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ORIGINAL ARTICLE

Phonological picture–word interference in language mapping with transcranial magnetic stimulation: an objective approach for functional parcellation of Broca's region

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Abstract

Functional imaging data suggest different regions for semantic, syntactic, and phonological processing in an anterior-to-posterior direction along the inferior frontal gyrus. Language mapping by use of neuro-navigated transcranial magnetic stimulation (TMS) is frequently applied in clinical research to identify language-related cortical regions. Recently, we proposed a high spatial resolution approach for more detailed language mapping of cortical sub-areas such as Broca's region. Here, we employed a phonological picture–word interference paradigm in healthy subjects to reveal functional specialization in Broca's region for phonological processing. The behavioral phonological priming effect is characterized by accelerated naming responses to target pictures accompanied by phonologically related auditory distractor words. We hypothesized that the inhibitory effects of TMS on language processing would reduce phonological priming only at stimulation sites involved in phonological processing. In active as compared to sham TMS, we found reduced phonological facilitation specifically at sites overlapping with the probabilistic cytoarchitectonic area 44. Our findings complemented functional imaging data by revealing structure–function relationship in Broca's region. The introduction of a reaction time based interference paradigm into TMS language mapping increases the objectivity of the method and allows to explore functional specificity with high temporal resolution. Findings may help to interpret results in clinical applications.

Keywords Broca's region · Cytoarchitectonic mapping · Language mapping · Phonological picture–word interference · Transcranial magnetic stimulation

Introduction

Neuro-navigated transcranial magnetic stimulation (TMS) for cortical mapping of language functions is predominately used in clinical research to identify individual language-related regions of the cortex (e.g., Espadaler and Conesa 2011; Picht et al. 2013; Tarapore et al. 2013; Rösler et al. 2014; Ille et al. 2015a, b; see also e.g., Lioumis et al. 2012; Rogić et al. 2014, for language mapping studies in healthy participants). Most language mapping protocols employ a simple object naming paradigm. Both frequency and quality of TMS-induced speech and language errors are assessed. For a more detailed mapping of cortical sub-areas, we recently proposed a high spatial resolution approach (Sakreida et al. 2018). By targeting Broca's region with a multitude of stimulation sites covering the pars opercularis and pars triangularis of the left inferior frontal gyrus as well as parts of the ventrolateral premotor cortex, we found a 'focus of TMS susceptibility' for language inhibition in the

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dorsal portion of area 44 and close to the inferior frontal junction area, associated with mainly performance errors including articulatory symptoms during object naming. However, more specific paradigms are required for more detailed investigations into the organization of language processing within Broca's region.

Broca's region is known to hold several functional roles in language processing, which have been explored in numerous task-related functional activation imaging studies (for comprehensive reviews, see Price 2010, 2012; for a meta-analysis on functional imaging data, see Clos et al. 2013; Vigneau et al. 2006). Cytoarchitectonic and receptor-architectonic mapping data show a variety of structural sub-areas in Broca's region (Amunts et al. 1999, 2010; Amunts and Zilles 2012). The degree of structure–function overlap is still a matter of discussion (see Lindenberg et al. 2007, for a cluster analysis of functional and spatial ascriptions to "Broca's area" in a large body of older publications).

Functional specialization in the inferior frontal gyrus for different aspects of language processing, especially semantics and phonology, has been addressed by many functional magnetic resonance imaging (fMRI) studies (see, e.g., Poldrack et al. 1999; Hagoort 2005; Heim et al. 2008, 2009a, b). Such empirical data supported the proposal of separated semantic, syntactic, and phonological processing in an anterior-to-posterior order, with sentence-level processes that engage the anterior left inferior frontal gyrus, and word-level processes that engage the posterior left inferior frontal gyrus (for reviews, see Bookheimer 2002; Friederici 2002; Hagoort 2005). Specifically, the anterior–ventral inferior frontal gyrus (pars orbitalis) has been related to semantics, the middle inferior frontal gyrus (pars triangularis) at the intersection of areas 44 and 45 has been associated with syntax, and the posterior–dorsal inferior frontal gyrus at the border of areas 44 and 6 has been linked to phonology. Uddén and Bahlmann (2012) integrated sequential semantic, syntactic, and phonological processing at the sentence and word levels in a model of a "rostro–caudal temporal abstraction gradient": areas 44d and 6v—according to receptor-architectonic parcellation (Amunts et al. 2010; Zilles et al. 2015)—are engaged in phonological processing at the word level; areas 44v and 45p are involved in processing of syntactic rules at the word and sentence level, and perhaps also semantic rules at the sentence level; and areas 45a along with Brodmann area 47 (Brodmann 1909) integrates these processes with the goal of extracting the meaning at a longer time scale.

Complementary, intra-cranial recordings from unaffected brain tissue during periods of normal activity in patients with epilepsy with chronically implanted depth electrodes for clinical evaluation yielded distinct spatiotemporally patterned neuronal activity within Broca's region for lexical (~200 ms), grammatical (~320 ms), and phonological (~450 ms) processing during covert word production or reading (Sahin et al. 2009; see also the commentary by Hagoort and Levelt 2009). An anterior–posterior dissociation in the inferior frontal gyrus for semantic and phonological processing, respectively, was likewise shown by non-invasive TMS in healthy volunteers (e.g., Gough et al. 2005; see also Devlin and Watkins 2007). A meta-analytic summary of TMS studies plotting the stimulation sites with modulation effects in phonological and semantic tasks revealed clearly spatially separated posterior and anterior foci, respectively (Cattaneo 2013). However, these TMS studies used single stimulation targets in the inferior frontal gyrus.

To complement functional activation studies and inhibitory TMS studies by the high-resolution TMS language mapping approach, we addressed functional specialization in Broca's region for phonological processing and adapted a phonological picture–word interference paradigm to the mapping application. In the cross-modal phonological interference paradigm, a to-be-named picture of a target noun is shown, while an acoustically presented distractor noun interferes, which is phonologically unrelated or phonologically related to the target noun. A phonological priming effect leads to facilitation (acceleration) of naming responses with phonologically related distractors as compared to unrelated distractors (see, e.g., Damian and Martin 1999; Jescheniak and Schriefers 2001). We hypothesized that the inhibitory effects of TMS in language processing reduce this phonological facilitation only at stimulation sites within Broca's region which are specifically involved in phonological processing. A behavioral pilot experiment confirmed the effect of acceleration in naming latencies due to phonological priming. The language mapping procedure consisted of two sessions: active TMS and sham TMS which served as control baseline for unspecific TMS effects. We also correlated functional findings and brain structure by determining the overlap of stimulation sites with probabilistic cytoarchitectonic areas 44 and 45.

Materials and methods

Participants

Our experimental standards were in accordance with the Declaration of Helsinki (Rickham 1964) and approved by the local ethics committee of the Medical Faculty of RWTH Aachen University (EK 054/13). Prior to investigation, we obtained written informed consent from 12 volunteers (6 female, age range 21–47 years, mean age 28.7 ± 7.0 years) for the TMS-mapping experiment, and from six volunteers (4 female, age range 22–42 years, mean age 28.7 ± 7.0 years) for the behavioral pilot experiment. One participant took part in both the behavioral and the TMS-mapping experiment.

All participants were 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. Apart from one ambidextrous participant (laterality quotient = 20) of the TMS-mapping experiment, who also took part in our previous study, all participants were strongly right-handed (TMS mapping experiment: mean laterality quotient = 96.2, range 77.8–100; behavioral pilot experiment: mean laterality quotient = 93.9, range 81.8–100) according to the Edinburgh Handedness Inventory (Oldfield 1971). The data of one participant in the behavioral pilot experiment had to be excluded from the analysis due to his misunderstanding of the task instruction. All data were anonymized.

Paradigm

In our cross-modal phonological picture–word interference paradigm, the task instruction for the participant was to name the target picture as fast and accurately as possible, while an acoustically presented distractor noun interferes, which was phonologically unrelated or related. Phonological priming is characterized by facilitation of naming responses to target pictures in the condition of phonologically related as compared to unrelated distractors (see, e.g., Damian and Martin 1999; Jescheniak and Schriefers 2001). For example, the presentation of the target noun *Katze* (cat) presented with the phonologically related distractor *Karte* (card) would provoke an accelerated naming latency as compared to the presentation of the same target noun *Katze* (cat) with the unrelated distractor *Fliese* (tile). We used the related distractor words dedicated to specific target pictures also as unrelated distractors for other targets. Target nouns and their related distractor nouns were similar in at least the first two phonemes and were required not to be semantically related. The auditory distractor noun followed the target picture by a stimulus onset asynchrony (SOA) of + 150 ms since this time interval had proved most effective for phonological priming in the previous behavioral studies (Schriefers et al. 1990; Meyer and Schriefers 1991; Jescheniak and Schriefers 2001; Jescheniak et al. 2003; for an overview, see Abel et al. 2009).

Stimulus materials

Word material included two-syllabic German nouns and was controlled with regard to the number of letters and phonemes, semantic category, and frequency in spoken German language (CELEX database; Baayen et al. 1996). To exclude effects of specific items on naming latencies, i.e., to reduce possible covariation of lexical frequency with reaction times, we only included words with low frequency in spoken German language ranging from 0 to 50 words on 1.000.000 words (median = 2). As target pictures, we employed 90 black–white line drawings of objects (Snodgrass and Vanderwart 1980), which were presented for a duration of 2000 ms. The 90 distractor nouns were presented via audiotracks of a female speaker in standard German.

