

Examination of optimal parameters for language mapping using transcranial magnetic stimulation

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Abstract. Minimizing postoperative language decline is a key objective during neurosurgical interventions in the language-dominant hemisphere. Transcranial magnetic stimulation (TMS) can be used to establish language-eloquent brain regions and tailor the extent of resection. Meanwhile, stimulation parameters (such as frequency and onset) can significantly affect the sensitivity and specificity of TMS language mapping. Still, few studies have systematically investigated optimal stimulation parameters and targets. The current study aimed to consistently test various TMS parameters to identify those that robustly interfere with language function in the language-dominant hemisphere. We developed an Object Naming language paradigm of 75 pictures with corresponding Russian names. We tested the paradigm using four TMS protocols with different frequency (5/10 Hz) and onset (0/300 ms) parameters in a control group of 45 healthy participants. This study firstly employed TMS language mapping over 46 standardized brain regions across the whole left hemisphere using a robotic system, Axilum TMS-Cobot. The results revealed significant main effects of TMS frequency and onset, with the highest error rate associated with the 10 Hz 0 ms protocol. The selected protocol will be further validated using an Action Naming paradigm and tested in the right hemisphere. Finally, the optimal paradigms will be clinically validated.

Keywords: language mapping, transcranial magnetic stimulation, object naming, protocol optimization, stimulation parameters, frequency, onset

Апробация протоколов картирования речи методом транскраниальной магнитной стимуляции

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Аннотация. Предотвращение постоперационного речевого дефицита является одной из ключевых задач при нейрохирургическом вмешательстве в доминантном по речи полушарии. Транскраниальная магнитная стимуляция (ТМС) может применяться при планировании нейрохирургического вмешательства для выявления участков коры головного мозга, критически значимых для речевой функции. При этом параметры стимуляции (такие как частота и задержка) могут значительно влиять на чувствительность и специфичность протокола картирования речи с помощью ТМС. Лишь в ряде исследований проводилось систематическое сравнение эффективности различных параметров стимуляции. Настоящее исследование было направлено на последовательное тестирование различных параметров ТМС для выявления тех, которые надежно локализуют речевую функцию в доминантном по речи полушарии. Мы разработали парадигму "Называние объектов", состоящую из 75 изображений с соответствующими русскими номинациями. Мы протестировали парадигму, используя четыре протокола ТМС с различной частотой (5/10 Гц) и задержкой (0/300 мс) в контрольной группе из 45 здоровых участников. В исследовании было впервые проведено речевое картирование с помощью ТМС по стандартизированной системе координат 46 участков коры головного мозга по всему левому полушарию с использованием роботизированной системы Axilum TMS-Cobot. Результаты показали значимый эффект частоты и задержки ТМС, при этом при этом наиболее оптимальными параметрами оказались 10 Гц 0 мс. Разработанный протокол будет валидирован с использованием парадигмы "Называние действий" и протестирован в правом полушарии. Наконец, будет проведена клиническая валидация разработанных парадигм.

Ключевые слова: речевое картирование, транскраниальная магнитная стимуляция, называние объектов, оптимизация протокола, параметры стимуляции, частота, задержка.

Introduction. Minimizing postoperative language deficits is crucial when neurosurgical interventions involve language-dominant hemisphere. While direct electrical stimulation (DES) during awake surgery is the gold standard for mapping eloquent cortex, a large cohort of patients cannot be awakened due to psychological or anatomical considerations, childhood, or insufficient experience of the medical team. Alternatively, repetitive transcranial magnetic stimulation (rTMS) can support or potentially replace DES. rTMS applies a magnetic field to induce a small electric current through electromagnetic induction to interfere with language function by creating a “virtual lesion” when a patient is performing the task. Although rTMS provides high temporal and spatial resolution, it was reported to have high sensitivity and relatively low specificity compared to DES (Ille et al., 2015), possibly due to stimulation parameters (Krieg et al., 2014).

First, the rTMS frequency significantly influences its efficacy for language mapping by differentially modulating cortical excitability (Nettekoven et al., 2021; Sollmann et al., 2018). Preliminary studies employed a wide range of 5-50 Hz frequencies, but still only a few studies (Hauck et al., 2015; Krieg et al., 2014; Nettekoven et al., 2021; Sollmann et al., 2018) systematically examined rTMS frequency effect on language mapping. While 5 pulses/5 Hz rTMS has been recommended as a more reliable and tolerable clinical standard (Krieg et al., 2017), there was evidence that higher frequencies (>20Hz) could increase reliability by eliciting more naming errors, even potentially improving patient comfort (Hauck et al., 2015; Nettekoven et al., 2021). Moreover, optimal frequencies may also vary for anterior and posterior brain regions (Sollmann et al., 2018). Hence, systematic investigation of TMS parameters for language mapping remains sparse, and further research is required to determine the most effective frequency parameters.

