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Abstract

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Neuro-navigated transcranial magnetic stimulation (TMS) helps to identify language-related cortical regions prior to brain tumour surgery. We adapted a semantic picture-word interference (PWI) paradigm from psycholinguistics to high-resolution TMS language mapping which prospectively can be used to specifically address the level of semantic processing. In PWI, pictures are presented along with distractor words which facilitate or inhibit the lexical access to the picture name. These modulatory effects of distractors can be annihilated in language-sensitive areas by the inhibitory effects of TMS on language processing. The rationale here is to observe the distractor effect without active stimulation and then to observe presumably its elimination by interference of the TMS stimulation. The special requirements to use PWI in this setting are (1) identifying word material for accelerating reliably naming latencies, (2) choosing the ideal presentation modality, and (3) the appropriate timing of distractor presentation. These are then controlled in real TMS language mapping. To adapt a semantic PWI naming paradigm for TMS application we employed 30 object-pictures in spoken German language. Part-whole associative semantic related or unrelated distractors were presented in two experiments including 15 healthy volunteers each, once auditorily and once visually. Data analysis across the entire stimulus set revealed a trend for facilitation in the visual condition, whereas no effects were observed for auditory distractors. In a sub-set, we found a significant facilitation effect for visual semantic distractors. Thus, with this study we provide a well-controlled item set for future studies implementing effective TMS language mapping applying visual semantic PWI.

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Keywords

60 language mapping, semantic picture-word interference, distractor modality

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Highlights

Adaptation of reaction-time based picture-word interference paradigm for future use
 in language mapping with transcranial magnetic stimulation

- Trend for facilitation in visual mode of presentation in a semantic picture word interference paradigm compared to the auditory mode of presentation
- Linguistically well-controlled item set for effective TMS language mapping applying
 visual semantic picture word interference

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- 77 public, commercial, or not-for-profit sectors.
- 78 Abbreviations
- 79 Transcranial Magnetic Stimulation TMS
- 80 Picture-Word Interference PWI
- 81 Inferior frontal gyrus IFG
- 82 Stimulus onset asynchrony SOA

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84 Author contributions

- 85 MJ contributed in Conzeptualization, Data curation, Formal analysis, Roles: Writing -
- 86 original draft
- 87 SH contributed in Conzeptualization, Investigation, Methodology, Resources, Validation,
- 88 Roles: Writing Review & editing
- 89 GN contributed in Conzeptualization, Resources, Validation, Roles: Writing Review &
- 90 editing
- 91 MG Data curation, Formal analysis
- 92 KS contributed in Project administration, Software, Supervision, Validation, Visualization,
- 93 Roles: Writing Review & Editing

1. Introduction

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"Language mapping" is the identification of brain areas relevant for speaking and language comprehension. In neurosurgical brain-tumour resection, intraoperative language mapping by means of direct cortical stimulation interfering language processing is used to identify language-related cortex and to monitor language function during operation in order to avoid post-operative language deficits [1]. This method is also used with epilepsy patients [2, 3, 4] for language mapping and evaluation of treatment approaches. While direct cortical stimulation during awake craniotomy has been the gold standard for decades, neuronavigated transcranial magnetic stimulation (TMS) has become a widely-used non-invasive method that can provide comparable accuracy [5, 6, 7, 8]. TMS enables to induce speech disturbances due to a focal temporary inhibition of language processing when applied on language-related cortex [9]. In both language mapping applications, the patient is employed in an expressive language task, i.e. to produce overt speech. While in brain tumour surgery, either production of highly automated sequences (e.g. counting from 1 to 10) or object naming are used [10, see also 11], simple object naming is commonly applied in TMS language mapping. In direct cortical stimulation during awake craniotomy, object naming was in fact shown to be more sensitive to language inhibition than number counting [12]. The inhibitory effect of TMS on language processing similarly impairs naming performance in language sensitive areas and is expressed in naming errors that are categorized qualitatively, frequently following a classification scheme suggested by Corina et al. (2010) for intraoperative electrical mapping in neurosurgical procedures [13]. Typical error categories are no-response, delay, speech disruption, or performance errors [e.g. 14, 15, 16; cf. 17, for comprehensive language error categorization and semi-quantitative evaluation of error severity and frequency].