Experimental design and procedure

Based on 90 target nouns and 90 distractor nouns, we created six mapping blocks with 30 different pseudo-randomized target–distractor pairs per block (for 30 stimulation targets per block, see Sect. "TMS language mapping protocol"). Each of the 90 target pictures was required to be presented with the related/unrelated distractor word at the same anatomical location within the stimulation target grid in two (out of the six) mapping repetitions (see Fig. 1, for an exemplary first trial stimulating the first target per mapping block). The stimulus material of these six blocks was controlled independently by two speech-language therapists to avoid any accidental semantic or phonological relations in the order of target–distractor pairs. Finally, the order of the six mapping blocks was pseudo-randomized between participants.

Experimental stimuli were presented with the Presentation® software (Version 16.3, NeuroBehavioral Systems, Berkeley, CA, USA), which also synchronized stimulation onset and picture presentation onset. Each trial started with an auditory cue presented via speakers (Behringer MS40 Multimedia Speaker). The cue lasted 100 ms and was triggered by the examiner with a custom-made foot pedal button. After 500 ms, the target picture appeared, followed by the auditory distractor noun with an SOA of 150 ms. Simultaneously with the target picture, the TMS onset was triggered, and a stimulation marker, including the information of the exact position of the coil hotspot at the time of first stimulation pulse and its perpendicular projection onto the cortical surface, was recorded by the neuro-navigation system. These stimulation markers were used for further offline analyses (see Sect. "Generation of TMS-based volumes of interest, normalization, and anatomical labeling").

In a separate session (mean = 3.2 months after the experiment with active TMS) we conducted the control experiment with sham stimulation, but with a randomized order of the experimental blocks. Participants were informed that the first experiment would be performed again, however, with a different coil which could induce a different sensation of stimulation. Since TMS experienced subjects would identify sham stimulation, and our study included participants with TMS experience as well as TMS naïve ones, we implemented the sham condition after the active TMS experiment. In the behavioral pilot experiment, which we conducted prior to the TMS mapping experiment, no stimulation was applied, but the coil was placed next to the participant to simulate the TMS noise for comparable analysis of naming latencies. Prior to the experimental session, participants

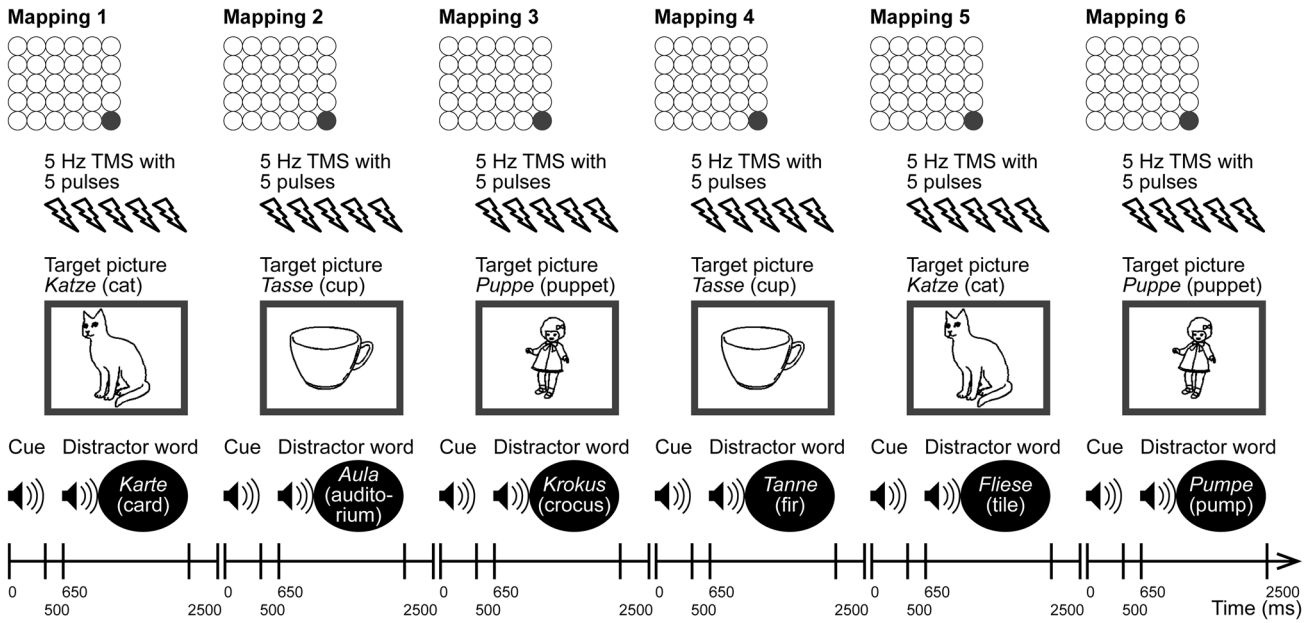

Fig. 1 Phonological picture–word interference paradigm. The task instruction for the participant is to name the target picture as fast and accurately as possible, while an acoustically presented distractor noun interferes, which can be phonologically unrelated or phonologically related to the target noun presented as an object picture. An exemplary first trial stimulating the first target per mapping block is shown. Each target picture was required to be presented with the unrelated/related distractor word at the same anatomical location within the stimulation target grid in two (out of the six) mapping repetitions. See text in Sect. "Experimental design and procedure" for further details about the trial procedure

were familiarized with the target pictures accompanied with their required naming using a booklet. Even if familiarization or repeated presentation of the word material does not prevent frequency effects on naming latencies (Jescheniak and Levelt 1994), possible frequency effects on reaction times were minimized by selecting word material with a reduced frequency range. Participants also performed a practice session, showing all 90 target pictures with unrelated distractor words to train fast naming responses. Here, naming responses deviating from the target were corrected by the investigator.

TMS language mapping protocol

We used the TMS protocol as previously described and discussed in detail (Sakreida et al. 2018). In summary, repetitive TMS over a dense 30-points cortical target array was applied using a frameless stereotactic system for neuronavigation (LOCALITE Biomedical Visualization Systems GmbH, Sankt Augustin, Germany) and a MagVenture MagPro X100 stimulator equipped with a C-B60 butterfly coil or a MCF-P-B65 placebo butterfly coil for sham stimulation (MagVenture A/S, Farum, Denmark). The target array was positioned individually for each participant according to macro-anatomical landmarks to cover the entire pars opercularis and pars triangularis of the left inferior frontal gyrus. In detail, the top row was aligned with the inferior frontal sulcus, with the most posterior target at the junction of the inferior frontal sulcus and the inferior precentral sulcus. Thus, the inferior posterior corner of the array covered the anterior part of the inferior-most precentral gyrus (area 6) in most participants. Figure 2 shows the anatomical location of the stimulation target arrays in all 12 participants. All 30 targets were stimulated in sequential order from posterior-to-anterior, and from inferior-to-superior, with target 1 located posteriorly in the most inferior row and target 30 located anteriorly in the most superior row.

In each naming trial, we applied a 5 Hz stimulation train with 5 pulses for a total stimulation time of about 800 ms with inter-pulse-intervals of 200 ms, including a pulse width of 280 µs. Stimulation intensity was equal to our first study (Sakreida et al. 2018) defined as the language inhibition threshold on the basis of the individual resting motor threshold (rMT; Rossini et al. 1994, 2015). The mean rMT obtained from the dominant right hand (first dorsal interosseous muscle) was 41.7 ± 5.0% of maximum stimulator output. The mean stimulation strength determined by this method was 160 ± 17.6% of rMT. Hence, mean stimulation amplitude was 66.6 ± 7.3% of maximum stimulator output. Protocol parameters were in line with common safety parameters (Belmaker et al. 2003; Wassermann 1998; see also Epstein et al. 1996). Side effects from TMS including discomfort and