Second, optimization of rTMS language mapping can be achieved by carefully timing the rTMS stimulus to align with the stages of word production, such as object recognition, conceptualization, lexical retrieval, phonological encoding, and articulation, distributed across the cortex with approximately 100 ms intervals (Sollmann et al., 2017). While the timing of rTMS onset correlates with the spatial distribution of naming errors (Sollmann et al., 2017), studies validating rTMS results with DES indicated greater specificity of immediate (0 ms) than delayed onset (Ille et al., 2015; Krieg et al., 2017). Thus, further research is needed to determine the optimal rTMS onset parameters for both precisely delineating individual language processes and maximizing overall mapping accuracy.

Finally, precise spatial resolution and coil orientation are crucial for accurate rTMS language mapping. Previous navigated rTMS studies used manual coil placement with the Nexstim NBS system and lacked standardized coordinates, potentially introducing inter-study inconsistencies. The Axilum TMS-Cobot's robotic system with predefined MNI coordinates can offer a significant advancement in spatial accuracy and protocol standardization, enhancing reliability and comparability.

This study was aimed at systematically evaluating different rTMS frequency and onset parameters to identify the optimal ones for language mapping in the dominant hemisphere. This will be the first study using an Axilum TMS-Cobot controlled with a Localite neuronavigation system and standardized coordinates of targeted regions across the entire left hemisphere. This research would establish a novel methodological approach to navigated rTMS language mapping.

Method. Forty-nine volunteers aged between 18 and 45 years old ($M_{age} = 23.41$, $SD = 5.36$; 33 females) participated in the experiment. We excluded the data from four participants who did not complete the experimental session due to intolerable pain elicited by TMS. In total, data from forty-five participants ($M_{age} = 23.07$, $SD = 5.09$; 29 females) were included in the analysis. All participants were right-handed native Russian speakers, had normal or corrected vision and hearing, and had no history of neurological deficits or language-related impairments. Participants signed a written informed consent form prior to taking part in the research and completed the TMS safety screening form to reveal any contraindications. The study was approved by the HSE Committee on Interuniversity Surveys and Ethical Assessment of Empirical Research.

We developed two linguistic paradigms, Object Naming and Action Naming. For the first experimental study primarily focused on validation of optimal TMS parameters, we used only an Object Naming task, which is a commonly accepted task for cortical language mapping (Krieg et al.,

2017). The task consisted of 75 drawn black-and-white pictures of living and non-living objects with corresponding Russian names sourced from a psycholinguistic database (Akinina et al., 2015). To ensure correct response identification during rTMS mapping, only items with four or fewer alternative names were included. Stimuli were controlled for their naming parameters (age of acquisition: $M = 1.89$, $SD = 0.46$, range: 1.14 – 2.86; name agreement: $M = 93.72$, $SD = 8.27$, range: 70 – 92.5; frequency: $M = 26.86$, $SD = 27.74$, range: 2 – 122.7; length in syllables: $M = 2.50$, $SD = 0.70$, range: 1 – 4; length in phonemes: $M = 6.30$, $SD = 1.39$, range: 3 – 9). The experiment was programmed via E-Prime 3.0 software.

Participants completed a baseline Object Naming task prior to rTMS mapping to familiarize them with the procedure, identify challenging stimuli, and minimize false positive errors during rTMS mapping. Stimuli pictures were presented with a 1000 ms presentation time and a 3000 ms inter-picture interval, preceded by a 500 ms fixation cross. Participants were seated 60 cm in front of the screen and were asked to name the pictures in Russian using the phrase "Eto..." (*This is...*), promoting nominative case noun production (e.g., *Eto vilka* 'This is a fork'). Pictures not named fluently and correctly were excluded from subsequent rTMS mapping.

Stimulation was applied over 46 targeted regions based on Corina et al. (2005) and standardized in the MNI space via manual segmentation of the MNI152 T1-weighted template using MRIcroGL. Individual coordinates for each participant were obtained by realigning participants' individual T1-weighted images to AC-PC space and applying inverse mapping of the predefined coordinates from the MNI space to the native participants' space based on spatial normalization parameters using SPM.

