

# Chronometric interleaved TMS-fMRI shows state-dependent network effects underlying speech production

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## ABSTRACT

**Introduction:** Speech production engages a distributed network of cortical regions, but the causal dynamics within this system remain incompletely understood. Transcranial magnetic stimulation (TMS) offers a unique opportunity to modulate brain activity and assess functional contributions to behavior. However, the temporal specificity of these effects and how stimulation timing during speech impacts behavior and neural activity remains unclear.

**Materials and methods:** We developed a novel chronometric interleaved TMS-fMRI paradigm to deliver TMS during an overt object naming task while simultaneously recording whole-brain BOLD responses. Stimulation was applied to the left superior temporal gyrus (STG) at two task-relevant stages: during early conceptual processing and during subsequent linguistic processing. Task-related BOLD activation patterns were analyzed across conditions.

**Results:** TMS delivered during linguistic processing consistently induced speech arrest outside of the scanner environment and was associated with increased activation in key language areas, including the inferior frontal gyrus (IFG) and STG. In contrast, stimulation during early conceptual processing had minimal effects on neural activation. These findings suggest that stimulation-induced disruption of speech is mediated by task-state-dependent overactivation rather than suppression.

**Conclusion:** Our results challenge the classic “virtual lesion” view of TMS by demonstrating that stimulation can amplify neural activity in a state-dependent manner. This work establishes a novel methodological framework for temporally precise causal mapping of speech networks and emphasizes the critical role of cognitive state in shaping brain responses to stimulation.

## 1. Introduction

Speech production is a highly complex human ability requiring the precise coordination of multiple neural processes, including conceptual preparation, lexical access, and articulatory planning. Decades of research have provided insights into the functional neuroanatomy of speech production, with models offering detailed spatiotemporal predictions for its underlying processing stages [1–4]. Different stages of speech production are thought to involve distinct brain regions, word retrieval is linked to temporal areas, phonological processing to posterior temporal regions, and articulatory planning to inferior frontal

regions. While these models yield robust spatial and temporal predictions, they are primarily based on correlational evidence from neuroimaging and lesion studies and thus cannot resolve causal relationships or precisely track timing during speech production [5,6].

Here, we address how activity in speech-relevant regions dynamically interacts during different stages of speech production and how state-dependent factors influence these interactions. Functional magnetic resonance imaging (fMRI) offers high spatial resolution, but its limited temporal resolution makes it challenging to capture the millisecond-scale transitions characteristic of language processing. Conversely, electrophysiological methods such as

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electroencephalography (EEG) and magnetoencephalography (MEG) provide high temporal resolution but lack the spatial specificity needed to fully localize neural processes. Mapping the network-level spatio-temporal dynamics of speech production therefore requires an approach that integrates both high temporal and spatial resolution.

Previous studies have leveraged fMRI to delineate the organization of speech production networks. A widely cited meta-analysis of neuroimaging studies by Indefrey and Levelt identified characteristic spatial and temporal activation patterns during speech production [3]. Their model assigns word retrieval to the mid-to-posterior middle temporal gyrus (MTG), phonological code retrieval to the posterior superior temporal gyrus (STG), or Wernicke’s area, and syllabification to the inferior frontal gyrus (IFG), or Broca’s area. Subsequent reviews and updates of this model [4] provided estimated onset times and durations for individual stages of word production. Conceptual processing is thought to predominate during the first 200 ms after stimulus onset, with linguistic processes such as lemma activation, lexeme retrieval, and articulatory preparation emerging around and beyond this time window (Table 1). However, because of the sluggish nature of the BOLD response, fMRI alone cannot directly confirm these timing estimates.

Electrophysiological techniques have helped refine this temporal model. MEG, in particular, provides millisecond-level resolution, allowing researchers to track the sequential activation of language-related brain regions [7]. Findings from MEG and EEG studies confirm a hierarchical progression of neural activation during speech production, supporting prior models [8,9]. MEG studies have demonstrated that word retrieval engages the left temporal cortex around 200 ms post-stimulus, followed by phonological encoding (250–350 ms) and articulatory planning (350–500 ms). EEG studies similarly show early lexical processing (~150–250 ms post-stimulus), followed by phonological and motor-related activity (~300–600 ms). Sequential combinations of fMRI and MEG have improved the reliability of language mapping [10,11]. Still, these methods remain correlational and cannot directly test the causal contributions of individual brain regions to specific stages of speech production.

Transcranial magnetic stimulation (TMS) provides a unique opportunity to directly perturb neural activity and assess the causal role of brain regions involved in speech production. TMS has often been described as creating a “virtual lesion” temporarily disrupting processing in the targeted region [12–16]. When applied during speech production tasks, TMS can delay or disrupt naming by targeting language-relevant regions. [17–21]. Chronometric TMS, in particular, enables the investigation of the temporal characteristics of regional involvement by applying stimulation at specific time windows post-stimulus onset. Schuhmann et al. (2012) employed a neuronavigated, multisite TMS protocol during a picture naming task and found distinct time windows of vulnerability for different regions: the MTG around 225 ms, IFG around 300 ms, and STG around 400 ms. A subsequent replication confirmed these findings with minor methodological adjustments [23, 24]. These studies demonstrate the potential of chronometric TMS for

mapping the temporal organization of speech production. However, because TMS lacks the spatial resolution and whole-brain coverage of imaging methods, it cannot capture network-level effects or determine how stimulation of one region influences activity across the broader language system.

A critical and often underappreciated factor in interpreting TMS results is the state-dependency of stimulation effects. The neural response to TMS depends on the ongoing activity in the targeted region at the moment of stimulation [25–29]. Behavioral and neurophysiological studies have shown that TMS effects differ depending on whether neurons are in an active or resting state. In the motor domain, this distinction is reflected in differences between active and resting motor thresholds [30–32]. Similar principles appear to apply to higher-order cognitive domains [33,34]. A possible explanation for these effects is that neurons with lower activation levels at time of stimulation are more susceptible to TMS compared to neurons with high activation levels; neurons already at the peak of activation might be subject to ceiling effects which could lead to inhibitory outcomes [13,35]. While these state-dependent effects have been documented in various domains, their application to the language system remains rare [22,36–38].

In the present study, we investigate the state-dependent temporal characteristics of speech production using a novel chronometric interleaved TMS-fMRI approach. This method combines the high temporal resolution of TMS with the whole-brain spatial resolution of fMRI, enabling continuous image acquisition during time-locked stimulation [39–41]. This approach has previously been applied successfully in the motor system and other cognitive domains, but has not yet been used to probe causal dynamics in the language network [33,42–46].

We conducted two experiments in healthy native German speakers (Fig. 1). Experiment 1 (Speech mapping) combined fMRI-based functional localization with offline, neuronavigated TMS to identify and functionally verify speech-relevant stimulation sites [21]. Experiment 2 (Online TMS-fMRI) implemented chronometric interleaved TMS-fMRI during an object naming task. Stimulation was delivered to the posterior temporal cortex at two time points corresponding to dominant stages within the unfolding speech production process, here described as conceptual and linguistic processing [4,47,48]. While these processes are known to occur in close temporal proximity and with partial overlap, we used these terms as operational labels to distinguish earlier (stimulus-driven conceptual activation) from later (lexical–phonological) processing stages. Based on prior models of speech production [3,4], we hypothesized that stimulation during conceptual processing would not disrupt naming performance, while stimulation during linguistic processing would lead to speech arrest. Moreover, we expected that TMS effects on the BOLD response would vary depending on the timing of stimulation, reflecting state-dependent network-level dynamics. This study provides the first whole-brain investigation of state-dependent causal interactions in the language system using TMS-fMRI. We provide a novel framework for assessing state-dependent neural perturbations in the language network, advancing models of speech production [49–53]. Our findings challenge the traditional “virtual lesion” model of TMS and support a dynamic, state-sensitive view of brain stimulation effects. This work contributes to a more nuanced understanding of the temporal dynamics of speech production and highlights the value of combining causal and whole-brain imaging approaches in language research.