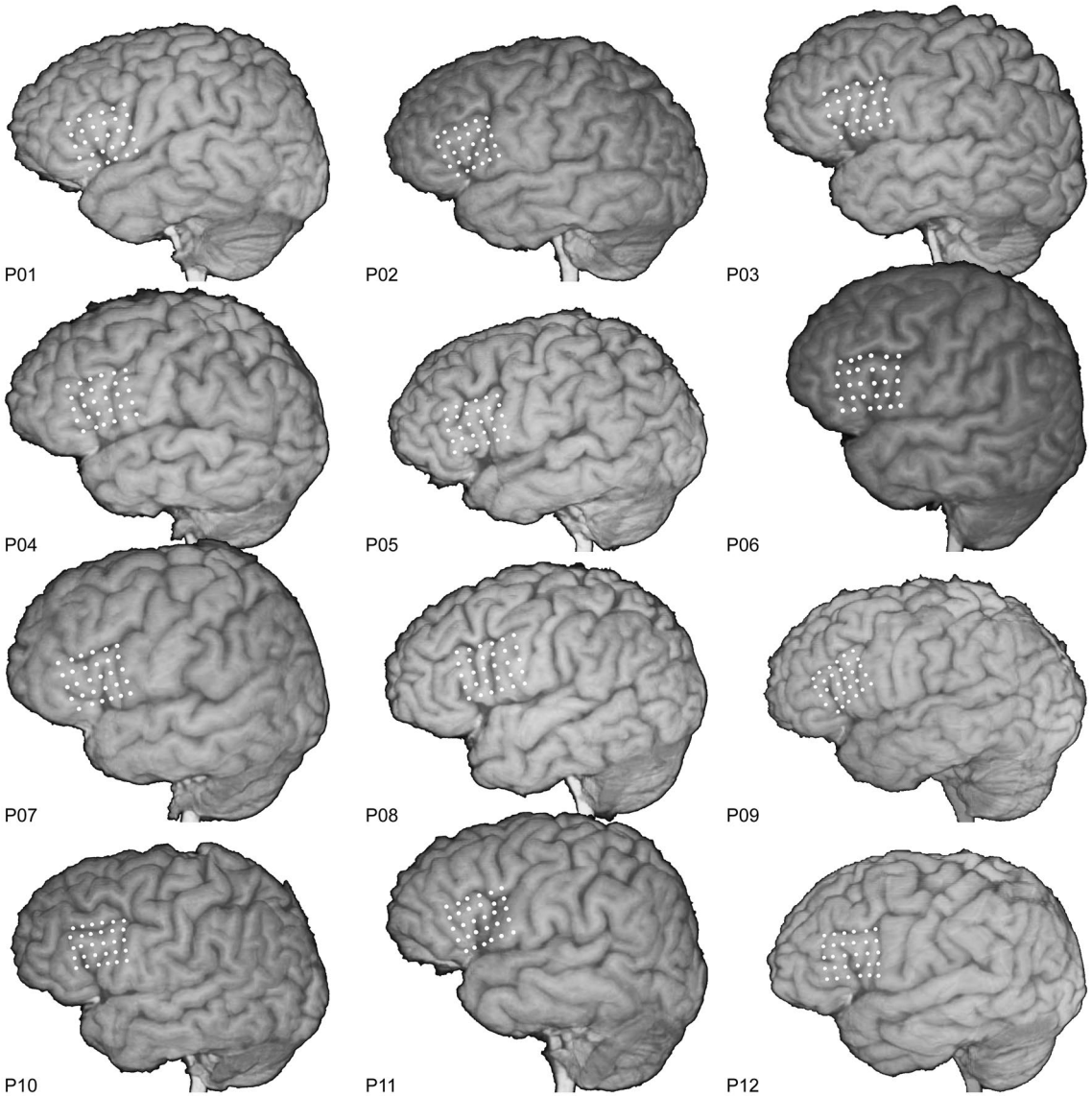

Fig. 2 Anatomical location of individual stimulation target arrays. The stimulation target array was obtained by projecting a 5 × 6 points array with 6 mm distance between adjacent points onto the target cortical area. For each participant, the grid was aligned according to local topographic structure and macro-anatomical landmarks to cover the entire pars opercularis and pars triangularis of the left inferior frontal gyrus, as well as the anterior part of the inferior precentral gyrus in most cases

facial muscle twitching occurred with high inter-individual variability. Self-ratings of discomfort (inquired per button press after each stimulation trial) were not correlated with stimulation intensities across participants (Pearson $r = 0.261$, $p = 0.412$). Sham stimulation was applied with 30% of maximum stimulator output for all participants, since this amplitude was reported to produce a clicking sound when discharging that was like active single-pulse TMS at 50% of maximum stimulator output (Duecker et al. 2013). At this intensity, a sham TMS pulse is too weak to produce any neural effect and hardly, any sensation on the head can be perceived, except for weak vibrations of the coil.

The overall procedure was video-taped with a high-definition webcam (Logitech HD Pro Webcam C920) on top of the presentation monitor and a measurement microphone (Behringer ECM-8000) connected to the audio-interface M-AUDIO M-Track Plus (Avid Technology, Inc., Burlington, MA, USA). For control purposes in the evaluation, we recorded picture presentation within the video track analogously using a small mirror in front of the presentation monitor. By analyzing the audio track 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. This set up allowed for reliable offline identification of true naming latencies (see Fig. 3). For quality control purposes, naming latencies of one sample participant were assessed independently by two speech-language therapists. Intra-class correlations (two-way random, single measure) indicated excellent absolute agreement between evaluators within experimental blocks (mapping block 1: $r = 0.999$, mapping block 2: $r = 0.999$, mapping block 3: $r = 0.999$, mapping block 4: $r = 0.999$, mapping block 5: $r = 0.999$, mapping block 6: $r = 0.999$).

Analysis of naming latencies and statistical analysis

First of all, naming latencies were excluded from further analysis in the following cases: (1) semantic paraphasia, i.e., naming by use of a not expected name, for instance, *Käfer* (beetle) instead of *Biene* (bee); and (2) strikingly delayed naming response, or hesitation. More precisely, trials were excluded, if a non-speech sound preceded the utterance of the picture name (e.g., *ehhh Biene*), or if the first naming response and the correct target word were interrupted (e.g., *BeBeBiene*). Note that TMS-induced performance errors such as coherent transient blocks (e.g., *BBiene*) were included in our data analysis. On the basis of these criteria we ensured true naming latencies of correct responses. Naming latencies were measured from the onset of picture presentation until the first phonetic output (Fig. 3).

Second, since we presented three target pictures at each of the 30 stimulation targets, we calculated three (at maximum, depending on the number of valid trials) differences 'unrelated minus related' by subtracting the naming latency for the related target–distractor pair from the naming latency for the unrelated target–distractor pair, respectively. Third, aggregation of these maximally three differences using their arithmetic mean (or, in the case of an individual data point, this particular difference value) represented the value of interference at each of the 30 stimulation targets for each participant. Finally, we calculated the 30 group based mean values of interference.

Assuming that unrelated target–distractor pairs would provoke longer naming latencies than related target–distractor pairs, a positive difference value would confirm an acceleration due to phonological priming, whereas a negative difference value would indicate a deceleration despite phonological priming, or merely the reduction of any priming effect due to the stimulation. However, these differential behavioral effects are hardly interpretable when considering solely the data from the active TMS experiment, since confounding factors such as increased attention and/or distracting TMS noise could have any impact on the results. Therefore, to deduct confounding factors and to actually attribute the differential phonological priming effects to the specific cortical effects of TMS, such as a reduction of phonological facilitation, we related the naming latencies obtained in the active TMS stimulation experiment to those obtained in the control experiment with sham stimulation by calculation of the difference 'active minus sham'. Data of the control experiment were analyzed in the same way as described in the two paragraphs before. Figure 4b displays the differences of the group based mean values of interference of the active TMS experiment minus the sham control experiment for the 30 stimulation targets. Supplementary Fig. 1 shows the

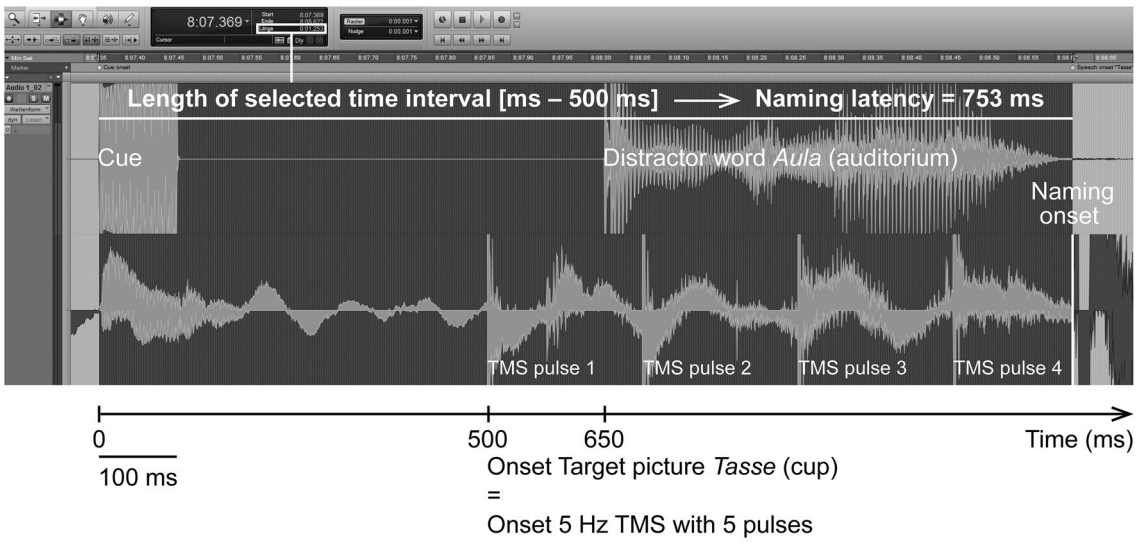

Fig. 3 Analysis of naming latencies. Naming latencies on a milliseconds scale were assessed offline by identification of the cue onset and the onset of speech in the audio track and by subsequent subtraction of 500 ms from the selected time interval using the software Pro Tools 10 (Avid Technology, Inc., Burlington, MA, USA)