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The original object naming paradigm requiring simple object naming is well-established for language mapping application in both research and clinical setup [18]. Using synchronized audio-video recording, naming errors evoked by stimulation of different brain areas can be analyzed and data can provide information on related functional processing [18]. However,

object naming seems to evoke fewer naming errors and thus seems less efficient than action naming, but action naming might be more favourable for investigation of specific areas [9]. Object and action picture naming in healthy participants showed also a good convergence of overall activation patterns in both functional magnetic resonance imaging and magnetoencephalography, although systematic inter-individual discrepancies have been reported [19]. Regarding semantic processing more closely, Graessner, Zaccarella, and Hartwigsen (2021) used a two-word paradigm in functional magnetic resonance imaging investigating distinct processes during basic semantic composition in healthy participants. As a result, it was shown that neural recruitment is task-dependent, e.g. regarding phrasal plausibility [20]. Evoked errors in naming, however, reflect the whole process of word retrieval and thus errors can often be hardly assigned clearly to an error category.

Recently, TMS language mapping has thus been applied beyond the clinical motivation of whether a cortical region is "language-sensitive". By implementation of a cognitive paradigm into TMS language mapping, it enables to indicate which particular aspect of language is being processed in the defined stimulation area (e.g. content [semantics], sound [phonology], word order [syntax], or articulation; see 21, for addressing the level of phonological processing in Broca's region]. This more fine-grained application of TMS language mapping supports neuroimage-based evidence that language areas such as Broca's region in the inferior frontal gyrus (IFG) can be parcelled into functionally distinct sub-regions [for reviews see e.g. 22, 23, 24, 25; for a meta-analysis see e.g. 26]. As such, the anterior portion of Broca's region (area 45) is known to be involved in lexical-semantic processing, while the posterior portion of Broca's regions is supporting phonological processing [e.g. 27, 28].

For a detailed language mapping of Broca's region a high spatial resolution approach that goes beyond previous approaches stimulating the vicinity of the geometrical centre of Broca's region was proposed [e.g. 29] or of areas 44 and 45 [e.g. 30, 31]. By using a high

density of target sites systematically covering the entire pars opercularis and pars triangularis of the left inferior frontal gyrus as well as the anterior part of the inferior precentral gyrus a clear focus of TMS susceptibility in object naming at dorso-posterior target sites was identified [17]. Though a semi-quantitative evaluation of error severity and frequency was introduced, this (and also otherwise used) data analysis approach comprised the qualitative rating of the speech output, and that is without a doubt experience-dependent [see consensus by 32].

Thus, a more objective tool for the assessment of qualitative aspects of language processing is provided by the introduction of reaction time measurement in TMS language mapping. The picture-word interference (PWI) paradigm is an established paradigm in cognitive neuropsychology to investigate phonological and semantic facilitation/priming and inhibition and their time course [33, 34]. In the PWI task, the participant is required to name the presented target picture while a visual or auditory distractor word is presented. In doing so, the participant is instructed to ignore the distractor word and name the target as accurately and as quickly as possible. Depending on the nature of the relationship of the distractor and the target (e.g. semantic, phonological, or unrelated), naming latencies are showing to be affected due to an interference of processing in the mental lexicon [33, 35]. There are some well-established patterns frequently reported in the literature. (1) Phonological relations are reported to lead to shorter naming latencies as compared to unrelated distractors (phonological facilitation/priming) while (2) semantic relations mostly lead to semantic interference with longer naming latencies [e.g. 34, 36, 33].

Beyond this rather coarse distinction between *semantic* and *phonological* relations, more sophisticated types of relations have been investigated in the recent past. With regard to semantics, *categorical* relations (e.g. DOG – CAT) was shown to lead to interference, whereas *associative* relations (e.g. DOG – LEASH) were observed to facilitate naming [e.g. 37, 38]. This *semantic* facilitation/priming of associate relations was mostly found to occur on the single-word level but was also observed for multi-word utterances [39, 40]. Moreover,

Semantic picture-word interference in language mapping associative relations can be further sub-categorised into functional (CAR – GARAGE) vs. part-whole (CAR – MOTOR) relations, both showing facilitation effects [41, 38], but which

were stronger for part-whole than for functional relations (see Figure 1).

<Please insert Figure 1 here: Hierarchical structure of semantic relations>

- There are additional factors that modulate the influence of a distractor word on the picture naming latency: (1) presentation *modality* (visual/auditory), (2) *timing* of the presentation SOA, and (3) *lexical frequency of occurrence* of the distractor.
 - 1. Distractor modality can turn the behavioural effect (facilitation or inhibition) into its opposite [42]. Auditorily presented distractors are known to support phonological facilitation [43]. In contrast, visually presented distractors with part-whole semantic relation have been revealed semantic facilitation effects [38, 40].
 - 2. The importance of the SOA is based on the fact that not all types of linguistic information are active at all times during speaking. According to the Levelt model [e.g. 44], language production is a serial process that runs from the conceptual preparation through the levels of syntactic, morphological, and phonological processing up to the level of planning and execution of articulation. Each of these serial processes take some amount of time between 100 and 200 ms [see e.g. 45, or 46, for summaries]. Consequently, a distractor word can exert a maximum influence when it is presented during a time window in which its relation to the target picture name is relevant (i.e. a semantic distractor earlier than a phonological distractor). Moreover, since a visual distractor can be processed as a whole whereas an auditory distractor only unfolds over time, the SOA between target and distractor should differ depending on distractor modality. Sass et al. [40] suggested simultaneous presentation (SOA = 0 ms) for visually presented semantic distractors.