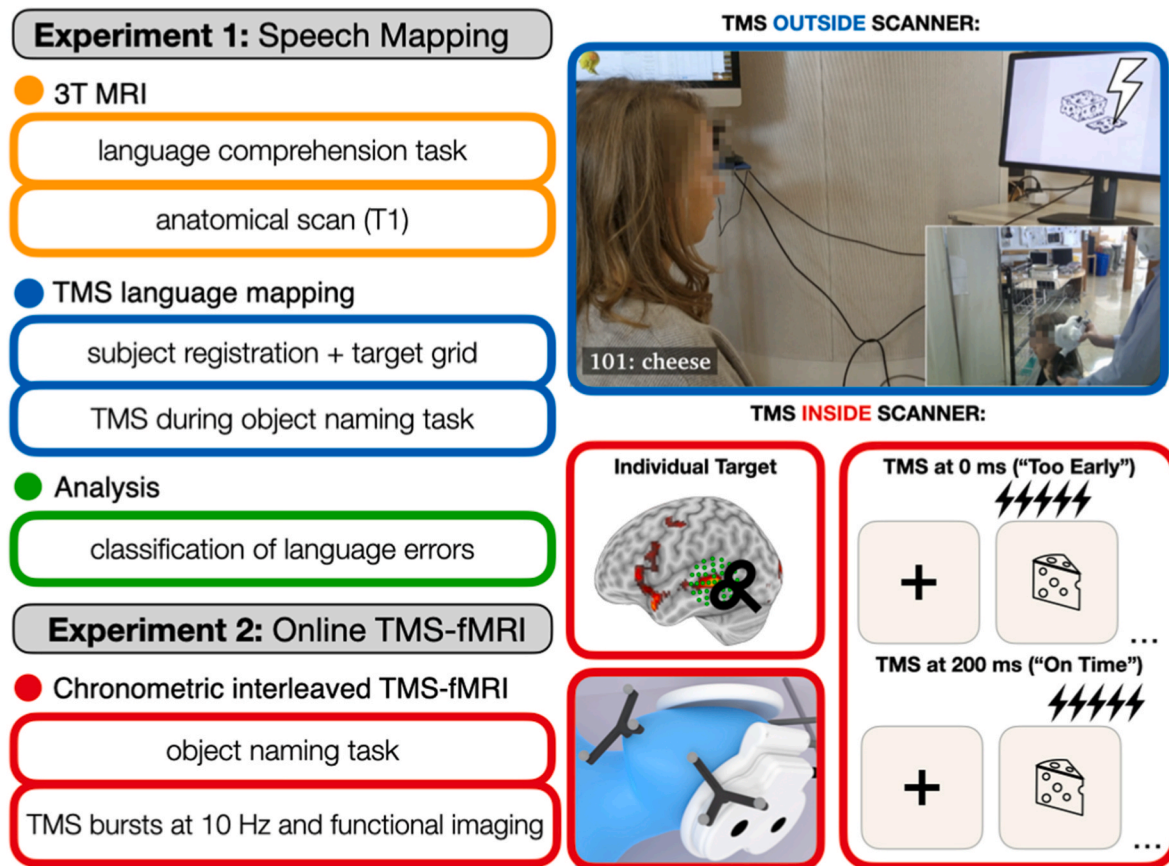
2. Material and methods

2.1. Participants

Twenty-one healthy, right-handed native German speakers (10 female, 11 male, mean age: 25.95, SD: 5.23) participated in this study. All participants were screened for contraindications to MRI and TMS, including implanted devices, claustrophobia, pregnancy as well as history of epilepsy, neurological or psychiatric diseases and severe chronic

**Table 1**  
Estimated Onset Times and Durations for Processes in Speech Production (Adapted from Indefrey, 2011). \*Upper limit \*Continues after the relevant conceptual data for accessing lexicon has been retrieved.

| Processes                  | Onset (ms) | Duration (ms)                         |
|----------------------------|------------|---------------------------------------|
| Conceptual processing:     |            |                                       |
| Conceptual preparation     | 0          | 200*                                  |
| Linguistic processing:     |            |                                       |
| Lemma activation/retrieval | 200        | 75*                                   |
| Articulatory preparation   |            |                                       |
| Phonological retrieval     | 275*       |                                       |
| Syllabification            | 355        | 20 per phoneme,<br>50-55 per syllable |
| Phonetic encoding          | 455*       |                                       |
| Articulation               | 600        |                                       |



**Fig. 1.** Overview of the experimental procedure for speech mapping (Experiment 1) and interleaved TMS-fMRI (Experiment 2). Experiment 1 included an MRI session featuring a language localizer task, followed by a TMS language paradigm conducted outside the scanner. In Experiment 2, chronometric interleaved TMS-fMRI, TMS bursts (10 Hz, 5 pulses at 100 % rMT) were applied to a predefined critical language target during an object naming task, with stimulation delivered at two distinct time points. Stimulation at image onset served as an active control condition.

illnesses. None of the participants reported any language deficits. Participants were recruited from the general public and financially compensated for their participation. The study was approved by the Ethics Board of the Medical University of Vienna and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

## 2.2. General procedure

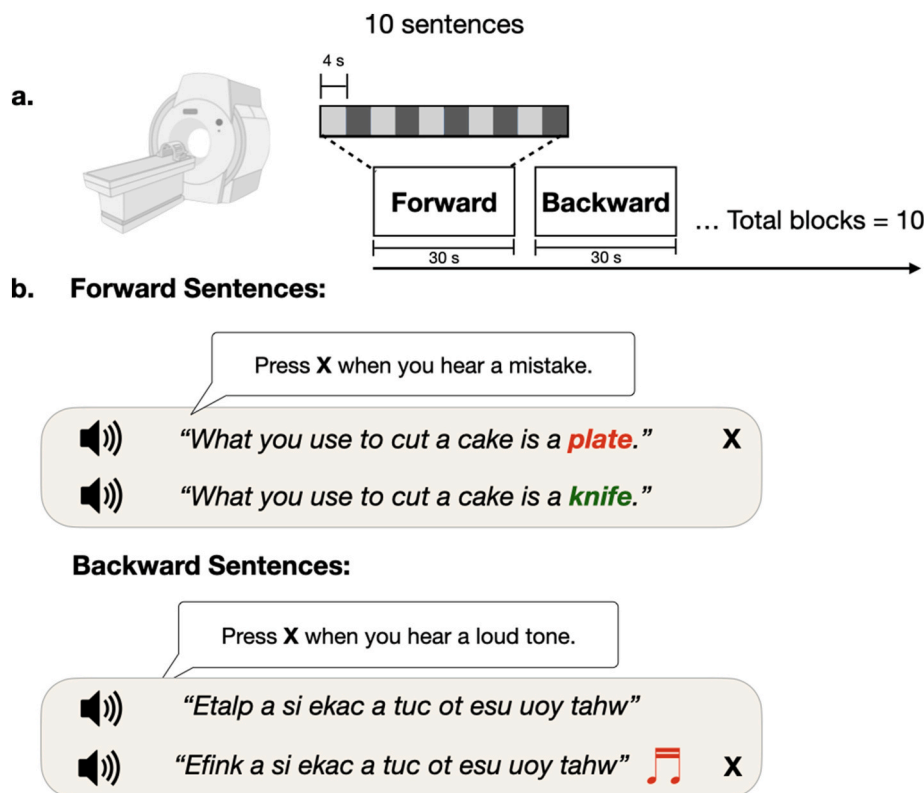
This study consisted of two experiments conducted one week apart. Previous research has demonstrated minimal variability in intra- and inter-observer reliability in repeated language mapping sessions [54]. Experiment 1 aimed to functionally localize language-related areas and identify cortical regions causally linked to speech difficulties using fMRI and TMS mapping. This first experiment followed the same experimental setup as in our previous study [21]. Experiment 2 involved a chronometric interleaved TMS-fMRI paradigm to assess the temporal effects of TMS on language processing during an object naming task. TMS pulses were precisely timed to target two cognitive processing stages: stimulation initiated at picture onset (0 ms delay) during conceptual processing and stimulation initiated at 200 ms post-picture onset during linguistic processing. The chronometric approach was based on prior models of language production and our own pilot data. In preliminary tests outside the scanner, stimulation delivered at 0 ms and 100 ms post-stimulus onset did not consistently induce naming errors, whereas stimulation at 200 ms reliably elicited speech arrest.