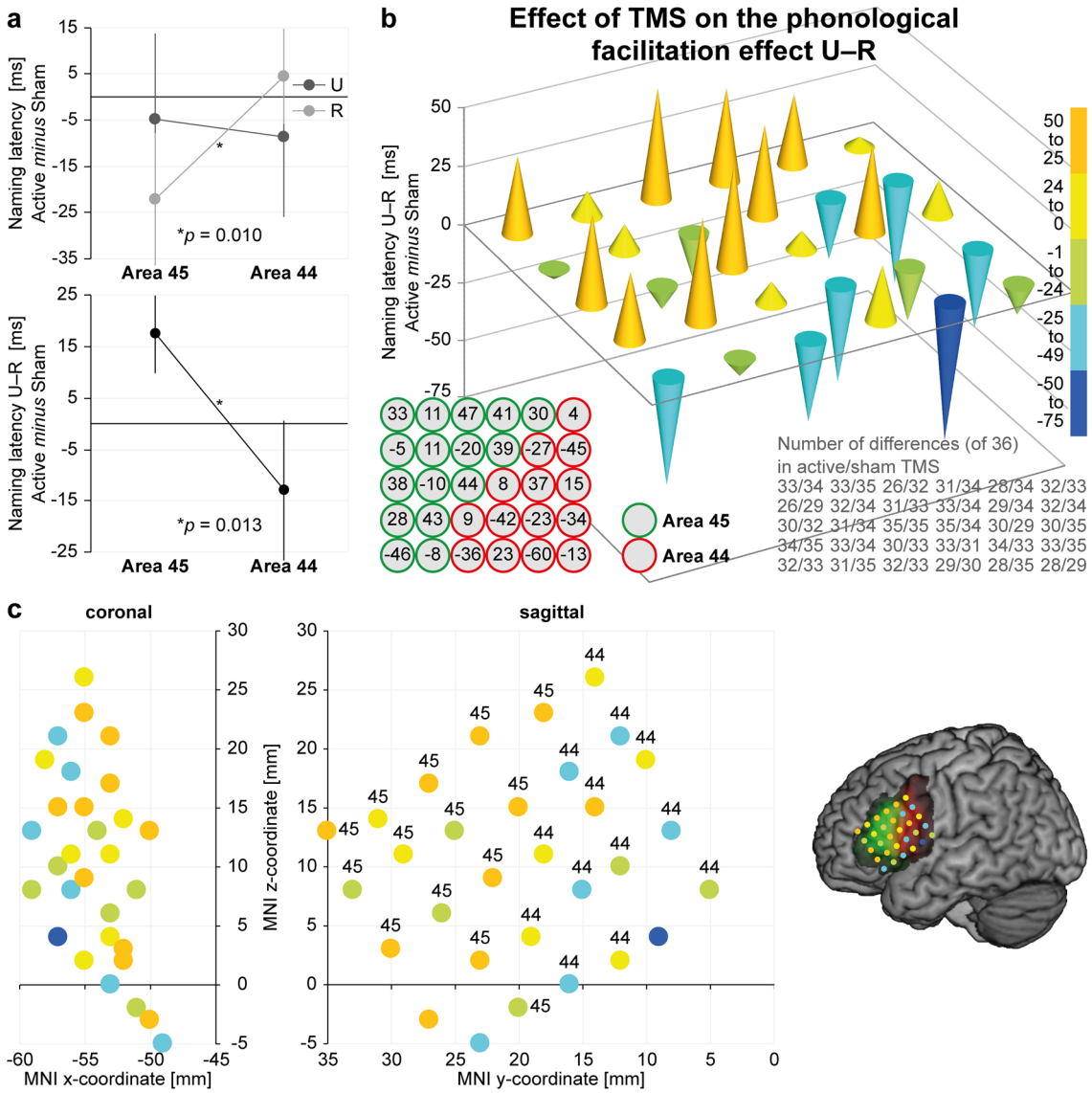

Fig. 4 TMS effects on phonological priming at the 30 stimulation sites, and anatomical assignments. **a** Upper panel: interaction PHONOLOGICAL RELATION × CYTOARCHITECTONIC AREA as obtained by the two-factorial repeated-measures ANOVA on naming latencies from active stimulation minus sham baseline. *U* unrelated target–distractor pairs, *R* related target–distractor pairs. Lower panel: TMS effect on phonological facilitation averaged over the stimulation sites overlapping with probabilistic cytoarchitectonic areas 44 and 45. Group based means and standard errors are displayed. **b** Illustration of the TMS effect on the differential phonological facilitation effect of unrelated [U] minus related [R] target–distractor pairs on naming latencies from active stimulation minus sham baseline for the 30 stimulation targets, i.e., the significant interaction PHONOLOGICAL RELATION × TMS × CYTOARCHITECTONIC AREA as reported in detail in the supplement. Group based mean naming latencies are shown per stimulation site in a schematic illustration with red and green edging according to the overlap with probabilistic cytoarchitectonic areas 44 and 45, respectively. The number of differences U–R per stimulation site (of 36 possible differences, i.e., maximally three differences per participant by 12 participants) contributing to the statistical analysis is indicated for active and sham TMS. **c** Illustration of the center of mass MNI coordinates of the TMS-related stimulation clusters in coronal and sagittal plane, including related color codes, as well as the schematic illustration of the stimulation target grid with these color codes, overlaid on the left view of the volume rendered MNI template using the software MRIcron Version 6/2015 (http://www.nitrc.org/projects/mricron/) with superimposed probabilistic cytoarchitectonic maps of both area 44 (red) and area 45 (green). If a center of mass was assigned to the probabilistic cytoarchitectonic area 44 or 45, the respective number is shown at each center of mass MNI coordinate in the sagittal plane.

group based mean raw naming latencies at the 30 stimulation sites, separately for unrelated and related target–distractor pairs as well as the active and the sham TMS experiment.

The group based statistical analyses were performed using IBM© (New York, NY, USA) SPSS© Statistics Version 22.0.0.0. To test for TMS effects of active

stimulation, we (1) aggregated the maximally three raw naming latencies for all stimulation clusters overlapping with probabilistic cytoarchitectonic area 44 (targets 1, 2, 3, 4, 7, 8, 9, 10, 13, 14, 15, 19, 20, and 25; see Table 1, Figs. 4c, and 5) and 45 (targets 5, 6, 11, 12, 16, 17, 18, 21, 22, 23, 24, 26, 27, 28, 29, and 30; see Table 1, Figs. 4c, and 5) per participant, separately for the conditions with unrelated and related target–distractor pairs both for the active TMS and the sham control condition, and (2) subtracted those aggregated values for the sham baseline condition from the aggregated values for active TMS. Here, negative values indicate decelerated naming latencies under active TMS as compared to sham stimulation, and positive values indicate accelerated naming latencies under active TMS as compared to sham stimulation. For the statistical analysis, we (3) subjected these participant-wise naming latencies from active stimulation minus sham baseline to a two-factorial repeated-measures analysis of variance (ANOVA) with the two-level factors PHONOLOGICAL RELATION (unrelated/related target–distractor pairs) and CYTOARCHITECTONIC AREA (44/45). The significance level for the two-tailed paired *t* tests, which was used to analyze simple main effects, was adjusted to $p = 0.025$ (corresponding to

Table 1 Left macro-anatomical structure and MNI coordinates (*x*, *y*, *z*) of the center of mass of the 30 TMS-related functional clusters as well as cytoarchitectonic area(s) ($Area_{cyto}$) and probability for the respective cytoarchitectonic area(s). Stimulation cluster represents the stimulation markers which were recorded simultaneously with each stimulation onset. Thirty merged stimulation markers, each including four stimulation markers reflecting the mapping repetitions were generated for each participant. Individual TMS-based *volumes of interest* were then normalized and merged per stimulation target across participants

TMS site	Macro-anatomical structure	MNI coordinates			$Area_{cyto}$	Probability for $Area_{cyto}$ in % [for surrounding voxels]
		x	*y*	*z*		
Target 1	Rolandic operculum	−59	5	8	**Area 44**	**34 [29–41]**
Target 2	Rolandic operculum	−57	9	4	Area 44	31 [25–37]
Target 3	Inferior frontal gyrus (Pars opercularis)	−55	12	2	**Area 44**/Area 45	**50 [36–71]**/8 [5–10]
Target 4	Inferior frontal gyrus (Pars opercularis)	−53	16	0	**Area 44**/Area 45	**56 [48–74]**/23 [4–35]
Target 5	Inferior frontal gyrus (Pars triangularis)	−51	20	−2	**Area 45**/Area 44	**42 [31–49]**/11 [0–35]
Target 6	Inferior frontal gyrus (Pars orbitalis)	−49	23	−5	Area 45	16 [10–23]
Target 7	Inferior frontal gyrus (Pars opercularis)	−59	8	13	**Area 44**	**52 [43–62]**
Target 8	Inferior frontal gyrus (Pars opercularis)	−57	12	10	**Area 44**/Area 45	**71 [58–83]**/7 [0–8]
Target 9	Inferior frontal gyrus (Pars opercularis)	−56	15	8	**Area 44**/Area 45	**70 [70–83]**/25 [6–28]
Target 10	Inferior frontal gyrus (Pars triangularis)	−53	19	4	**Area 44**/Area 45	**44 [24–59]**/21 [13–29]
Target 11	Inferior frontal gyrus (Pars triangularis)	−52	23	2	**Area 45**	**51 [35–65]**
Target 12	Inferior frontal gyrus (Pars orbitalis)	−50	27	−3	Area 45	12 [10–31]
Target 13	Inferior frontal gyrus (Pars opercularis)	−58	10	19	**Area 44**	58 [44–64]
Target 14	Inferior frontal gyrus (Pars opercularis)	−57	14	15	**Area 44**/Area 45	**71 [57–81]**/25 [0–32]
Target 15	Inferior frontal gyrus (Pars triangularis)	−56	18	11	**Area 44**/Area 45	**68 [45–71]**/26 [22–46]
Target 16	Inferior frontal gyrus (Pars triangularis)	−55	22	9	**Area 45**/Area 44	**42 [29–67]**/10 [7–33]
Target 17	Inferior frontal gyrus (Pars triangularis)	−53	26	6	**Area 45**	**66 [54–73]**
Target 18	Inferior frontal gyrus (Pars triangularis)	−52	30	3	**Area 45**	**41 [16–51]**
Target 19	Inferior frontal gyrus (Pars opercularis)	−57	12	21	**Area 44**/Area 45	**34 [30–56]**/6 [0–18]
Target 20	Inferior frontal gyrus (Pars opercularis)	−56	16	18	**Area 44**/Area 45	**62 [40–72]**/38 [28–47]
Target 21	Inferior frontal gyrus (Pars triangularis)	−55	20	15	**Area 45**/Area 44	**50 [43–58]**/27 [16–42]
Target 22	Inferior frontal gyrus (Pars triangularis)	−54	25	13	**Area 45**/Area 44	**53 [40–75]**/11 [9–12]
Target 23	Inferior frontal gyrus (Pars triangularis)	−53	29	11	**Area 45**	**86 [75–89]**
Target 24	Inferior frontal gyrus (Pars triangularis)	−51	33	8	**Area 45**	**49 [33–66]**
Target 25	Inferior frontal gyrus (Pars opercularis)	−55	14	26	**Area 44**/Area 45	**58 [29–70]**/17 [8–31]
Target 26	Inferior frontal gyrus (Pars triangularis)	−55	18	23	**Area 45**/Area 44	**33 [24–48]**/24 [15–36]
Target 27	Inferior frontal gyrus (Pars triangularis)	−53	23	21	**Area 45**	**43 [32–72]**
Target 28	Inferior frontal gyrus (Pars triangularis)	−53	27	17	**Area 45**	**53 [41–77]**
Target 29	Inferior frontal gyrus (Pars triangularis)	−52	31	14	**Area 45**	**78 [74–90]**
Target 30	Inferior frontal gyrus (Pars triangularis)	−50	35	13	**Area 45**	**49 [33–61]**