3. As per *lexical frequency*, low-frequency distractors produce more interference than high-frequency distractors [47]. Therefore, behavioural effects may be stronger with low-frequent items in a naming paradigm.

These considerations became relevant when using the advantages of a PWI paradigm over a simple naming paradigm in TMS language mapping. The rationale of this protocol is to observe the distractor effect in the condition of no active (sham) stimulation and then to observe the interference of the TMS stimulation with this distractor effect, i.e. its elimination. When elimination of the distractor effect can be observed, one can conclude that the particular stimulation site at which this pattern was obtained is relevant for the type of relation of the distractor with the target picture name: When stimulation at a site in area 45 causes the disappearance of a semantic facilitation effect, apparently this site in area 45 is relevant for semantic processing and cannot fulfil its function when inhibited by TMS. Following this logic, Sakreida et al. [21] investigated the effects of TMS on phonological facilitation with distractors that were phonologically related or unrelated to the target picture names. In line with the literature, phonological facilitation effects were reduced by TMS at stimulation targets in area 44, but were still present when sites in area 45 were stimulated.

The objective of the present study was to adapt a *semantic* variant of the behavioural PWI paradigm under the conditions of non-active TMS to investigate the special requirements of using PWI paradigms in future TMS language mapping applications. As in psycholinguistic studies small and well-controlled item sets lead to specific results [34, 43, 48], the adaptation procedure was guided by the aim (1) to identify a specific and well-controlled set of target pictures with related and unrelated distractors that would produce behavioural facilitation effects in a robust and reliable way even when the disturbing noise of the TMS coil was present and (2) to identify whether auditory or visual distractors would produce these effects more robustly when appropriate SOAs were used. To this end, the target-distractor relations were defined as *part-whole associative* since this type of semantic relation was reported in the literature to produce facilitation (see above).

2. Materials and methods

2.1 Participants

The study protocol was approved by the local ethics committee (EK 092/18) as being in accordance with the Declaration of Helsinki [49]. We obtained written informed consent from 30 volunteers to took part in a behavioural experiment without active TMS stimulation. Participants were randomly assigned to the two experimental conditions with balanced age and sex, i.e. 15 participants (8 females, 7 males, age range 19–37 years, mean age 25.7 ± 4.8 years) took part in the condition of visual distractor presentation and 15 participants (8 males, 7 females, age range 20-39 years, mean age 25.5 ± 6.2 years) in the auditory condition with spoken distractors. All participants were strongly right-handed [mean laterality quotient in the unimodal/visual condition group = 94.3, range: 69.2–100; mean laterality quotient in the multimodal/auditory condition = 83.7, range: 62.5–100; according to the Edinburgh Handedness Inventory by 50], exclusively native German speakers, and never had any linguistic anomalies. Moreover, they were neurologically and mentally healthy, and had normal or corrected-to-normal visual acuity and hearing. None of the participants reported any discomfort during the experiment and there was no drop-out. The participants received an expense allowance of 5 € for participation. All data were anonymised.

2.2 Stimulus materials

A set of 33 target pictures from a standardised set [51] and 33 semantically part-whole related distractors was compiled (Table 1), with three stimuli serving as dummy items at the beginning of each block. In particular in the active TMS setting this would help to exclude the influence of startle effects. The same set of related distractors was used as unrelated distractors in a coupling with other targets. Item selection of the semantic PWI paradigm was based on the following parameters: (1) frequency in spoken German language according to the CELEX database [52], (2) number of syllables, (3) number of phonemes,

(4) number of graphemes, and (5) semantic category. We only included words with low frequency in spoken German language, i.e. below 30 words per million words (target words: mean = 7, distractor words: mean = 524). Word length and complexity were controlled by using words with two or three syllables, two to six phonemes, and three to seven graphemes. The word material covered different semantic categories such as animals, furniture, and clothing. Category allocation of both target and distractor words was defined with the help of the GermaNet database provided by the University of Tübingen (Germany) which groups lexical units and defines semantic relations between them [53, 54]. Semantic associative relation was indirectly controlled by the allocation of words to different semantic categories. Care was taken that no semantic categorial relation and no phonological relation occurred between the target and distractor couplings.