## 3. Experiment 1: speech mapping

The TMS language mapping procedure and experimental setup of the first experiment has previously been described [21].

### 3.1. fMRI-Based Localization of Language Networks

Language-relevant cortical areas were localized using a correlative approach by administering an auditory description decision task (ADDT) [55] while functional imaging data was acquired on a 3 T MRI scanner (Siemens PRISMA Fit, 64-channel head-coil) using the CMRR EPI sequence [56] (TR = 1000 ms, TE = 38 ms, flip angle 62°, multiband factor = 4, 40 slices, 500 vol, voxel size = 2.3 × 2.3 × 3 mm<sup>3</sup>). The paradigm (Fig. 2) consisted of alternating blocks of experimental and baseline conditions. The task consisted of 10 blocks (five of each condition), each block lasting 30 s. Each block consisted of 10 stimuli which were presented every 4 s. In the experimental condition participants were presented with sentences either accurately or inaccurately describing a common, concrete noun embedded in the same syntactic frame (e.g., “What you write with is a pen.”, “What you sit on is a window.”). Participants indicated the incorrect items via button press. The sentences from the original paradigm [55] were translated and recorded by a native female German speaker and presented using MRI compatible, passively noise reducing in-ear headphones. In the baseline condition the sentences were played in reverse and some items were followed by a tone. Participants were instructed to indicate the presence of the tone by pressing a button. The baseline items matched the experimental items in required responses, length of utterances and presentation volume. The ADDT paradigm was chosen because it



**Fig. 2. fMRI-Based Localization of Language Networks.** (a) Schematic representation of the auditory description decision task (ADDT) paradigm, showing the sequence of trial blocks. Each block lasted 30 s and contained 10 sentences, each presented for 4 s, with alternating experimental and baseline conditions. (b) Example sentences from the experimental (forward speech) and baseline (backward speech) conditions. "X" marks indicate trials where participants were required to press a button—responding to incorrect descriptions in the experimental condition and to tones in the baseline condition. Functional imaging data were acquired using a 3 T MRI scanner, with preprocessing performed in SPM12.

reliably elicits activation within the core dorsal-stream language network, including the posterior superior temporal and inferior frontal regions, providing robust individual activation maps for defining stimulation targets. This task has been successfully used in previous work [21] to localize posterior temporal regions causally involved in speech disruption.

A T1-weighted image was acquired for anatomical reference (TR = 2100 ms, TE = 3.67 ms, flip angle 8°, voxel size = 1 mm<sup>3</sup> isotropic). Preprocessing of the functional task fMRI data was performed in SPM12 (realignment, normalization to MNI space and smoothing with a Gaussian kernel of 6 mm FWHM).

### 3.2. Neuronavigation-guided TMS for language mapping

TMS language mapping was performed using the MRi-B91 MR-compatible TMS coil connected to a Magventure MagProX100 stimulator (Magventure, Farum, Denmark). For each participant, task-fMRI activation was overlaid onto their anatomical scan using a neuronavigation system (Brainsight 3, Rogue research Inc., Canada) in combination with our in-house developed precision stimulation software (PPS). PSS was developed to optimize TMS precision by integrating neuronavigation, TMS control, and data acquisition. Unlike existing software, PSS actively manages TMS triggering, requiring the operator to engage a foot pedal while ensuring stimulation only occurs when the coil is precisely on target ( $\leq 2$  mm displacement,  $\leq 5^\circ$  tilt/rotation,  $\leq 5$  mm coil-to-cortex distance).

Stimulation intensity was individually calibrated based on each participant's resting motor threshold (MT). The resting MT was defined as the lowest stimulator output that produced at least 5 visible twitches of the right first dorsal interosseous muscle out of 10 consecutive pulses.

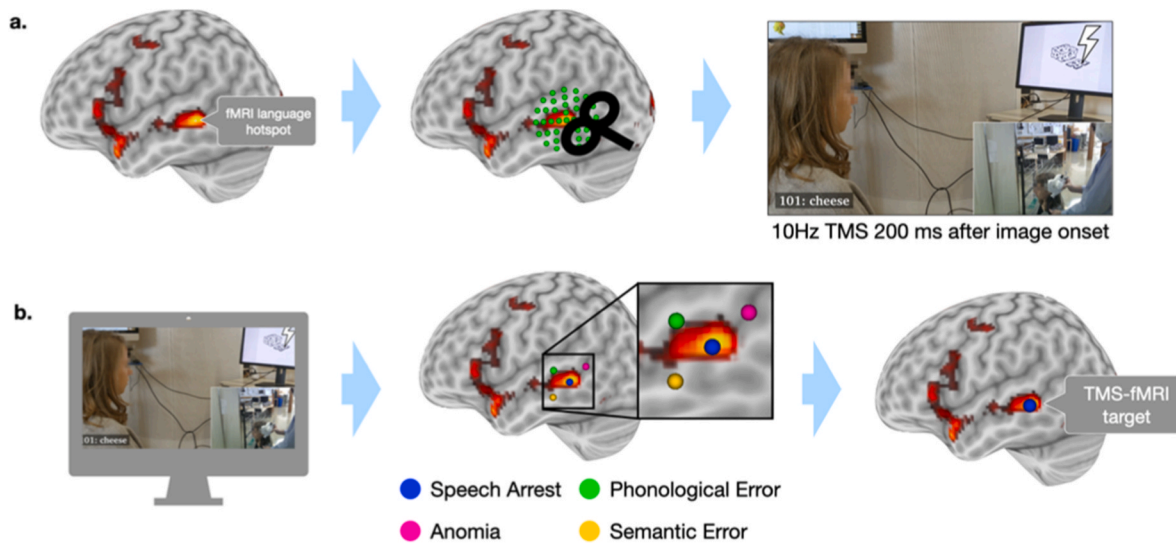
The individual peak activation in the posterior temporal gyrus

defined the center of a circular TMS target grid (5 rings, 40 nodes, 5 mm spacing). Following established posterior language mapping protocols [57], 10 Hz TMS bursts (5 biphasic pulses) were applied to each node, with coil orientation 90° to the gyrus at 100 % of the resting MT. Each node was stimulated three times in a randomized order during an object naming task. Stimuli (60 black-and-white object drawings [58]) were presented for 500 ms, with TMS onset at 200 ms post picture onset to allow for visual processing [47]. The 200 ms delay was tested on a small dataset prior to full data collection, and it consistently resulted in reliable speech arrests. The language mapping procedure was video recorded and data analysis involved detecting and categorizing speech errors [59]. The experimental setup is depicted in Fig. 3. For each subject, the stimulation position leading most reliably to speech arrest/anomia was selected as the TMS-fMRI target for Experiment 2.