If the voxel can be assigned to a cytoarchitectonic area, the $Area_{cyto}$ and the probability are indicated in bold

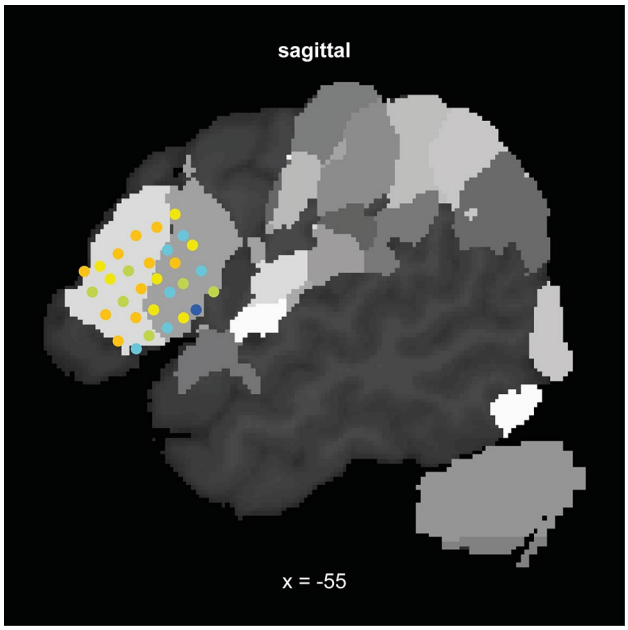

Fig. 5 Overlap with probabilistic cytoarchitectonic maps. Overlap of the center of mass MNI coordinates with the probabilistic cytoarchitectonic areas 44 and 45 as exported by the Anatomy Toolbox (see Table 1 for cytoarchitectonic probabilities). Color codes were assigned to the stimulation targets according to the color scale in Fig. 4b. Note that all x coordinates were projected to $x = -55$ for illustration purposes

uncorrected $p < 0.05$) by applying Bonferroni correction for multiple comparisons (here two tests for analyzing each of the simple main effects). ANOVA effect sizes were estimated as partial eta^2 values. To estimate the achieved power for the paired t tests, we computed Cohen's d_z employing the program G*Power (http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3/). Please see the Supplement for the basic repeated-measures ANOVA on the aggregated (maximally three) raw naming latencies with the two-level factor TMS (active/sham) as the additional third within-subjects factor.

In addition, for each of the 30 stimulation targets we calculated (1) a one sample t test of the interference value for active stimulation, i.e., the aggregated three (at maximum, depending on the number of valid trials) differences of naming latencies of 'unrelated minus related' distractors with the same target, versus the estimated expected value 'mean (of 30 targets) interference value for sham stimulation' of 52 ms and (2) a one sample t test of the interference value for active stimulation versus the estimated expected value 'mean interference value for sham stimulation' of the respective stimulation target (see third column in Supplementary Table). We also calculated (3) paired t tests for each of the 30 stimulation targets with the interference values of active versus sham stimulation.

Generation of TMS-based volumes of interest, normalization, and anatomical labeling

The procedure of processing the stimulation markers for anatomical assignment at the group level is comparable to that previously described in detail (Sakreida et al. 2018). In summary, stimulation markers from 180 trials of active TMS were projected perpendicular onto the brain surface and exported as single 1 mm^3 voxel *volume of interest* into the NIfTI file format, followed by merging the single voxel volumes (up to six, depending on the number of valid trials) from repeated stimulations per target. This generated 30 *volumes of interest* per participant, corresponding to the 30 stimulation target sites, each of the size of up to six voxels from up to six stimulation trials. The 30 individual TMS-based *volumes of interest* were spatially normalized with the Statistical Parametric Mapping software SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm/) running under MATLAB (Version R2014a; MathWorks, Inc., Natick, MA, USA) to the Montreal Neurological Institute (MNI) standard space, and were finally merged for each stimulation target across participants.

Table 1 lists the left-hemispheric macro-anatomical structure and the MNI coordinates of the center of mass of the 30 cluster TMS-based *volumes of interest* as exported by the SPM Anatomy Toolbox v2.1 (Eickhoff et al. 2005, 2007) with the cluster volume threshold of 48 continuous voxels at minimum. The probability that the center of mass of each of the 30 stimulation clusters overlaps with the probabilistic cytoarchitectonic areas 44 and 45 (Amunts et al. 1999) was quantified by the tool "Cytoarchitectonic coordinates at defined MNI coordinates", and these probability estimates are given in Table 1. In addition to the probability at the directly corresponding voxel, the probability ranges for the surrounding voxels were also calculated by the toolbox and are given in square brackets to inform about the reliability of the anatomical allocation. Bold labeling in Table 1 indicates that a center of mass was assigned to the probabilistic cytoarchitectonic area 44 or 45 in the maximum probability map. Details on the cytoarchitectonic maps of area 44 and area 45 were reported by Amunts et al. (1999).

Results

Exclusion of item effects

Though we controlled our stimulus set for homogeneous word frequencies in spoken German language to avoid any covariation of lexical frequency with reaction times, we analyzed the possible impact of specific items of the word material containing 90 two-syllabic German nouns on naming latencies. We therefore calculated the mean naming

latency per target picture across 12 participants, separately for the unrelated and related target–distractor trial as well as the sham and the active TMS condition. Naming latencies in all conditions were not found to correlate with the word frequency in spoken German language (CELEX database; Baayen et al. 1996): naming latencies for target pictures with unrelated distractor words during sham TMS (Pearson $r = -0.062$, $p = 0.561$), naming latencies for target pictures with related distractor words during sham TMS (Pearson $r = -0.071$, $p = 0.508$), naming latencies for target pictures with unrelated distractor words during active TMS (Pearson $r = -0.142$, $p = 0.180$), and naming latencies for target pictures with related distractor words during active TMS (Pearson $r = -0.091$, $p = 0.392$). Findings indicated that specific items of the word material presented at specific anatomical positions are unlikely to have any impact on the results.

Pilot experiment

Inaccurate naming responses resulted in the exclusion of 4.1 ± 0.8% of 180 trials on average (range 2.8–5.0%). The mean interference value, i.e., the mean difference of unrelated target–distractor pairs and related target–distractor pairs, across the five participants was 76 ± 40 ms (range 43–144 ms), showing a phonological priming effect. It is important to mention that in this pilot experiment without any TMS, we could not calculate the interference value per stimulation target as described above, but were required to consider the difference of naming latencies of all 90 target pictures with their unrelated distractors and their related auditory distractor words, respectively. Thus, the mean interference value per participant involved 90 differences at maximum (depending on the number of valid trials there was a range of 82–86 valid differences).

TMS language mapping results

In the control experiment using sham stimulation, the proportion of trials, i.e., naming latencies excluded due to inaccurate naming responses, was comparable to the pilot experiment without stimulation (mean = 5.0 ± 4.5% of 180 trials, range 0.6–15.0%) resulting in a mean of 83 ± 6 valid differences (of 90 differences at maximum). A minor overall proportion of trials was excluded from the analysis of the active stimulation experiment (mean = 7.9 ± 5.9% of 180 trials, range 2.8–20.0%); thus, 78 ± 8 valid differences on average (of a maximum of 90 differences) entered the analysis. In Fig. 4b, the number of differences 'unrelated minus related' per stimulation site (of 36 possible differences, i.e., maximally three differences per participant by 12 participants) contributing to the statistical analysis is indicated separately for active TMS and sham baseline. We considered this number of values to be sufficient, though we observed slightly more errors in three participants during both active TMS (error rates of 15.5, 16.1, and 20.0%) and sham stimulation (error rates of 9.4, 11.7, and 15.0%). Overall phonological facilitation in these three participants of 99/49, 39/43, and 26/81 ms in the active/sham session, respectively, was, however, no outlier as compared to the group statistics (active TMS: mean = 56 ± 32 ms, range 15–110 ms; sham stimulation: 52 ± 22 ms, range 18–87 ms).