2.3 Procedure and experimental conditions

In several preliminary tests, we adapted the parameters to the setting of TMS language mapping by means of modification of (1) number of trials, (2) distance between participant and screen, (3) font size of the written distractor word, (4) image size, (5) SOA, and (6) TMS-noise. According to Sakreida et al. [21], 30 target pictures were presented in pseudorandomised order within six experimental blocks. In order to meet the requirement of active TMS mapping already here, each of the target pictures was required to be presented with the related/unrelated distractor word at the same position in two (out of the six) experimental blocks. The visual distractors were presented simultaneously to the target pictures (SOA = 0 ms) as written words (font size = 60 pt.) in the centre of the target picture. Target pictures had a size of 354×354 pixel with a resolution of 300 dpi and were shown with a scaling factor of 1.1 on a 19 inch monitor with 1152×864 pixel resolution. In the auditory condition, the distractors were presented as spoken words in standard German language via speakers 200 ms prior to the picture onset (SOA = -200 ms) in order to use the highest interference in the processing of target and distractor (Figure 2).

<Please insert Figure 2 here: Course of one trial>

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2.4 Experimental procedure

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Prior to the experiment, participants were familiarized with the target pictures accompanied with their required naming using a booklet. The importance of familiarisation with the stimulus material as a precondition for lexical competition and thus to support semantic interference effects was recently shown by Gauvin, Jonen, Choi, McMahon and de Zubicaray [55]. Participants also performed a practice session, showing all target pictures without distractors to train fast naming responses. It was important to train the participants with regard to the aim to investigate reaction times more than naming errors. Here, naming responses deviating from the target were corrected by the investigator, whereas during the experiment, false responses were not corrected. Participants were instructed not to feel distracted in this case and to proceed with naming. Task instructions in the experiment were as follows: "Name the picture as fast and as accurately as possible with one word! Do not pay attention to the written/spoken word! Please speak loudly and clearly! In the pauses between picture presentation, fix the mark in the middle of the screen!". The focus of the participant's attention was thus controlled by presenting a fixation point in the middle of the screen (except during picture presentation) for the complete time interval of each experimental block and by presenting an auditory attention cue to start each trial.

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In order to simulate a real TMS setting, especially with respect to the audio recordings, we applied a 5 Hz stimulation train with 5 pulses in each naming trial using a MagPro X100 stimulator equipped with a C-B60 butterfly coil (MagVenture A/S, Farum, Denmark). To prevent active stimulation, the TMS coil was positioned flipped so that one wing was tangential to the scalp. The TMS pulses were applied 300 ms after cue onset and 200 ms prior to the picture onset.

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Experimental stimuli were presented with the Presentation® software (Version 16.3; NeuroBehavioral Systems, Berkeley, CA, USA). As illustrated in Figure 2, each trial started with an auditory cue lasting 100 ms presented via speakers (Behringer MS40 Multimedia Speaker), followed by the TMS trigger onset starting at 300 ms, and picture presentation onset starting at 500 ms after the onset of the trial. Picture prestation aborted after 2000 ms after that a fixation point appeared for a rest interval of 2500 ms. Hence, the entire trial duration was 5000 ms. Naming responses of the participant as well as the TMS noise were recorded by a measuring microphone (DBX DriveRack RTA-M). The six experimental blocks were separated by breaks to offer the opportunity for a rest to the participants. The overall experiment lasted about last 35-45 minutes.

2.5 Analysis of naming latencies

In a first step, the naming errors and their number were documented to exclude these trials from further analysis. Naming errors were categorised as no response, delayed naming (e.g. "Fl..Flasche" (bottle)), elongation (e.g. "Sch...t...iefel (boot)), and (a very likely) semantic paraphasia (e.g. "Kä..Spinne" (spider)). Such divergent naming was the most frequent cause of invalid responses. By using the software Pro Tools 10 (Avid Technology, Inc., Burlington, MA, USA), we assessed the latency between the onset of the auditory cue (or rather the picture onset 500 ms later) and speech onset for each trial on a millisecond scale. Though this procedure was done for each trial manually, it however allowed for reliable offline identification of true naming latencies. This procedure also allowed to differentiate between speech and TMS noise and to identify different categories of phonemes, such as plosives and sibilants. The main differences were revealed in the wave form of the audio signal. Whereas plosives can be identified by peaks in the wave form, sibilants often show fluent onsets. Therefore, standards for the identification of onsets for specific sounds appear important to define, such as stating the first peak in the wave as the speech onset. These determinations were described in a protocol that served to ensure a consistent procedure of naming latencies evaluation among the two raters. Confirming results in our previous

studies, independent random sampling assessment of naming latencies by two raters showed excellent absolute agreement between evaluators (within nine randomly chosen experimental blocks among three participants) by means of a median intra-class correlation (two-way random, single measure) of r = 0.983 (range: 0.916-0.996).