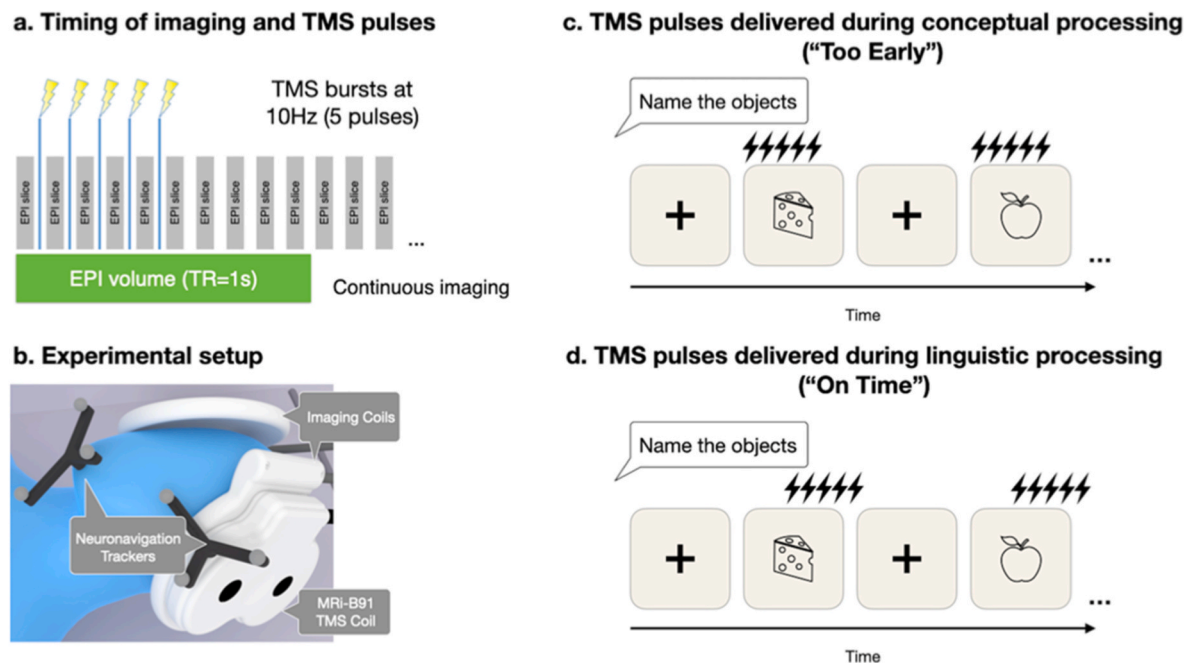
## 4. Experiment 2: online TMS-fMRI

### 4.1. Setup and technical procedure

For TMS-fMRI we used a custom built setup consisting of three 7-channel surface RF-coils with one being mounted directly below the TMS-coil [33,60,61]. The TMS-fMRI coil array was positioned over the language target derived from the first experiment using scanner-adapted metal free neuronavigation trackers. To ensure whole-brain coverage we used two additional 7-channel RF coils and placed one on the contralateral side and one below the subject's head. TMS-bursts of 10 Hz (5 pulses per burst) were applied at 100 % of the resting MT to the target region during an object naming task. Motor threshold determination was performed inside the MRI suite using the sandwiched TMS setup and the 7-channel receive-only coil array. The experimental setup is shown in Fig. 4.



**Fig. 3. TMS Language Mapping Setup.** (a) The TMS language mapping procedure, illustrating the stepwise process: (1) Identification of the individual language hotspot in the superior temporal gyrus (STG) using task-fMRI activation, (2) Placement of the circular TMS target grid (5 rings, 40 nodes, 5 mm spacing) centered on the peak activation, and (3) A screenshot of the object naming task during which TMS was applied. TMS was delivered in bursts of five pulses at 10 Hz, 200 ms after image onset, at each node three times in randomized order. (b) Post-hoc analysis pipeline: video recordings of the session were analyzed for speech errors, classified into different categories, and used to identify the most reliable target site leading to speech arrest or anomia. This site was then selected as the TMS-fMRI target for Experiment 2.



**Fig. 4. Experimental Setup for Chronometric interleaved TMS-fMRI.** a) Schematic of TMS pulse timing between EPI acquisition slices, ensuring continuous imaging and no interference with image quality, b) configuration of the custom-built TMS-fMRI setup, including three 7-channel RF coils: one directly below the TMS coil at the target site, one contralaterally, and one beneath the subject's head for whole-brain coverage. Scanner-adapted, metal-free neuronavigation trackers were used to position the TMS coil over the language target identified in Experiment 1, c) illustration of TMS delivery at image onset during the object naming task, resulting in stimulation during conceptual processing ("Too Early"), d) optimized TMS timing during linguistic processing ("On Time"), ensuring effective targeting of speech-related neural activity.

#### 4.2. Object naming paradigm

Interleaved TMS-fMRI consisted of two runs of the object naming paradigm using the same dataset of images as during the language mapping procedure in the first experiment. The participants were instructed to name the objects appearing on the screen without moving their head. To ensure motion restriction, the participants' head was

fixed and kept in place with MR compatible pillows and straps while keeping participant comfort in mind. The paradigm consisted of a single run of object naming without TMS and two runs with TMS. For each participant, the paradigm started with a stimulation run, followed by a non-stimulation run and ended with a stimulation run. Each run consisted of 6 blocks, including 120 images of common objects. The images were displayed for 500 ms. In the TMS condition, two of the blocks

included stimulation timed at 200 ms after image onset during linguistic processing (“On Time”) and two of the blocks included stimulation timed at 0 ms after image onset during conceptual processing (“Too Early”). The timings were based on Indefrey (2011) and our own pilot data which demonstrated effective linguistic interference resulting in reliable speech errors when stimulation occurred 200 ms post image onset. In the “No Stimulation” condition the task was performed without interference of TMS pulses. In the stimulation blocks 12 out of 20 images were accompanied with bursts of TMS pulses.

#### 4.3. Imaging acquisition and TMS parameters

Functional images were acquired using EPI with (TR = 1000 ms, TE = 38 ms, flip angle 60°, multiband factor = 4, 40 slices, 345 vol, voxel size =  $3 \times 3 \times 3.6 \text{ mm}^3$ ). For interleaved TMS-fMRI we precisely timed the TMS pulses to be administered between EPI slice excitations. Settings were chosen to force exact slice timing and send sequence slice triggers to the TMS stimulator according to the paradigm. Before in-vivo investigations, we optimized the delay time in a phantom by increasing the trigger delay on the stimulator in 1 ms steps from 40 to 80 ms in order to avoid artifacts in EPI as well as in k-space data. Optimal delay was determined as 80 ms. TMS was delivered at 10 Hz (bursts of 5 pulses, pulse train length = 400 ms). In addition to the functional images, a T1-weighted image was acquired for anatomical reference (TR = 2100 ms, TE = 3.67 ms, flip angle 8°, voxel size =  $1 \text{ mm}^3$  isotropic).

#### 4.4. Preprocessing and statistical analyses

The preprocessing pipeline for the TMS-fMRI EPIs consisted of ANTS bias field correction (N = 4), despiking (AFNI), and SPM12 realignment, normalization to MNI space and smoothing with a Gaussian kernel of 6 mm FWHM. A quality assurance protocol was implemented in which each image set was visually inspected. Participants runs were excluded from the study if the calculated mean framewise displacement surpassed a threshold of 0.15 mm.