The participant wise naming latencies from active stimulation minus sham baseline were analyzed by a two-factorial repeated-measures ANOVA which revealed no main effect of the two-level factor PHONOLOGICAL RELATION ($F_{1,11} = 0.057$; $p = 0.816$; $\eta_p^2 = 0.005$) and a marginal ($0.05 < p < 0.10$) main effect of the two-level factor CYTOARCHITECTONIC AREA ($F_{1,11} = 3.664$; $p = 0.082$; $\eta_p^2 = 0.250$) with higher means for area 44 (mean = −2.063) as compared to area 45 (mean = −13.427). The interaction PHONOLOGICAL RELATION × CYTOARCHITECTONIC AREA yielded statistical significance ($F_{1,11} = 6.629$; $p = 0.026$; $\eta_p^2 = 0.376$), indicating a differential TMS-induced effect of naming latencies for unrelated and related target–distractor pairs depending on stimulation at targets overlapping with probabilistic cytoarchitectonic areas 44 and 45. Thus, this interaction requires analysis of simple main effects using paired *t* tests (see upper panel in Fig. 4a). Please see the Supplement for the basic three-factorial repeated-measures ANOVA on the aggregated maximally three raw naming latencies with TMS as the additional third repeated-measures factor.

The analysis of simple main effects revealed the following: The naming latencies of unrelated target–distractor pairs (U) during active as compared to sham TMS did not differ from related target–distractor pairs (R) when stimulating at targets overlapping with probabilistic cytoarchitectonic area 44 (U_44 versus R_44: $t_{11} = -0.962$; $p = 0.357$; $d_z = 0.278$). The comparison 'U_45 versus R_45' did not reach the $p = 0.025$ for each of the two tests for the simple main effect of factor PHONOLOGICAL RELATION ($t_{11} = 2.315$; $p = 0.041$; $d_z = 0.668$). For the analysis of the simple main effects of factor CYTOARCHITECTONIC AREA, we found that the comparison of the naming latencies for unrelated target–distractor pairs (U) during active as compared to sham stimulation TMS did not differ for stimulation at targets overlapping with probabilistic cytoarchitectonic area 44 as compared to area 45 (U_44 versus U_45: $t_{11} = -0.458$; $p = 0.656$; $d_z = 0.132$), but we found the comparison for related target–distractor pairs (R) to yield a significant difference between areas 44 and 45 bearing with the adjusted significance level of $p = 0.025$ (R_44 versus R_45: $t_{11} = 3.118$; $p = 0.010$; $d_z = 0.900$). The TMS effect was larger at targets in area 44 (mean R_44 = 4.411) as compared to area 45 (mean R_45 = −22.078), driven by prolonged naming

latencies for related target–distractor pairs when stimulating at targets in area 44 as compared to area 45.

To visualize our hypothesis that the inhibitory effects of TMS on language processing would reduce the phonological priming effect (as characterized by longer naming latencies when presenting unrelated target–distractor pairs compared to related target–distractor pairs which accelerate naming responses), we displayed the TMS-induced differential effect 'U minus R' in Fig. 4b. Negative differences/peaks indicate reduced phonological priming due to TMS, while positive differences/peaks mark a behavioral effect of acceleration due to phonological priming. To confirm the anatomical specificity of TMS-induced effects as already yielded by the 2×2 ANOVA, we calculated a one-tailed paired t test for the directional hypothesis of a reduced phonological priming effect in area 44 as compared to area 45 (see lower panel of Fig. 4a). As expected, the negative values associated with area 44 (mean $= -12.946 \pm 46.607$) differed significantly from the positive values associated with area 45 (mean $= 17.302 \pm 25.890$): $t_{11} = -2.589$; $p = 0.013$; $d_z = 0.748$.

To sum up, our results point to a reduced phonological priming effect due to active TMS specifically at sites overlapping with probabilistic cytoarchitectonic area 44, while stimulation at sites overlapping with probabilistic cytoarchitectonic area 45 does not seem to have an effect on phonological priming. In fact, at these anterior stimulation sites phonological priming occurred as shown by larger differences when subtracting accelerated (facilitated) naming latencies linked with the related target–distractor pairs from the naming latencies of the unrelated target–distractor pairs.

Results of the t tests for each single stimulation target are shown in the Supplementary Table. These specific difference analyses using one-sample t tests and paired t tests pointed to relevant TMS-induced reduction of the phonological priming effect at targets 2, 6, and 19, whereas at targets 11, 16, and 18 accelerated naming responses seemed to be associated with any sustained phonological priming despite TMS (see Fig. 4b and Supplementary Table).

Discussion

First, we will discuss the novel introduction of a reaction time based picture–word interference paradigm in language mapping with neuro-navigated TMS. Subsequently, we will discuss the found TMS-induced inhibitory effect on phonological processing in area 44 as compared to the previous data from both invasive and non-invasive brain stimulation studies as well as functional imaging data. Finally, we will give an outlook and discuss implications for future research.

Introduction of a picture–word interference paradigm in TMS language mapping

In this study, we introduced for the first time a reaction time based interference paradigm into the neurophysiological cortical mapping of language functions with TMS. The phonological picture–word interference paradigm was established in numerous behavioral experiments to investigate phonological priming and its time course (see e.g., Schriefers et al. 1990; Meyer and Schriefers 1991; Damian and Martin 1999; Jescheniak and Schriefers 2001; Jescheniak et al. 2003), and was also employed in brain stimulation studies using transcranial direct current stimulation (tDCS; Pisoni et al. 2017; see also Henseler et al. 2014, for application of a semantic picture–word interference paradigm). We hypothesized that the inhibitory effects of TMS on language processing would reduce the cognitive effect of phonological priming. In a pilot experiment without TMS we could confirm a robust phonological priming effect with our stimulus material. Active TMS as compared to sham TMS indeed induced an inhibition (i.e., reduction) of the facilitating effects of phonologically related as compared to unrelated target–distractor pairs on the naming latencies. Thus, we were able to address and control the specific level of phonological processing directly by the paradigm. Interval-scaled naming latencies served as the quantitative dependent variable in data evaluation. As yet, studies on TMS language mapping (e.g., Lioumis et al. 2012; Picht et al. 2013; Tarapore et al. 2013; Rösler et al. 2014; Rogić et al. 2014; Hauck et al. 2015) and invasive direct cortical stimulation (DCS) mapping (e.g., Duffau 2007; Duffau et al. 2003a, 2008; Ojemann et al. 1989, 2008; Tate et al. 2014) related the TMS-induced erroneous naming output—mostly in a simple object naming paradigm—to different levels of language processing. In most protocols, qualitative error categorization by type and frequency follows a classification scheme suggested by Corina et al. (2010) for intraoperative electrical mapping in neurosurgical procedures. Although we previously found a very good inter-rater agreement in qualitative data evaluation conducted by speech-language therapists (Sakreida et al. 2017), error rating remains a rather subjective approach which may be accompanied by a higher degree of variance in the data. In addition, qualitative data analysis requires the need to distinguish TMS-induced speech and language errors from side effects of stimulation such as discomfort and muscle twitching. In contrast, our reaction time-based interference paradigm allows for specific exploration of language processing proper.

Inhibition of phonological processing in area 44

We found reduced phonological facilitation of naming latencies under active as compared to sham TMS at stimulation

sites overlapping with probabilistic cytoarchitectonic area 44. No such effect was observed in area 45 (in contrast, the data suggest some kind of opposite effect there, as discussed below). This is in line with our hypothesis of anatomical specificity of TMS-induced inhibition of the phonological priming effect. Phonological inhibition occurred at stimulation sites overlapping with entire area 44, which appears to be in contradiction to the previously described focus of TMS inhibition in naming close to the inferior frontal junction (Sakreida et al. 2018). However, this previous focus of TMS susceptibility reflected mainly so-called performance errors, which may include phonological aspects of speech production, but also rather unspecific impact from 'motor-associated' white matter fiber tracts such as component I of the superior longitudinal fasciculus (which terminates in the middle/dorsal premotor cortex and supplementary motor area) and the frontal aslant tract (which connects the dorsal inferior frontal gyrus with the supplementary motor area and the pre-supplementary motor area, Catani et al. 2012, 2013; Kinoshita et al. 2015). In contrast, the arcuate fasciculus which supports language processing from temporo-parietal to frontal cortical areas (Catani et al. 2005; Friederici 2009, 2011, 2015) is assumed to subserve phonological processing that we found to be affected by TMS. In recent models of language processing, the arcuate fasciculus together with the ventral component III of the superior longitudinal fasciculus forms the so-called "dorsal pathway for language" which connects the posterior superior temporal gyrus with area 44, passing through the inferior parietal lobule (Saur et al. 2008, 2010). We consider our findings in line with these models, and with the elicitation of phonemic paraphasias by stimulation of fibers of the dorsal pathway in DCS mapping (Duffau et al. 2002, 2003b; Moritz-Gasser et al. 2009; Fernández Coello et al. 2013).

Behavioral data in a lexical decision paradigm revealed the need of lexical access to initiate phonological priming (Kotz et al. 2010). This lexical-phonological interaction was specifically interfered by online single-pulse TMS over the pars opercularis of the inferior frontal gyrus. Kotz et al. (2010) concluded: "It is likely that two distinct processes act in the frontal lobe at the same time. The first, potentially located in the upper portion of the ventral pre-motor cortex, could be considered a low-level motor resonance, involved in the analysis of phonemes, a process that is meaning independent. The second, located in the pars opercularis (Brodmann area 44) may be concerned with word-level analysis." (p. 10; see also Meister et al. 2012 and Roy et al. 2008, for further support of a motor resonance effect during phonological processing). Repetitive TMS data by Berent et al. (2015) supported the hypothesis that speech processing indeed automatically triggers motor action, but argues that the language and motor system are not causally linked to computation of linguistic structure.