2.6 Statistical analysis

Prior to the statistical analysis, naming latencies were also corrected for outliers. Latencies more than two standard deviations above or under the mean values for unrelated and related target-distractor couplings, respectively, were excluded. The statistical analysis was performed using IBM® SPSS® Statistics software (Version 25.0; New York, NY, USA). To test for facilitatory effects per target picture and participant, we (1) calculated the mean of the maximally three naming latencies for the unrelated (U) and related (R) target-distractor couplings, respectively, and (2) subtracted the mean value U from the mean value R. Thus, this results in 30 difference values per participant representing positive or negative interference per target picture. We subjected these participant-wise interference values to a two-factorial repeated-measures analysis of variance (ANOVA) with the two-level factors RELATION (unrelated/related target-distractor couplings) and MODALITY (unimodal-visual/multimodal-auditory distractor presentation). The significance level was set to p < 0.05.

3. Results

Inaccurate naming responses resulted in the exclusion a minor portion of trials (5 errors on average in the unimodal/visual condition = 2.9 % of 180 trials; 9 errors on average in the multimodal/auditory condition = 4.7% of 120 trials). In addition, reaction times were corrected for outliers that exceeded two standard deviations of the mean. By doing this, 126 trials were excluded in the visual (unimodal) condition and 130 trials were excluded in the auditory (multimodal) condition.

3.1 Analysis of the entire item set

As shown in left panel of Figure 3, we found the group-based mean semantic facilitation effect 'U minus R' in the unimodal/visual condition to be numerically higher (6.40 \pm 14.25 ms) than in the multimodal/auditory condition (-2.53 \pm 15.45 ms). Thus, in the unimodal/visual condition, the expected facilitation by means of slower responses to unrelated as compared to related target-distractor couplings was present, but to a small extend, which was –by trend– confirmed by a one-tailed paired t test for the resulting directional hypothesis of a larger facilitation effect in the visual as compared to the multimodal/auditory condition (t_{28} = 1.645; p = 0.056). As however can be assumed from this, the two-factorial repeated-measures ANOVA revealed no significant main effect for the within-subject factor RELATION ($F_{1,28}$ = 0.507; p = 0.482), no main effect for the between-subject factor MODALITY ($F_{1,28}$ = 1.980, p = 0.170), and no interaction RELATION × MODALITY ($F_{1,28}$ = 2.705, p = 0.111).

<Please insert Figure 3 here. Results of the analysis of the entire item set comprising 30 items and the item selection comprising the 10 most facilitating items >

3.2 Analysis of a reduced item set including only reliably facilitating target pictures

Following our aim to provide a stimulus set for TMS language mapping specifically addressing semantic processing that is associated with robust and reliable behavioural facilitation effects, we created a sub-set of ten items for further analysis. Target pictures that showed a facilitation effect 'U > R' in the unimodal/visual condition in more than 50% of the participants were selected (see items highlighted in bold in Table 1). This reduced item set also contained words with one or two syllables from different semantic categories.

The semantic facilitation effect 'U minus R' was now even larger in the unimodal/visual condition (27.40 \pm 30.60 ms) and also present in the multimodal/auditory condition (4.67 \pm 32.81 ms; see right panel of Figure 3). The ANOVA thus yielded a main effect for the within-subject factor RELATION (F_{1,28} = 7.663, p = 0.010), but no main effect for the between-subject factor MODALITY (F_{1,28} = 1.582, p = 0.219). The interaction RELATION \times MODALITY was found to be marginally significant (F_{1,28} = 3.851, p = 0.060). More important, however, is the result of a one-tailed paired t test confirming a significant larger behavioural facilitation effect induced by the ten-items sub-set in the visual as compared to the multimodal/auditory condition (t₂₈ = 1.963; p = 0.030).

4. Discussion

This behavioural study investigated an adaptation of a semantic PWI paradigm to language mapping with TMS, studying healthy participants. The adaptation procedure aimed at (1) the identification of a stimulus set robustly triggering behavioural facilitation effects with the question (2) whether auditory or visual distractors are more appropriate to do this. Our data from two experiments employing visual or auditory distractors, respectively, in part-whole associative semantic relations to target pictures revealed a preference for the unimodal presentation mode in which the visually presented written distractor word appeared simultaneously to the target picture presentation. Out of the stimulus set of 30 target pictures, we identified ten stimuli that induced strongest facilitation effects. By doing this we provided reliable material for future TMS language mapping application.