Single subject, i.e. first level, analyses were performed using a general linear model (GLM). Linear regression was performed for each voxel based on generalized least squares with a global approximate AR(1) autoregression model. For GLM analysis, task blocks were convolved with SPM’s canonical HRF and used as regressors of interest. This resulted in 3 regressors: object naming without TMS, TMS at 200 ms delay, TMS at 0 ms delay. In addition, the realignment parameters obtained from the previous preprocessing steps were included in the model as nuisance regressors.

The resulting single-subject beta maps of BOLD responses were used for the second level analysis. A flexible factorial design was created to investigate the effects between stimulation during conceptual processing and stimulation during linguistic processing. Linear regression was performed at each voxel, using generalized least squares with a global repeated measures correlation model. Contrasts were calculated for TMS at 200 ms (“On Time”) and TMS at 0 ms (“Too Early”), versus the naming without TMS (“No Stimulation”). For direct comparison of the state-dependent effect of stimulation, the contrast TMS “On Time” versus TMS “Too Early” was calculated. Significance levels for all group level image analysis were defined with  $p < 0.001$  for cluster detection and  $p < 0.05$  for cluster-level family-wise error (FWEc) correction. To further investigate the effect of the interference of TMS during different states on the language network, region of interest (ROI) analysis of parameter estimates was performed using Python. The ROIs were defined a-priori as spheres with 10 mm radius. One ROI was centered around the hotspot derived from the fMRI group activation map in Experiment 1 in the inferior frontal gyrus (IFG), i.e. Broca’s area (MNI: 54, 32, 4) and another one around the target region in the STG, i.e. Wernicke’s area (MNI: 56, -26, 16).

## 5. Results

All subjects successfully completed both experiments. Consequently, the results reported here are based on data from all 20 recruited subjects.

## 6. Experiment 1: speech mapping

### 6.1. Language network activation during speech comprehension

Whole-brain fMRI analysis revealed robust activation within the core language network during the auditory description decision task (ADDT) [55]. The contrast forward speech > backward speech revealed significant activation in the inferior frontal gyrus (IFG; peak at MNI: 56, 28, 2,  $t = 7.10$ ), anterior midline (peak at MNI: 2, 24, 37,  $t = 7.60$ ), the left superior temporal gyrus (STG; peak at MNI: 56, -40, 0,  $t = 9.21$ ) and anterior insula (peak at MNI: 30, 20, 0,  $t = 6.61$ ). These clusters survived whole-brain FWE correction at  $p < 0.05$ , confirming their involvement in speech comprehension and lexical-semantic processing (Fig. 5). Given that these regions are critical for language processing [51,62], the activation patterns informed the selection of TMS stimulation sites for the subsequent neuronavigated TMS language mapping. Specifically, the area around the fMRI hotspot in the left STG was chosen as stimulation target for the mapping procedure based on its established role in speech production [5,63,64].

### 6.2. Identifying individual TMS targets for speech disruption

All participants successfully completed the TMS language mapping protocol, receiving stimulation at 100 % of their individually determined resting motor threshold (rMT). None reported any serious discomfort during or after stimulation. Across the full sample, 239 naming errors were observed over 2400 trials (120 per participant), corresponding to an overall error rate of 9.95 %. Errors were categorized as anomia (no response), speech arrest (delayed or halted speech), semantic paraphasia (e.g., saying “car” instead of “tractor”), and phonological paraphasia (e.g., “ectopus” instead of “octopus”). The most common error type was speech arrest (32.64 %), followed by anomia (28.87 %), semantic paraphasias (22.18 %), and phonological paraphasias (16.32 %). Based on prior findings linking speech arrest and anomia to posterior temporal stimulation, we identified the most consistently implicated site per participant as the individualized target for Experiment 2 (Fig. 6).

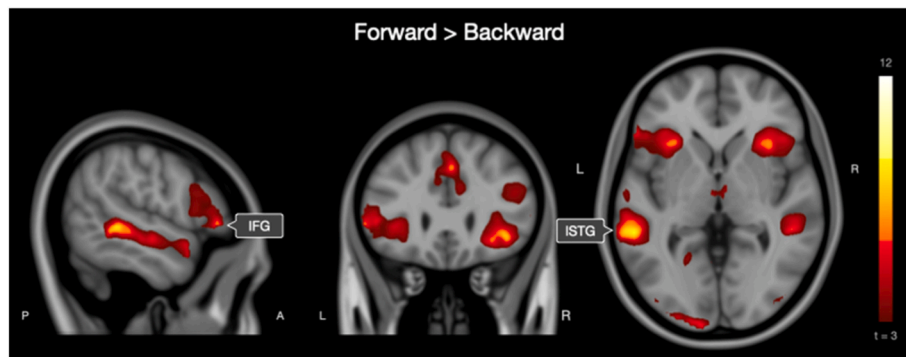
## 7. Experiment 2: online TMS-fMRI

### 7.1. Baseline language activation during object naming

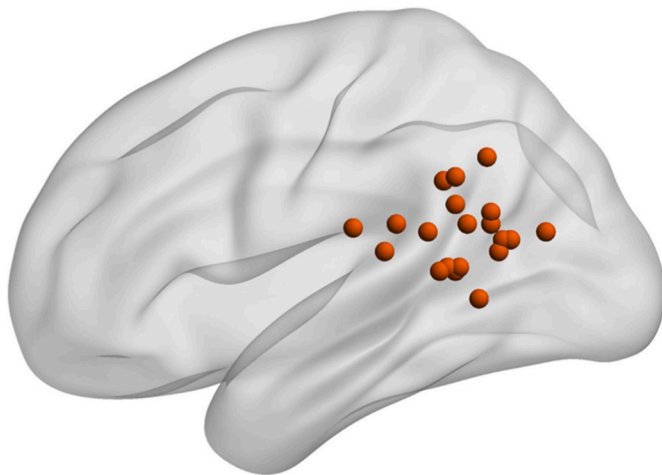
Prior to examining TMS-induced effects, we analyzed fMRI data from naming trials without stimulation to establish a baseline activation profile. Whole-brain analysis revealed strong activation in canonical language regions, including the left posterior temporal lobe (MNI: 52, -41, 12;  $t = 5.65$ ) and IFG (MNI: 50, 11, -3;  $t = 5.77$ ), with all results surviving FWE correction at  $p < 0.05$ . These activations reflect engagement of the dorsal language stream, which supports phonological-to-articulatory transformations during speech production (Fig. 7). This baseline served as a reference for subsequent comparisons involving TMS conditions.

### 7.2. TMS effects depend on stimulus-timing phase

We next analyzed how the timing of stimulation modulated brain responses. TMS was delivered either at image onset (0 ms; “Too Early”) or at 200 ms post-onset (“On Time”) targeting distinct phases of the naming process. Based on prior literature, the “Too Early” condition was expected to coincide primarily with visual and early conceptual processing, while the “On Time” condition overlapped with core linguistic



**Fig. 5. Forward vs. Backward fMRI Contrast in Auditory Description Decision Task.** The activation map indicates regions of increased neural activity during the forward condition compared to the backward condition, highlighting areas, such as the IFG and the left STG, involved in auditory processing and comprehension. This activation pattern displays t-values at  $p < 0.05$  (FWE corrected at cluster level, with a  $p < 0.001$  cluster-defining threshold). Location cursor at MNI -55, 27, 0.



