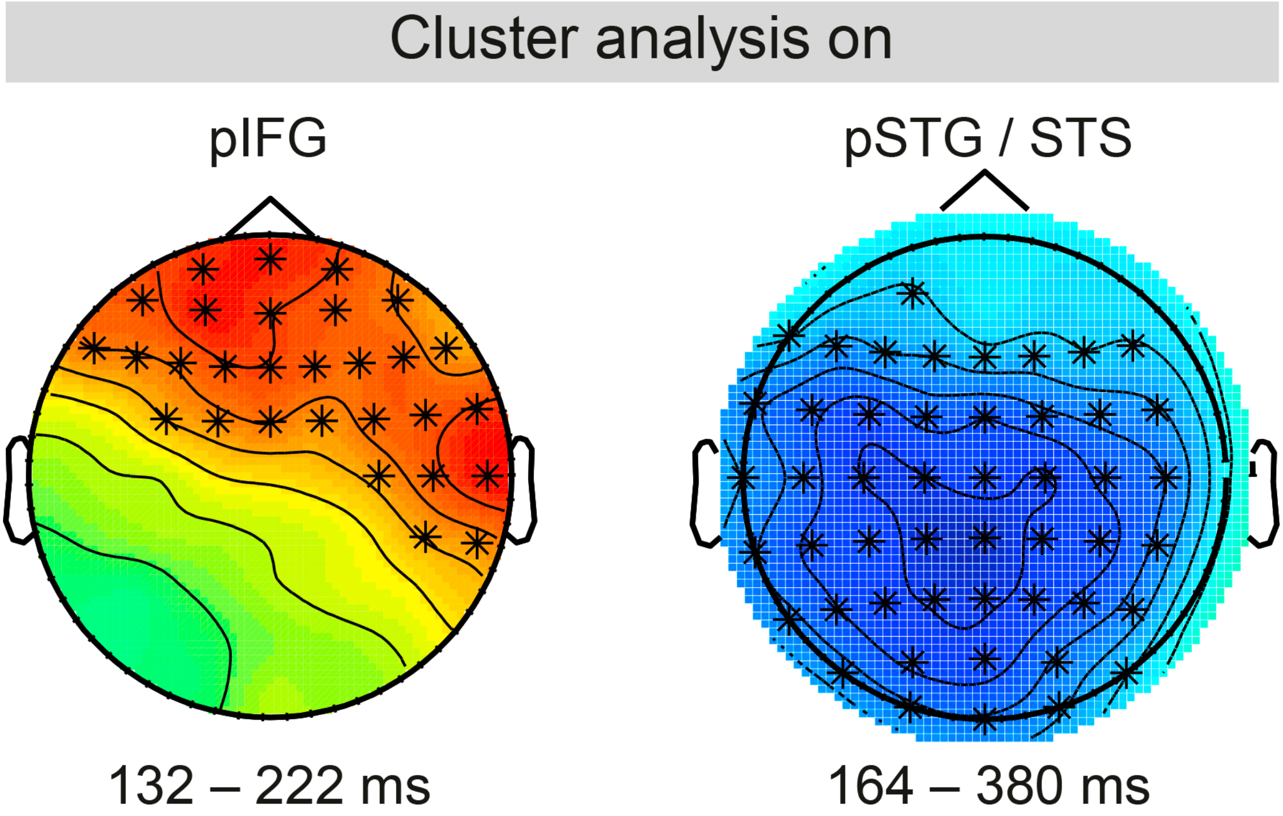
Behavioral Effects of TMS on the noun



SI Figure 4. Effects of TMS on the noun. Behavioral data for all three TMS conditions as found in the lexical decision task. Error bars reflect the SEM.

Interaction of TMS and verb predictability: Cluster-based permutation tests

In order to evaluate the effects of TMS on verb prediction without an a-priori selection of electrode ROIs, a non-parametric cluster-based permutation test was conducted on the ERP data at the verb position. All channels and time-points were entered into the analysis. Correction for multiple comparisons was performed by establishing a reference distribution using Monte Carlo simulations (Maris & Oostenveld, 2007). In order to test for the interaction of *TMS* and *verb prediction*, we first calculated the difference between high and low predictive verbs for each TMS condition and participant. Next, these data were entered into a cluster-based permutation test using a univariate F-test for dependent samples (“depsamplesFunivariate”) with *TMS* as independent variable. Multiple comparison correction was performed using the Monte Carlo method (“clusterstatistic = maxsum, minnbchan = 2, correct = cluster”, 1000 randomizations). This analysis revealed significant differences between TMS conditions in a time window of 132 – 380 ms in all scalp electrodes. In the next step, cluster-based permutation tests were performed on the TMS conditions separately using the time-window of 132 – 380 ms, by comparing conditions of high and low predictive verbs (two-sided paired t-test; ”depsamplesT”). Again, Monte-Carlo simulations (1000 randomizations) were used for statistical evaluation of the clusters (“clusterstatistic = maxsum, minnbchan = 2, correct = cluster”). There was no significant effect in the sham condition. For IFG stimulation, the analysis revealed a significant positive cluster between 132 and 222 ms in frontal electrodes. Furthermore, stimulation of pSTG/STS revealed a significant negative cluster in centro-parietal electrodes between 164 – 380 ms. In summary, the results reveal an early frontal effect of TMS in the IFG and a later centro-parietal effect for stimulation of the pSTG/STS (see SI Figure 5). These findings based on non-parametric cluster-tests confirm our findings from the initial analysis where electrode ROIs were selected based on previous findings in the literature and our pilot study.



SI Figure 5: Results of the independent cluster-based permutation test depicting the interaction between TMS and verb predictability, separately for each effective TMS condition.

References

Maris, E., and Oostenveld,R.(2007). Nonparametric statistical testing of EEG- and MEG-data. *J. Neurosci.Methods* 164, 177–190.doi:10.1016/j.jneumeth.2007. 03.024