4.1 Behavioural semantic PWI effects

Following the study by Muehlhaus et al. [38] in which visual part-whole associative related distractor words have been presented in a semantic PWI naming paradigm yielding facilitation effects, we developed our stimulus material features. In our study, the focus of semantic interference was on semantic priming effects. We aimed to investigate the

behavioural effect of semantic facilitation in a naming task, which in future studies can be neutralised by the inhibitory effect of TMS on lexical retrieval, thus identifying the stimulation sites relevant for semantic processing. This may give specific insights in lexical processing. The identification of ten stimuli that induced strongest facilitation effects may be explained by a stronger association between target and related distractor or it may be a word length effect. Other factors such as differences in semantic neighborhood density and similarity [56] may also be responsible for this pattern of results. By employing both visual and auditory of part-whole related semantic distractors in two experiments we confirmed that visual distractor presentation can induce higher facilitation effects than auditory distractor presentation. This is in line with findings that associative semantic target-distractor relations are not per se associated with facilitation effects [37, 38]. In this respect, Hantsch et al. [42] showed that the manipulation of distractor modality can enable the behavioural effect to reverse into its opposite. This seems to be indicated by our data, when considering the facilitation effect in the unimodal/visual condition (6.40 ± 14.25 ms) as compared to the multimodal/auditory condition (-2.53 ± 15.45 ms) in the analysis of the entire item set (t_{28} = 1.645; p = 0.056). However, our small sample size could have impact on this non-significant effect. In the analysis of the reduced item set, we indeed found a –albeit rather small– facilitation effect in the multimodal/auditory condition (4.67 ± 32.81 ms) supporting findings of semantic facilitation effects that have been also revealed for categorial relations in cross-modal tasks [57].

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Behavioural effects of facilitation and inhibition (interference) in PWI tasks have been explained by linguistic models in terms of a competition during lexical selection [46, 58]. The "swinging lexical network proposal" includes conceptual facilitation and lexical cohort activation in the process of lexical selection as well as a variable focus on one of them [59]. In other words, semantic picture-word facilitation or interference are supposed to depend either on the emphasis of conceptual facilitation or the activation of a range of lexical cohorts during the retrieval of an associative from the mental lexicon. Beyond that, lexical parameters such as the number of phonemes might also have an impact on the process of

lexical selection, but this parameter was among others carefully controlled in our stimulus

469 material.

4.2 Methodological aspects and limitations

Both the to-be-named target pictures and the distractor words stimuli were selected from low-frequent German object nouns. Our chose of low-frequent nouns was supported by the finding of distractor frequency effects in terms of greater interference for low as compared to high-frequent distractors [47]. Distractor frequency may account for our marginal facilitation effect in the analysis of the entire item set, but intraindividual differential naming latencies may also depend on other parameters such as the distractor modality. In the setting of cognitive behavioural studies further experiments would be necessary to disentangle the impact of distractor frequency and distractor modality, which was not the focus in this adaption of a semantic PWI task to the TMS setting. With regard to the distractor modality the processing of the visual distractors may have interfered more with image recognition than the auditory distractors. This may have affected the reaction times albeit the number of the outliers both in the visual and the auditory conditions did not show substantial differences.

Another important factor of the behavioural effect of picture-word interference in conditions concerning different modalities is the SOA. In the visual condition the distractor was presented simultaneously to the target word (SOA = 0 ms) so that the word processing may be simultaneous. According to the serial model of word processing by Levelt (2001) the SOA must be longer for auditory distractor words [44]. The interval of -200 ms was chosen here in order to elicit the maximum interference of processing between target and distractor word as in the Levelt model a time interval of 100-200 ms for processing of auditory stimuli is assumed [44].

With regard to our procedure of simulating a real TMS setting, the TMS noise may also have had an impact on our results. Nikouline, Ruohonen and Ilmoniemi [60] found that the amplitude of auditory-evoked potentials (as measured by electroencephalography) to the acoustic click of the TMS coil was depended on the mechanical contact of the coil with the head. Thus, TMS noise might have an influence on the lexical selection processes in semantic processing and this may affect the facilitation effect. Additionally, in the multimodal/auditory condition both distractor stimuli and TMS noise were auditorily perceived and processed. The auditory interference is one of the most difficult part in the adaption of the psycholinguistic paradigm to language mapping. We aimed to minimize any influencing factors, but the simultaneous auditory processing both of the TMS coil click and the auditory distractor may be problematic. In addition, the behavioural effect of semantic priming is not as stable as the facilitatory effect of phonological relations. Any additional influencing factors may further reduce the effects. Therefore also differences in the focus of attention may have caused interference such as naming facilitation or inhibition. Stringent instruction to focus the attention on the target picture and on the fixation point in the rest phases helped to control the focus of participants attention constantly during the experiment.