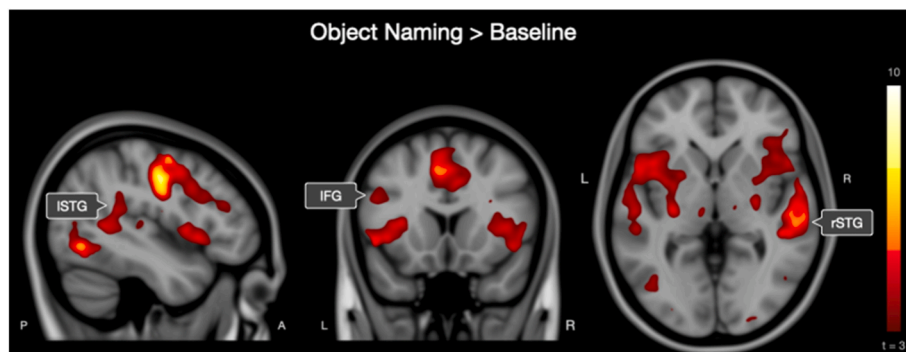
**Fig. 6. Distribution of TMS-fMRI stimulation targets.** For each subject, the location most reliably resulting in speech errors was selected as the stimulation target for the chronometric interleaved TMS-fMRI (Experiment 2). The locations are projected onto the cortical surface for visualization, each node represents an individual subject.

stages including semantic retrieval, phonological encoding, and articulation. In addition, whole-brain fMRI analysis confirmed that both stimulation conditions engaged sensorimotor regions. Significant activation was observed in the posterior STG (MNI: 42, -38, 18;  $t = 7.88$ ), supplementary motor area (MNI: 4, 4, 60;  $t = 7.17$ ), and left primary motor cortex (MNI: 48, -6, 52;  $t = 6.91$ ). All clusters survived FWE

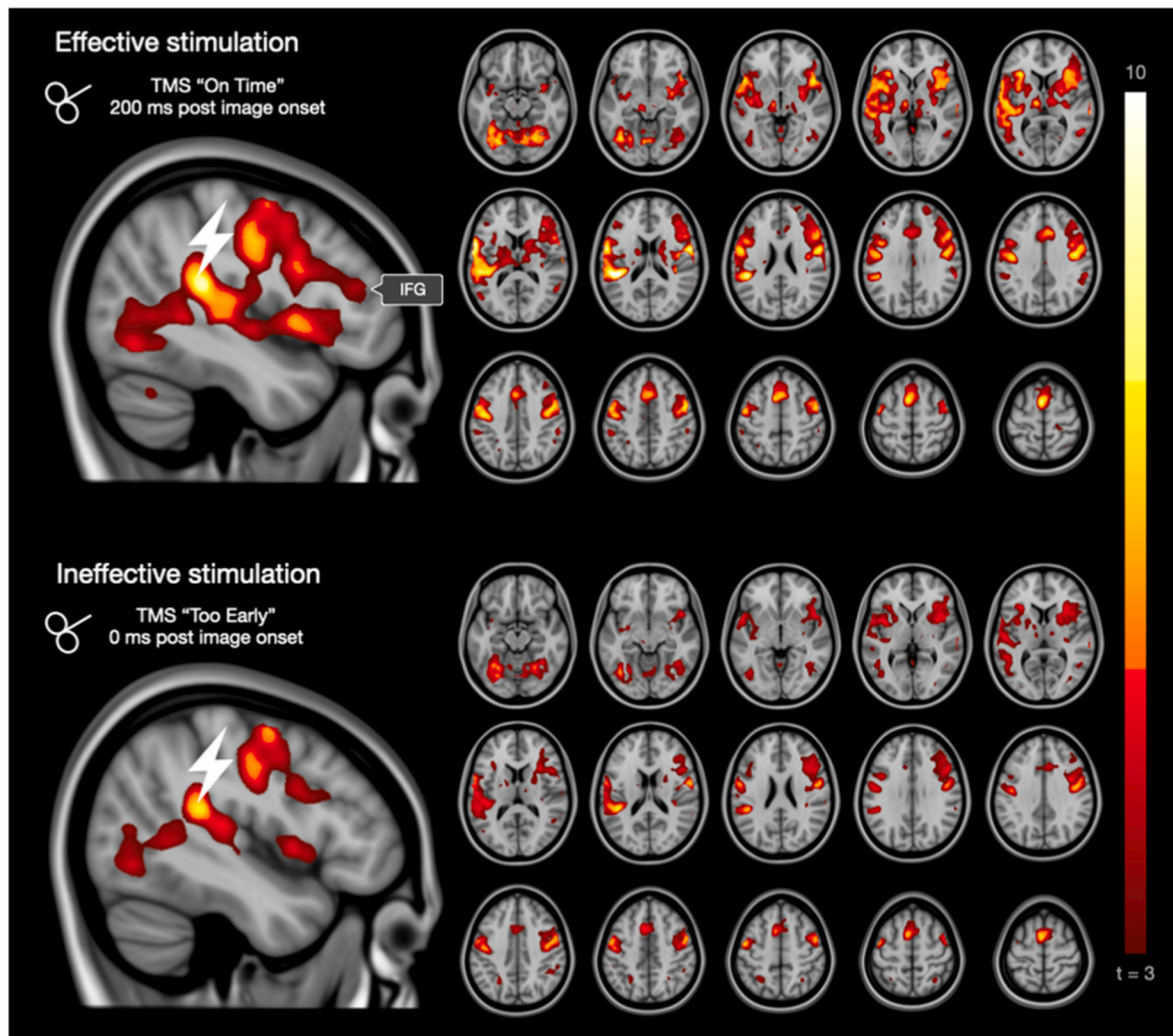
correction. In contrast, “On Time” stimulation led to widespread activation across the language network. Significant increases were observed in the posterior STG (MNI: 44, -37, 20;  $t = 10.21$ ), premotor cortex (MNI: 57, 2, 14;  $t = 8.89$ ), and IFG (MNI: 48, 34, 30;  $t = 4.77$ ), all  $p < 0.05$  FWE-corrected (Fig. 8). These results suggest that TMS during linguistic processing, but not earlier, actively engages language-related brain regions and disrupts ongoing speech production.

### 7.3. Direct comparison of stimulation timing

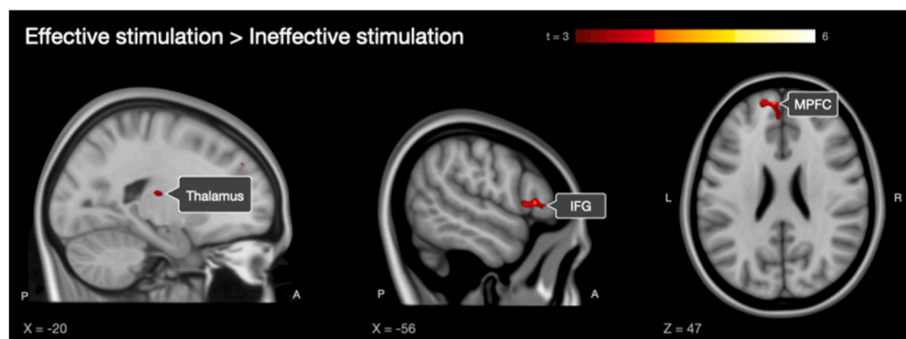
To determine whether TMS timing influenced neural activity differently, we directly compared TMS at 200 ms vs. TMS at 0 ms. The contrast (TMS at 200 ms > TMS at 0 ms) revealed significant differences in activation within cortical regions associated with linguistic processing and cognitive control, suggesting that stimulation timing alters neural engagement. Specifically, differences were observed in the left thalamus (peak at MNI: 20, -2, 13,  $t = 3.43$ ), medial prefrontal cortex (MPFC, peak at MNI: 7, 57, 25,  $t = 4.49$ ) and the IFG (peak at MNI: 56, 22, 7,  $t = 4.54$ ), all surviving  $p < 0.05$  FWE cluster-wise correction. The increased activation across both local (STG) and remote (IFG, thalamus) language areas in the “On Time” condition raises the possibility that stimulation at this later stage interacted with linguistic processing which led to speech impairments, though the precise functional impact remains to be determined. Overall, these results provide evidence that stimulation timing plays a role in shaping neural activity and that TMS at different time points could influence language processing and speech production. The results are summarized in Fig. 9. We additionally explored the contrasts between ineffective stimulation and no stimulation, as well as effective stimulation and no stimulation. These results are reported in the Supplements.