In the present study, we found preserved, and even enhanced facilitation at more anterior stimulation targets overlapping with probabilistic area 45. The apparent additional facilitation even drives the statistically significant interaction in the basic three-factorial ANOVA on collapsed naming latencies comparing areas 44 and 45 (see Supplement). This pattern does not allow for an unequivocal conclusion about the differential effects of TMS over these areas. Three possible explanations, partially complementing each other, could account for this effect. (A) Without additional constraints, this pattern might even suggest some kind of language-specific TMS effect solely over area 45, the reduction of the phonological facilitation effect in area 44 occurring through shorter naming latencies for unrelated target–distractor pairs. (B) However, there is ample evidence for an inhibitory effect of TMS on language production and this would fit with the lack of phonological facilitation in area 44 as discussed above. Moreover, the illustrative Supplementary Fig. 2 suggests shorter latencies under active TMS as compared to sham TMS stimulation in all conditions except for the related target–distractor pairs in area 44. This may hint at a potential effect of raised attention and expectation of discomfort during active TMS. Decreased response times and possibly even enhanced facilitation may occur, e.g., due to the more startling effect from active as compared to sham TMS (Smith et al. 2019), although sham coils are specifically designed to simulate the extracortical effects of TMS. The increment in response time differences between active and sham TMS at anterior stimulation targets might thus indicate that such an unspecific effect at all stimulation sites was abolished by TMS-induced inhibition within area 44, but not within area 45. Alternatively, discomfort might have been stronger at more anterior stimulation sites, e.g., through involvement of anterior meningeal branches of the trigeminal nerve. FMRI data reported by Heim et al. (2015) showing a specific increase of activation in the left inferior frontal gyrus (area 45) in children with reading problems after visual attention training, as compared to training in the domains of visual word recognition and phonology, might also support this hypothesis of raised attention. (C) TMS-induced phonological facilitation at sites in area 45 directly neighboring reduced facilitation in area 44 could reflect a compensatory mechanism, with the downregulation resulting in an adjacent boost of activation. The abolishment of an inhibitory influence of area 44 on area 45 in the active TMS condition might further contribute to this apparent upregulation, as suggested by dynamic causal modelling of areas 44 and 45 during language production by Heim et al. (2009a). Hartwigsen et al. (2017) likewise reported a compensatory recruitment or beneficial contribution of the supramarginal gyrus in the phonological network in neighborhood to the angular gyrus in the semantic network which was focally suppressed by continuous theta-burst stimulation,

and assumed this upregulation to reflect a mechanism to maintain task processing. In this study, different underlying structural properties could account for such mechanism. It would thus be interesting to show our data in overlap with the maps of areas 44 and 45 including the sub-parcellations of anterior–dorsal area 44d, posterior–ventral area 44v, anterior area 45a, and posterior area 45p as obtained in neurotransmitter mapping studies (Amunts et al. 2010; Zilles et al. 2015). In our view, explanations (B) and possibly (C) are best suited to account for the known inhibitory effects of TMS on language production. It must be emphasized, though all of the above interpretations are of rather hypothetical nature.

Pisoni et al. (2017) found that anodal tDCS over the left superior temporal gyrus before a picture–word interference task reduced phonological facilitation by decreasing reaction times in phonologically unrelated trials. In contrast, stimulation over the left inferior frontal gyrus did not affect the phonological priming effect, as slowed naming responses were found to be associated with both phonologically related and unrelated distractors. The authors suggested that the left inferior frontal gyrus is rather involved in attentional and control processes to be associated with managing the interference in this paradigm. In their study, Pisoni et al. (2017) positioned the frontal stimulation target at "the crossing point between Fz–T3 Cz–F7 electrode sites in the EEG 10–20 electrodes positioning system" (p. 110), which is clearly located anterior to area 44, or the pars opercularis of the inferior frontal gyrus. Presumably, their stimulation had been applied too anteriorly to affect phonological processing. Beyond that, non-focal effects on neuronal excitability induced by tDCS (Nitsche and Paulus 2000; Nitsche et al. 2008) are not fully comparable to the more focal effects of neuro-navigated TMS.

Phonological processing as a fundamental step in the perception and processing of speech is assumed to occur in a left-lateralized anatomical network connecting the posterior part of the superior temporal cortex and the supramarginal gyrus with the pars opercularis of the inferior frontal gyrus (Cattaneo 2013). As yet, the neural correlates underlying the phonological priming effect have rarely been investigated by functional imaging. De Zubicaray et al. (2002) employed a picture–word interference paradigm with written distractors in fMRI for the first time and found the left posterior middle and superior temporal gyrus, the so-called Wernicke's area, to be specifically involved in phonological retrieval during word production. Early behavioral studies have already attributed the phonological priming effect to the stage of phonological retrieval or encoding (e.g., Schriefers et al. 1990; Starreveld and La Heij 1995; Damian and Martin 1999). De Zubicaray et al. (2002) interpreted their finding to be in line with the cognitive model of word production by Indefrey and Levelt (2000, 2004; see also Indefrey 2011; and the basic studies by Levelt 1989; Levelt et al. 1999) that suggested activation in left posterior middle and superior temporal gyrus occurring at 200–400 ms after presentation of the object picture, but may last until the stages of phonetic encoding and articulation (Abel et al. 2009). These processing stages have been anatomically associated with Broca's region and premotor/motor cortex in the meta-analysis on picture naming and word generation tasks by Indefrey and Levelt (2004)—and are thus exposed to the effects of TMS directed at this region. Likewise, de Zubicaray and McMahon (2009) reported decreased activity accompanied by significant behavioral priming effects in left mid-to-posterior superior temporal gyrus during naming with phonologically related spoken distractors. They interpreted these findings of decreased activity as an indication for reduced competition during lexical selection due to phonological priming.

In contrast, Abel et al. (2009, 2012) reported activations within the left supramarginal gyrus and inferior parietal lobule (Brodmann area 40), when contrasting phonologically related with unrelated spoken distractors. However, increased activation of left mid-to-posterior superior temporal gyrus (Brodmann area 22) was revealed by a conjunction analysis concerned exclusively with phonologically related distractors. Increased activation in bilateral supramarginal gyrus associated with phonologically related relative to unrelated written distractor words during picture naming was also observed in the fMRI study by Diaz et al. (2014). Moreover, bilateral inferior parietal cortex and left insula were found to be activated for the phonological condition relative to both semantic conditions. Although there are some obvious inconsistencies in the functional imaging data reported so far, the above findings highlight the role of left posterior middle and superior temporal gyrus as well as left supramarginal gyrus in phonological priming in the context of a picture–word interference paradigm.

Several TMS studies addressed phonological processing and/or its time course by focusing on the causal functional contribution of anatomical areas yielding activation in fMRI studies. However, TMS also allows to investigate the contribution of areas that are not found to be activated by the blood-oxygenation-level-dependent (BOLD) contrast of fMRI in correlation to the task, possibly because these areas significantly contribute to several tasks, but 'disappear' in the contrast. Targeted at the supramarginal gyrus as found in the aforementioned fMRI studies, chronometric single-pulse TMS slowed reaction times during reading of visual presented words in the phonological task relative to the semantic and visual control task, with an early initiation and sustainability (Sliwinska et al. 2012). Deschamps et al. (2014), however, suggested the supramarginal gyrus to contribute rather to the more general cognitive function of verbal working memory than to the specific domain of phonology. The impact of verbal working memory in tasks

requiring phonological processing seems plausible when presenting either letters or words simultaneously or with a delay for a judgment regarding phonological aspects. Phonologically based verbal working memory processes have also been interfered by stimulation of the pars opercularis of the left inferior frontal gyrus (Nixon et al. 2004; see also Gough et al. 2005). Hartwigsen and colleagues used high-frequency repetitive TMS during phonological and semantic word decisions to investigate bilateral contribution of the supramarginal gyrus (Hartwigsen et al. 2010a) and inferior frontal gyrus (Hartwigsen et al. 2010b). Left and right as well as bilateral stimulation over the supramarginal gyrus and the posterior (as compared to the anterior) inferior frontal gyrus selectively affected accuracy and reaction times of phonological word decisions, supporting the role of these areas and their fronto-parietal connectivity in phonological processing.