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The TMS noise, however, makes the use of a threshold-sensitive microphone to automatically generate response times or a larynx microphone impossible. Hence, audio signals had to be audio-recorded during the TMS session and afterwards analysed manually trail by trial. It is hardly possible to automatize this labour-intensive and time-consuming procedure.

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The manual determination of the speech onset comes along with possible sources of errors. While fricatives and plosives can be found easily by their peaks in the wave form of the audio signal, the identification of the speech onset in sibilants is, however, more difficult. We therefore used an analysis protocol with determined standards for an improved interrater compatibility. To date, the procedure of identification of speech onsets cannot be

automatized though attempts exists. Vitikainen, Mäkelä, Lioumis, Jousmäki, and Mäkelä [61] used an accelerometer-based automatic voice onset detection in TMS language mapping for patients that were going through tumour or epilepsy surgery workup. The routine had a high accordance with manual analysis, but it was also accompanied with difficulties to define the starting point of voice in sibilants. There were erroneous latency detections due to throat movements before the actual response or extra voice before the response [61]. Indeed, this procedure was also used efficiently with epilepsy surgery patients [4].

The development of an automatized procedure for the analysis of naming latencies despite TMS noise in future studies would be a significant benefit by shortening analysis time and may also improve data accuracy as different standards between studies and inter-rater experience levels can confound results.

Another, albeit not methodological, limitation concerns the observed high degree of differential semantic facilitation effects among participants. In the familiarization phase prior to the experiment participants were trained to name the target pictures as accurately as possible so that the occurrence of naming errors was minimised, thus, enabling to use naming latencies for the analyses. The behavioural effect of semantic facilitation seems thus not as stable as in phonological facilitation/priming. Due to our sample size of 30 participants, it was not possible to identify a pattern regarding features of the participants or specialties in the experimental procedure. The small sample size for each condition (15 participants) may also be a reason for differences that were not statistically significant. The application of the reduced and well-controlled item set, which we found to be associated with strong facilitation effects, in a behavioural study employing a larger sample size and/or in active TMS language mapping would enable for deeper insights into the behavioural effects of semantic facilitation/priming.

5. Conclusion

In this behavioural study with healthy participants we adapted a semantic PWI picture naming paradigm with part-whole associative distractors to language mapping with TMS. Visual distractors presented simultaneously in the centre of the target picture induced stronger facilitation effects than auditory distractors presented 200 ms prior to the picture onset. In order to provide reliable material for future TMS language mapping application we further identified ten stimuli associated with strongest facilitation effects.

The implementation of a cognitive paradigm into language mapping application, in which usually qualitative language evaluation presents the focus, helps to specifically address levels of language processing and to improve the method by using the quantitative measure of reaction times. Moreover, the analysis of PWI effects can reveal more specific information on language processing as compared to the evaluation of language errors. Both approaches of analysis, quantitative naming latencies and qualitative naming errors, could complement each other in future language mapping studies. Comparative mapping using different paradigms may therefore reveal more detailed results. The applicability of a PWI paradigm in language mapping in brain tumour patients, however, also remains to be tested.

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Figure captions

Note: The artwork was created with Adobe Illustrator CS5.1. All figures are in grayscale mode with a resolution of 1000 dpi. Figure 1 and 2 were prepared in 90 mm width (single column), and Figure 3 in 140 mm width (1.5 column).

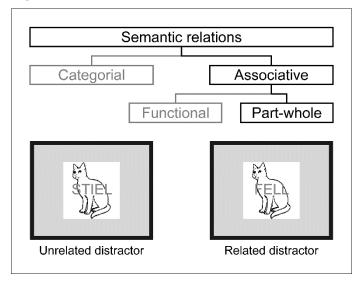
Figure 1. Hierarchical structure of semantic relations. Overview of the hierarchical structure of semantic relations –divided into categorial and associative– that led to the selection of part-whole associative semantic relations for this study. Categorial relations such as 'Katze' (cat) – 'Hund' (dog) contain words that are both from the same semantic category and mostly also from the same level as it is the case with cohyponyms. Subdivisions of categorial relations were excluded here. We adopted the subdivisions of associative relations in functional, such as 'Katze' (cat) – 'Milch' (milk), and part-whole, such as 'Katze' (cat) – 'Fell' (fur), from Muehlhaus et al. (2013). According to their results that higher facilitatory effects were observed with part-whole than functional relations (Muehlhaus et al., 2013), part-whole associative semantic relations were used. The target word 'cat' is shown with the related distractor 'Fell' (fur) and the unrelated distractor 'Stiel' (stem) as exemplary stimuli shown in the experiment.