**Fig. 7. Group activation map showing increased activity in typical language areas during the object naming task relative to the implicit baseline:** The activation is observed in the bilateral superior temporal gyrus and the inferior frontal gyrus. This activation pattern displays t-values at  $p < 0.05$  (FWE corrected at cluster level, with a  $p < 0.001$  cluster-defining threshold). The location cursor is set at MNI coordinates -45,15,0.



**Fig. 8.** Activation Maps Illustrating Chronometric TMS Effects on Object Naming Task for TMS effective vs. ineffective timing. Effective TMS timing not only enhances activity at the stimulation site, i.e. the superior temporal gyrus (STG), but also increases activation in key language network regions further removed from the stimulation site, such as the inferior frontal gyrus (IFG) and temporoparietal areas. Ineffective TMS timing results in activation increases mainly around the stimulation site, i.e. STG. Activation pattern display t-values at  $p < 0.05$  (FWE corrected at cluster level, with a  $p < 0.001$  cluster-defining threshold).



**Fig. 9.** The direct contrast between effective and ineffective TMS timing reveals significant activation increases in the thalamus, IFG, and medial prefrontal cortex (MPFC) for effective stimulation. The activation patterns are represented by t-values, thresholded at  $p < 0.05$ , with family-wise error (FWE) correction at the cluster level.

#### 7.4. ROI analyses reveal region-specific modulation by TMS timing

To assess region-specific effects of TMS timing, we conducted ROI analyses in two core language areas: the left IFG, traditionally associated with articulatory and syntactic processing, and the left STG, linked to

phonological processing [63,65]. Recent research has highlighted the functional heterogeneity within Broca's area, indicating that it consists of multiple subregions with distinct roles [65]. According to these recent findings, the ROI was chosen in the posterior left IFG which was found to be a language selective region [66]. Parameter estimates were extracted

for three conditions: TMS delivered during linguistic processing (“On Time”), during conceptual processing (“Too Early”), and task blocks without stimulation.

In the STG, activation varied significantly by condition ( $F(2, 1542) = 113, p < 0.001$ ). Post hoc tests revealed greater activation for “On Time” stimulation ( $M = 0.96, SD = 0.41$ ) compared to both “Too Early” and “No Stimulation” (both  $M = 0.79, p < 0.001$ ), with no difference between the latter two.

In the IFG, activation also differed by condition ( $F(2, 1542) = 22, p < 0.001$ ). The highest activation was observed during “No Stimulation” ( $M = 0.40, SD = 0.50$ ), followed by “On Time” ( $M = 0.24, SD = 0.27$ ), and lowest during “Too Early” ( $M = 0.09, SD = 0.14$ ). All pairwise differences were significant ( $p < 0.001$ ). These results are summarized in Fig. 10.

These findings suggest that TMS timing differentially affects local and network-level components of the language system: “On Time” stimulation enhances activation at the stimulation site (STG), while modulating downstream regions such as the IFG, possibly reflecting state-dependent suppression or disrupted network coordination. “Too Early” stimulation showed minimal impact.

## 8. Discussion

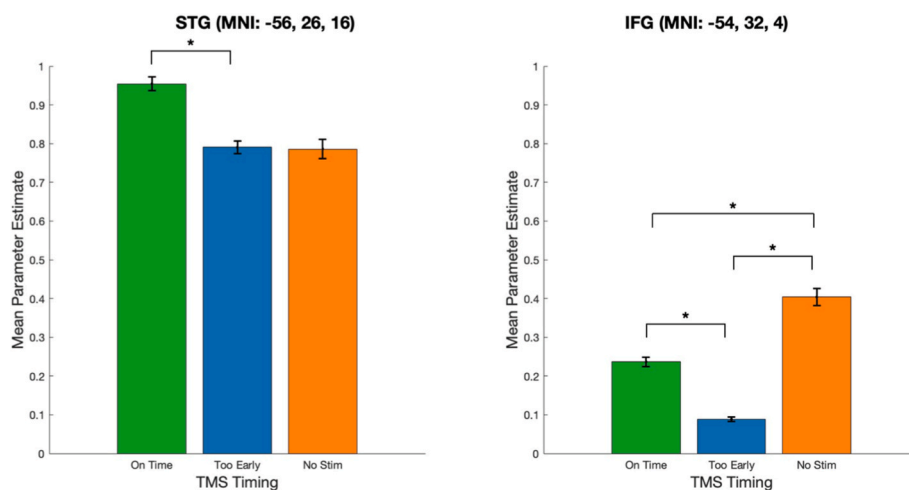
This study examined how the effects of TMS on speech production depend on the cognitive state at the time of stimulation. Using a chronometric interleaved TMS-fMRI paradigm during an object naming task, we investigated whether stimulation delivered during distinct cognitive stages (i.e. conceptual versus linguistic processing) differentially modulates cortical and subcortical activity within the language network. The results revealed three key findings: (1) stimulation at speech-sensitive cortical hubs induced increased activation across the language network; (2) this activation increase was significantly stronger when stimulation occurred during linguistic-compared to conceptual processing; and (3) late-phase stimulation evoked robust increases in left IFG, MPFC, and thalamus.

These results support a dynamic network model of TMS effects on language. While classic models of speech production [3,4,22] posit sequential activation of regions linked to discrete linguistic stages, including lemma selection, phonological encoding, and articulatory planning beginning approximately 200 ms post-stimulus, our findings suggest that stimulation during these later stages modulates coordinated processing across the network, rather than producing a purely local inhibitory effect. These timing-dependent effects suggest that the

targeted posterior temporal site is differentially engaged across stages of the naming process, with later stimulation coinciding with a more vulnerable processing window. Thus, the stronger effect at 200 ms reflects the region’s temporal involvement in the naming process rather than differences in stimulation efficacy. Instead of a purely local “virtual lesion” mechanism, the observed pattern is more consistent with connectivity-dependent perturbation, in which stimulation alters coordinated processing across a distributed language network.

Previous studies have shown that TMS applied to Broca’s or Wernicke’s area can disrupt speech [18,20,57,67–70]. However, the mechanism underlying such impairments remains a subject of debate. It is increasingly recognized that TMS effects extend beyond the target region and propagate through functionally and structurally connected networks. Neuroimaging and electrophysiological studies have demonstrated that stimulation can influence activity in distant cortical and subcortical areas [33,71–74]. Consistent with this literature, the observation of distant activations with 10Hz stimulation is not unexpected, yet our findings provide temporally specific evidence for such network-level propagation during active language processing. Stimulation of the posterior STG at 200 ms post-stimulus not only increased local activation but also modulated activity in left IFG, MPFC, and thalamus, regions implicated in language control and production. This supports our prior connectivity based work [21] suggesting that the functional impact of TMS on speech production depends not only on the targeted region but also on its integration within a broader network architecture.

The behavioral effects of TMS on language are highly time-sensitive, reflecting the sequential nature of speech production [3,4]. Neurophysiological studies using MEG and EEG have demonstrated that successful speech relies on precise temporal coordination across cortical regions [5,6]. Indefrey and Levelt’s model [3] offers a well-established framework for this process, suggesting that conceptual preparation occurs within the first 200 ms post-stimulus, followed by successive stages of linguistic processing. This temporal organization implies that the effectiveness of TMS in modulating speech depends critically on when stimulation occurs relative to these processing stages. In addition to timing, the current activation state of the brain also modulates the impact of stimulation. Regions engaged in ongoing processing may respond differently to TMS than those at rest, adding a layer of complexity to interpreting stimulation effects. Such state-dependent modulation has been observed across multiple cognitive domains, including language, and highlights the importance of both timing and neural context in shaping TMS outcomes [22,32–35,37].