The localization of phonological processing in the posterior inferior frontal gyrus, as revealed in our data, is supported by a multitude of fMRI studies. According to Uddén and Bahlmann (2012), the consistent anatomical location of phonological processing in the posterior rather than the anterior part of left inferior frontal gyrus can be explained by (1) the cyto-, receptor-, and myeloarchitectonic properties, i.e., the node properties or local connectivity of area 44 and (2) the relation of this node to other nodes in the language network, i.e., the global connectivity properties of the language network. Beyond this, considering that language might be processed as sequences of phonemes, syllables, words, and sentences, the role of the posterior inferior frontal gyrus in sequential speech processing appears well-founded (e.g., Price 2010, 2012). In meta-analyses of fMRI data, phonological tasks have been associated anatomically with both the inferior frontal junction area (area 6/area 44) and the area 44 proper (e.g., Lindenberg et al. 2007). Clos et al. (2013) carried out a functional parcellation of the probabilistic cytoarchitectonic area 44 by meta-analytic connectivity modeling of task-based functional MRI data. Their results indicated five sub-regions featuring distinct connectivity and functional profiles defined in terms of behavioral domains and paradigm classes (see Fig. 6). Two posterior clusters were identified to be primarily associated with phonology, language production (posterior–dorsal cluster 1, red), and rhythmic sequencing (posterior–ventral cluster 4, yellow), whereas three anterior clusters related to language comprehension (anterior–ventral cluster 3, blue), working memory (anterior–dorsal cluster 2, green) and task switching/cognitive control (inferior frontal junction cluster 5, cyan). Figure 6 illustrates the overlap of our sites of TMS-induced phonological inhibition with these functional clusters (grey circles), largely in accordance with their functional role in phonology and rhythmic sequencing.

In summary, functional brain imaging and non-invasive brain stimulation provided complementary evidence for a significant role of the posterior part of Broca's region, aside posterior middle and superior temporal gyrus (Wernicke's area) as well as the supramarginal gyrus in the inferior parietal lobe, in phonological processing. Whereas the entire functional network is shown in fMRI by BOLD contrasts in correlation to a task, TMS as a direct neurophysiological method allows to investigate the causal functional contribution of network components to this task (e.g., Pascual-Leone et al. 1999; Sack and Linden 2003; Ruff et al. 2009). Thus, we consider our data to provide complementary support of fMRI data. Future high-density TMS language mapping studies might also target the posterior regions in the language network as shown by fMRI to characterize structure–function overlap within these areas.

Outlook and implications for future research

Although it is not possible to determine the exact time point of the functional effect from repetitive as opposed to single-pulse TMS (Sandrini et al. 2011), variation in timing of distractor presentation in relation to the onset of stimulation and target picture presentation in an interference paradigm will allow for testing the time course of language processing at a very high temporal resolution. The combination of high temporal resolution with high spatial resolution in the mapping of a target area (see discussion in our previous study Sakreida et al. 2018) could be a unique feature in the application of a reaction time based paradigm in TMS language mapping. Since the interference paradigm allows for the investigation of TMS-induced language inhibition at specific levels of language processing, future paradigms for semantic and syntactic processing will contribute to a comprehensive functional mapping of Broca's region.

In clinical applications such as presurgical planning with brain tumors, TMS offers an individual approach to identify language-related regions (e.g., Espadaler and Conesa 2011; Picht et al. 2013; Tarapore et al. 2013; Rösler et al. 2014; Ille et al. 2015a, b). In analogy with cortical and subcortical electrical brain stimulation, a simple object naming task was employed in most clinical protocols, with qualitative data evaluation. Quantitative data such as naming latencies obtained with an interference paradigm could complement the assessment of qualitative aspects of language processing. However, the feasibility of such a more demanding task must be tested with patients potentially impaired by tumor-related attention deficits, in addition to the evaluation of the signal-to-noise ratio of data at the individual level.

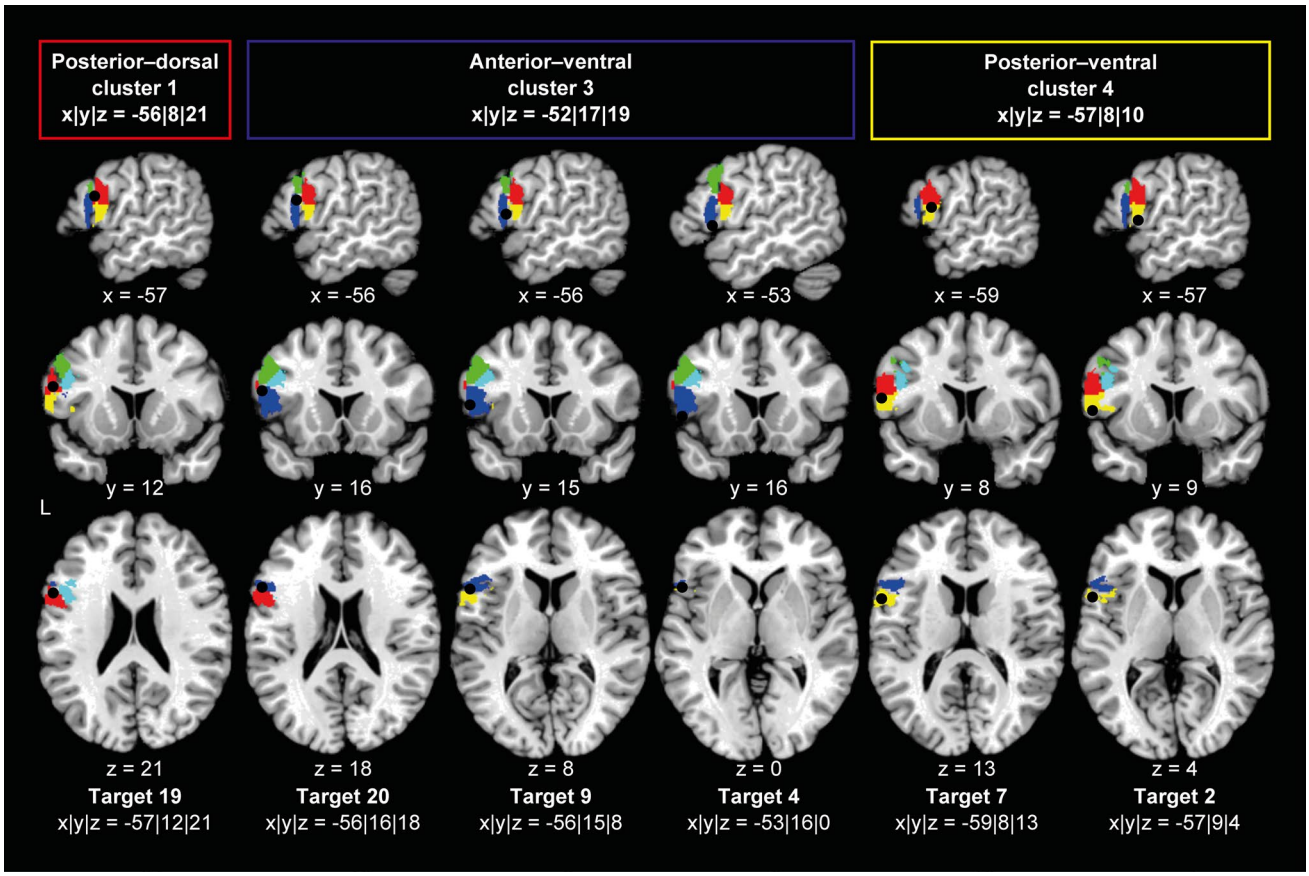

Fig. 6 Overlap of functional clusters as revealed by the meta-analytic connectivity modeling for parcellation of cytoarchitectonic area 44 by Clos et al. (2013) with those stimulation targets/volumes located in area 44 that were found to be related to a reduction of phonological facilitation induced by active as compared to sham TMS in the present study. Black circles indicate target 19 ($x=-57$, $y=12$, $z=21$) overlapping with the posterior–dorsal cluster 1 by Clos et al. (2013) colored in red ($x=-56$, $y=8$, $z=21$), which contributed specifically to phonological processes and overt articulation of speech, targets 20 ($x=-56$, $y=16$, $z=18$), 9 ($x=-56$, $y=15$, $z=8$), and 4 ($x=-53$, $y=16$, $z=0$) corresponding to the anterior–ventral cluster 3 by Clos et al. colored in blue ($x=-52$, $y=17$, $z=19$), which was associated with various key aspects of language processing such as semantics, syntax, and phonology. Stimulation targets/volumes 7 ($x=-59$, $y=8$, $z=13$) and 2 ($x=-57$, $y=9$, $z=4$) were related to the posterior–ventral cluster 4 in Clos et al. colored in yellow ($x=-57$, $y=8$, $z=10$), which was the only cluster not directly associated with language, but with action imagination and music perception, and thus with rhythmic sequencing. MNI coordinates correspond to the center of mass of the clusters. The NIfTI files (normalized to MNI space) of the five functional clusters from the parcellation of cytoarchitectonic area 44 by Clos et al. were downloaded from: http://www.fz-juelich.de/SharedDocs/Downloads/INM/INM-1/DE/Area44_Parcellation.html?nn=533946 and overlaid on the volume rendered MNI template using the software MRIcron Version 6/2015 (http://www.nitrc.org/projects/mricron/)

Conclusions

For the first time, we introduced an interference paradigm into TMS language mapping. By employing picture–word phonological interference in a naming task with high-resolution mapping in healthy volunteers, we suggest a specific inhibitory effect of TMS on phonological processing in area 44. The introduction of interference employing reaction time measurement in TMS language mapping provides an objective tool for the assessment of qualitative aspects of language processing, which may help to interpret TMS language mapping results in clinical applications. Moreover, interference paradigms allow for studying specific TMS language inhibition at high temporal resolution. Follow-up studies will help to create a comprehensive and dynamic functional mapping of Broca's region for a better understanding of the structure–function relationships within the language network.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no personal financial or institutional interest in any of the materials or devices described in this paper.

Ethical standards Our experimental standards and all procedures performed in this study involving human participants were in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki), as published in the British Medical Journal in 1964, and its later amendments or comparable ethical standards and were approved by the local ethics committee of the Medical Faculty of RWTH Aachen University [EK 054/13]. Prior to investigation, we obtained written informed consent from all our volunteers.

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