- Figure 2. Trial course in the unimodal/visual and in the multimodal/auditory condition. Illustration of the time course of an exemplary experimental trial with a simultaneous visual distractor presentation, i.e. a stimulus onset asynchrony (SOA) of 0 ms in the unimodal
- condition and an early auditory distractor presentation (SOA = -200 ms) in the multimodal
- section condition.

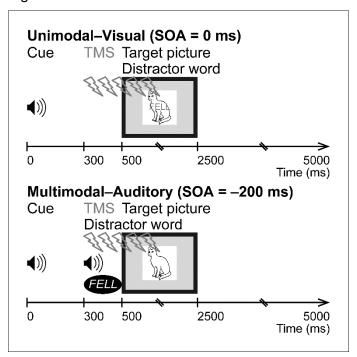
Figure 3. Results of the analysis of the entire item set comprising 30 items and the item selection comprising the 10 most facilitating items. Semantic facilitation is shown in the unimodal/visual condition by means of slower responses to unrelated (U) as compared to related (R) target-distractor couplings. Group based mean naming latencies and standard error rates are displayed.

- Table 1. Word material. 30 experimental target stimuli with the related and the unrelated
- distractor as well as three dummy items (in italic) used in the experiment given in the original language of the experiment (German) and in its English translations in brackets. The same
- set of related distractors was used as unrelated distractors in a coupling with other targets.
- 874 The ten items with facilitation effects in more than 50% of the participants in the
- unimodal/visual condition are highlighted in bold.

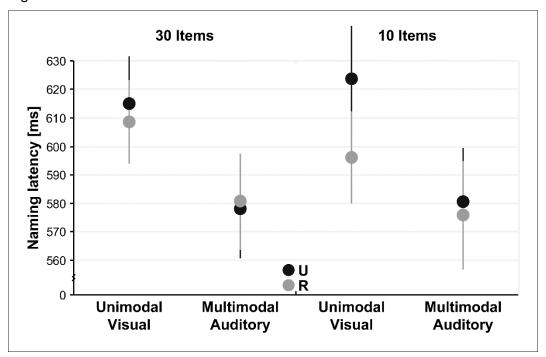
876 Figure 1



878 Figure 2



880 Figure 3



882 Table 1

Target	Related distractor	Unrelated distractor
Bein (leg)	Knie (knee)	Schnauze (snout)
Gabel (fork)	Zinke (prong)	Knie (knee)
Fuchs (fox)	Schnauze (snout)	Zinke (prong)
Adler (eagle)	Kralle (claw)	Henkel (handle)
Apfel (apple)	Stiel (stem)	Huf (hoof)
Besen (broom)	Holz (wood)	Fell (fur)
Blume (flower)	Knospe (bud)	Feder (feather)
Brille (glasses)	Glas (glass)	Hals (neck)
Brot (bread)	Kruste (crust)	Zacke (spike)
Flasche (bottle)	Hals (neck)	Stoff (cloth)
Glocke (bell)	Metall (metal)	Leder (leather)
Hirsch (stag)	Geweih (antlers)	Pfosten (post)
Hose (pants)	Stoff (cloth)	Schirm (shade)
Kaefer (beetle)	Fühler (feeler)	Metall (metal)
Katze (cat)	Fell (fur)	Stiel (stem)
Kerze (candle)	Wachs (wax)	Griff (holder)
Korb (basket)	Griff (holder)	Ohr (ear)
Kuh (cow)	Huf (hoof)	Wachs (wax)
Lampe (lamp)	Schirm (shade)	Haar (hair)
Leiter (ladder)	Sprosse (rung)	Mähne (mane)
Maus (mouse)	Pfote (paw)	Kissen (pillow)
Pfau (peacock)	Feder (feather)	Spitze (tip)
Pfeil (arrow)	Spitze (tip)	Lehne (back)
Pferd (horse)	Mähne (mane)	Sprosse (rung)
Schuh (shoe)	Sohle (sole)	Geweih (antlers)
Schwein (pig)	Ohr (ear)	Holz (wood)
Sofa (sofa)	Kissen (pillow)	Fühler (feeler)
Spinne (spider)	Haar (hair)	Glas (glass)
Stern (star)	Zacke (spike)	Pfote (paw)
Stiefel (boot)	Leder (leather)	Knospe (bud)
Stuhl (chair)	Lehne (back)	Kruste (crust)
Tasse (cup)	Henkel (handle)	Kralle (claw)
Zaun (fence)	Pfosten (post)	Sohle (sole)