Language mapping was performed using a MagProX100 MAGOPTION (MagVenture, Denmark) stimulator, equipped with a Cool-B65 coil, under control of robotic system Axilum TMS-Cobot (Axilum Robotics, France) and neuronavigational system Localite TMS Navigator (Localite, Germany). The experimental session started with the participant's registration in the neuronavigation system and estimation of individual resting motor threshold (rMT). During the mapping procedure, a participant had to name pictures with the rTMS stimulation applied at 110% of rMT with one of four protocols differing with frequency (5/10 Hz) and onset (0/300 ms). In total, there were three rounds of consecutive rTMS stimulation over 46 targeted regions. The region was marked as language positive if a participant made errors during $\geq 2/3$ stimulation trials. Oral participants' responses were audio and video recorded with a microphone, and naming errors and pain reports were documented in a paper protocol after each trial. Each participant completed two sessions with the same rTMS onset (0/300 ms) and different frequency parameters (5/10 Hz). The total duration of each session was 2–2.5 hours, including the participant's preparation and mapping procedure.

Data analysis was aimed at testing the main effect of rTMS frequency and onset on error rates during language mapping. Data processing and descriptive analysis were performed in Python 3.10. Error rates were calculated across all participants and visualized using SurfIce. Statistical analysis was performed in the R software using the *lme4* package: effects of rTMS frequency and onset on error rates were estimated using generalized linear mixed-effects models via the *glmer* function.

Results. No participants reported any side effects during or after stimulation, and the average tolerability was high. Descriptive statistics revealed a higher error rate for rTMS protocol with 10 Hz frequency and 0 ms onset (Figure 1). Statistical analysis revealed the main effect of frequency and onset on error rates; the 10 Hz 0 ms rTMS protocol was associated with higher error rates (Table 1).

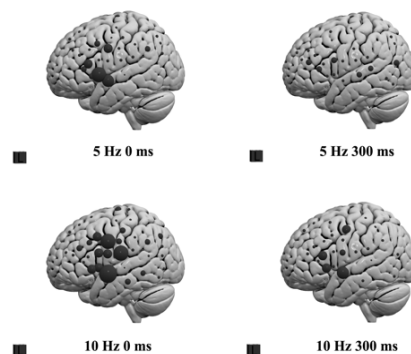


Figure 1. Error rates across all participants for four rTMS stimulation protocols. The size of each sphere represents a total number of naming errors elicited by rTMS across all participants.

Table 1. Results of generalized linear mixed-effects model for error rates

Contrast	Odds.ratio	SE	z-ratio	p-value
5 Hz 0 ms / 10 Hz 0 ms	0.72	0.06	-3.67	0.001
5 Hz 0 ms / 5 Hz 300 ms	1.57	0.35	2.02	0.131
5 Hz 0 ms / 10 Hz 300 ms	1.28	0.28	1.13	0.257
10 Hz 0 ms / 5 Hz 300 ms	2.18	0.48	3.51	0.002
10 Hz 0 ms / 10 Hz 300 ms	1.78	0.39	2.64	0.034
10 Hz 0 ms / 10 Hz 300 ms	0.82	0.09	-1.84	0.133

Note: Contrast is a pairwise comparison of rTMS protocols; Odds.ratio is an odds ratio; SE is a standard error. Significant effects at level $\alpha = .05$ are highlighted in bold

Discussion and conclusions. We developed two linguistic tests for rTMS language mapping and tested four protocols with various parameters of frequency (5/10 Hz) and onset (0/300 ms) in the control group of healthy participants. The results revealed a significant main effect of both frequency and onset, with 10 Hz and 0 ms being the optimal parameters. The results are in line with previous findings (Ille et al., 2015; Krieg et al., 2014; Sollmann et al., 2018).

Several limitations were revealed. First, the long duration of the mapping procedure can cause participants' fatigue. Second, the procedure cannot be fully automatized and requires partly manual control of coil placement due to limitations of the neuronavigation system. Third, participants could report pain sensations due to contraction of cranial muscles, especially when more anterior regions are stimulated. Finally, although currently validated TMS parameters were proven safe both in healthy and clinical cohorts (Krieg et al., 2017; Nettekoven et al., 2021), further clinical validation is crucial to ensure its safe applicability in the clinical group with a minimal risk of seizure induction.

During further research, we plan to validate the selected 10 Hz 0 ms rTMS protocol using the Action Naming paradigm. Also, we will validate the developed protocol in the right hemisphere in the control group of healthy participants. Finally, the optimal paradigms will be clinically validated.

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