**Fig. 10. Region-of-interest (ROI) activation across TMS timing conditions.** Mean parameter estimates ( $\pm$ SEM) are shown for the left STG (left panel) and left IFG (right panel) for three conditions: On Time stimulation, Too Early stimulation, and No Stimulation. Values were extracted from images at the peak coordinates of each ROI. Significant differences between conditions are indicated with asterisks (pairwise t-tests;  $p < 0.05$ ).

Our study adds to this body of evidence by demonstrating that the functional impact of TMS during language production is not fixed but varies according to the stage of processing. Stimulation during conceptual preparation had limited effects on the language network, whereas stimulation during linguistic processing resulted in broad network-level disruptions.

Experiment 1 confirmed the reliability of the auditory sentence comprehension task (ADDT) as a functional localizer for language-eloquent regions [62,75]. The ADDT robustly activated the dorsal language stream, and these activation patterns were used to guide individualized stimulation targets for TMS mapping. The language mapping procedure consistently elicited characteristic naming errors across participants, most notably speech arrest and anomia, which were used to identify individualized stimulation targets for Experiment 2. These targets were consistently localized within the posterior STG, aligning with prior research on TMS-induced speech disruption [18,76].

Experiment 2 employed chronometric interleaved TMS-fMRI, with stimulation precisely time-locked to either the conceptual preparation phase or the linguistic processing phase of the naming task. Stimulation during linguistic processing led to greater activation across the language network compared to stimulation during conceptual processing. These findings are consistent with prior chronometric TMS studies, which have shown that TMS delivered later in the naming process produces more substantial behavioral effects [22,23]. Notably, the precise timing of regional involvement in these earlier studies tended to occur later (~400 ms post-stimulus), which may reflect methodological differences. In our study, we applied bursts of five pulses at 10 Hz (400 ms train at 100 % MT), whereas prior protocols used triplets at 40 Hz (50 ms train at 120 % MT). Differences in stimulation parameters, including frequency, duration, and intensity, may affect the temporal window during which regions are functionally responsive to TMS. Indeed, previous studies have demonstrated frequency-dependent effects on regional cerebral blood flow and neural connectivity [77,78], and 10 Hz has been identified as optimal for posterior temporal stimulation in language mapping [57].

Our results challenge the idea that TMS acts as a local inhibitory mechanism as described by the “virtual lesion” approach [12–15]. Instead, stimulation appears to induce a hyperactive state that propagates across the language network. This overactivation likely disrupts the timing and coordination required for successful speech production. When stimulation was applied during linguistic processing, activation extended beyond the STG to include the IFG, MPFC, and thalamus. The IFG, particularly its posterior division, has been shown to support core language functions [66]. The MPFC, while more domain-general [66], has been implicated in semantic control [79,80]. The thalamus plays a critical role in coordinating cortico-cortical communication, and thalamic damage is associated with language deficits [81]. Concurrent activation in the IFG supports the idea that stimulation disrupts connectivity between thalamus and frontal regions [82]. These findings indicate that speech disruption may result from network-level dysregulation rather than local interference alone.

Additionally, the ROI analyses revealed a timing-dependent pattern of network modulation. When stimulation was delivered during the linguistic processing phase, activation at the stimulation site in posterior STG increased relative to the early TMS condition and the no stimulation condition, indicating stronger engagement of this region during a more vulnerable stage of the naming process. A similar timing effect was observed in the IFG, specifically within the posterior portion identified as a language-selective subregion [65], where stimulation during the linguistic phase produced greater activation relative to stimulation during the conceptual phase. However, IFG activation was highest during the no-stimulation condition, suggesting that TMS to posterior STG transiently disrupts or desynchronizes the normal flow of information to downstream frontal regions. Thus, the apparent “over-activation” of the IFG during the linguistic phase should be interpreted as relative to the stimulation during the conceptual phase rather than as

absolute hyperactivation. These patterns are consistent with our previous findings [21] and a network-level account in which posterior temporal stimulation modulates coordinated processing within a broader frontal–temporal system demonstrating connectivity-based propagation of TMS effects during speech production.

Importantly, this is the first study to integrate neuronavigated TMS targeting, chronometric precision, and interleaved whole-brain imaging to examine the causal architecture of the language network. By combining TMS and fMRI in real time, we were able to capture the spatiotemporal dynamics of TMS effects with a level of resolution not achievable using either method alone. While fMRI alone can reveal the spatial correlates of language processing, it lacks the ability to test causality or capture fast-changing cognitive states. TMS adds temporal and causal precision, enabling a more direct test of how—and when—specific brain regions contribute to language.

This study also has limitations. Most notably, due to technical constraints, we did not record behavioral speech output during interleaved TMS-fMRI. While we selected stimulation targets known to induce speech arrest and anomia in Experiment 1, the absence of concurrent behavioral data in Experiment 2 limits direct confirmation of speech disruption. In addition, the selection of stimulation delays (0 ms and 200 ms post-stimulus onset) is an operational approximation of early and late processing stages rather than a categorical distinction. Preliminary pilot tests conducted outside the scanner indicated that stimulation at 0 ms and 100 ms did not reliably elicit naming errors, whereas stimulation at 200 ms consistently produced speech arrest. This informed our choice of timing within the technical constraints of interleaved TMS-fMRI. Although previous studies have reported earlier TMS effects in other cortical sites [48,83], our results suggest that, for posterior temporal targets, interference becomes most robust during later, linguistically dominant stages of speech production. Nonetheless, conceptual and lexical processes likely overlap, and future work using denser temporal sampling could clarify the precise boundaries of these effects.

Further, stimulation targets were defined using an ADDT localizer task, which reliably activates the core language network and has been successfully applied in our previous work [21]. As this paradigm primarily engages receptive processes, its activation only partially overlaps with the production stages probed during TMS mapping. Stimulation sites were then selected individually based on these activation maps and TMS language mapping results, leading to some anatomical variability across participants. While this individualized approach enhances functional precision, it may also contribute to variability in activation patterns. Future studies could refine target specificity by employing a production-based localizer, such as an object naming task.

We also did not include a control condition in which TMS was applied during rest. Although non-specific stimulation effects (e.g., sensory discomfort) cannot be entirely ruled out, these factors were matched across timing conditions, minimizing their influence on the differential results reported here. Finally, the TMS burst duration (400 ms) introduced a degree of temporal overlap between the two stimulation windows. While this limits our ability to isolate the effects of individual pulses, it ensures reliable stimulation during the cognitive window of interest.

In summary, this study demonstrates that TMS-induced effects on speech production are highly dependent on both the timing of stimulation and the cognitive state of the language system. Rather than inducing a virtual lesion, TMS appears to produce a state of network overactivation that disrupts the coordination necessary for fluent speech. These findings advance our understanding of the neural dynamics of speech production and provide a methodological framework for future causal investigations of cognition. The integration of time-locked TMS with whole-brain imaging opens new opportunities to map how cognitive processes emerge from dynamic interactions within distributed neural networks.

## CRediT authorship contribution statement

**Maria Vasileiadi:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Anna-Lisa Schuler:** Writing – review & editing, Conceptualization. **Michael Woletz:** Software, Methodology. **Verena Witz:** Investigation. **Sarah Grosshagauer:** Writing – review & editing, Investigation. **John Coetzee:** Writing – review & editing. **Martin Tik:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

## Declaration of competing interest

The authors declare no competing financial or personal interests that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2025.103010>.

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