Study Design for Navigated Repetitive Transcranial Magnetic Stimulation for Speech Cortical Mapping

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Citation

Lioumis, P., Autti, S., Wilenius, J., Vaalto, S., Lehtinen, H., Laakso, A., Kirveskari, E., Mäkelä, J.P., Liljeström, M., Renvall, H. Study Design for Navigated Repetitive Transcranial Magnetic Stimulation for Speech Cortical Mapping. *J. Vis. Exp.* (193), e64492, doi:10.3791/64492 (2023).

Date Published

March 24, 2023

DOI

10.3791/64492

URL

jove.com/video/64492

Abstract

The cortical areas involved in human speech should be characterized reliably prior to surgery for brain tumors or drug-resistant epilepsy. The functional mapping of language areas for surgical decision-making is usually done invasively by electrical direct cortical stimulation (DCS), which is used to identify the organization of the crucial cortical and subcortical structures within each patient. Accurate preoperative non-invasive mapping aids surgical planning, reduces time, costs, and risks in the operating room, and provides an alternative for patients not suitable for awake craniotomy. Non-invasive imaging methods like MRI, fMRI, MEG, and PET are currently applied in presurgical design and planning. Although anatomical and functional imaging can identify the brain regions involved in speech, they cannot determine whether these regions are critical for speech. Transcranial magnetic stimulation (TMS) non-invasively excites the cortical neuronal populations by means of electric field induction in the brain. When applied in its repetitive mode (rTMS) to stimulate a speech-related cortical site, it can produce speech-related errors analogous to those induced by intraoperative DCS. rTMS combined with neuronavigation (nrTMS) enables neurosurgeons to preoperatively assess where these errors occur and to plan the DCS and the operation to preserve the language function. A detailed protocol is provided here for non-invasive speech cortical mapping (SCM) using nrTMS. The proposed protocol can be modified to best fit the patient- and site-specific demands. It can also be applied to language cortical network studies in healthy subjects or in patients with diseases that are not amenable to surgery.

Introduction

During neurosurgery due to cerebral disease (e.g., epilepsy or a tumor), the extent of resection must be optimized to preserve brain regions that support critical functions. Areas vital for patient integrity and quality of life, such as language-related ones, should be characterized prior to the removal of brain tissue. Typically, they cannot be individually identified merely based on anatomical landmarks[1]. The functional mapping of language areas for surgical decision-making is usually done invasively by electrical direct cortical stimulation (DCS), which enables the neurosurgeon to understand the organization of the crucial cortical and subcortical structures within each patient[2]. Although DCS during awake surgery is considered the gold standard of cortical mapping for speech functions, it is limited by its invasiveness, methodological challenges, and the high stress it induces for both the patient and the surgical team. This protocol describes non-invasive speech cortical mapping (SCM) using navigated transcranial magnetic stimulation (navigated TMS or nTMS). Accurate non-invasive mapping aids in surgical planning, and reduces the time, costs, and risks in the operation room (OR). It also provides an alternative for those patients who are not suitable for awake craniotomy[3].

Non-invasive imaging methods have already greatly benefited presurgical planning. Anatomical magnetic resonance imaging (MRI) is crucial for locating tumors and brain lesions; in neuronavigation[4] and in the navigated TMS mapping[5], it guides the operator to the cortical sites of interest. Diffusion-based MRI (dMRI) tractography provides detailed information on the white-matter fiber tracts that connect cortical regions[5,6]. During the last decade, functional imaging techniques, most notably functional MRI (fMRI) and magnetoencephalography (MEG), have been increasingly used for preoperative motor and speech cortical mapping (SCM)[2,8,9]. Each method brings benefits to the preoperative mapping procedure, and can, for example, provide information on the functionally related regions outside of the conventional language areas (Broca's and Wernicke's areas). fMRI has been the most commonly used method[1] due to its high availability; it has been compared to DCS in the localization of speech-related areas with variable results[2,10]. However, although functional imaging can identify the involved brain regions, it cannot determine whether these regions are critical for the function to be preserved.

Navigated repetitive TMS (nrTMS) is nowadays used as an alternative to the aforementioned methods for preoperative non-invasive SCM[11,12]. nrTMS SCM is especially efficient in identifying speech-related cortical areas within the inferior frontal gyrus (IFG), superior temporal gyrus (STG), and supramarginal gyrus (SMG)[11,13]. An advantage of the method is that the offline analysis of the errors evoked by the stimulation allows the analyzer to be unaware of the stimulation site. It is, thus, possible to judge the error without *a priori* information of the cortical site's relevance to the speech network. This is enabled by a video recording, which allows the analyzer to distinguish subtle differences in errors, such as semantic and phonological paraphasia, more reliably than during the actual examination[11,12]. The nrTMS SCM approach currently surpasses the performance of MEG or fMRI speech mapping alone[10,14], and additional functional or anatomical information may be used to fine-tune the nrTMS procedure. Preoperative mapping with nrTMS has been demonstrated to shorten operation times and reduce the required size of craniotomy and damage to the eloquent cortex[15]. It shortens the time of hospitalization and enables a more extensive removal of tumor tissue, thereby increasing patient survival rates[15]. nrTMS has been validated against intraoperative DCS mapping; specifically, the sensitivity of nrTMS in SCM is high, but its specificity remains low, with excessive false positives compared to DCS[13,16].

Currently, presurgical non-invasive SCM with nrTMS can assist in patient selection for operation, help in designing the surgery, and speed up the DCS conducted during the surgery[17]. Here, a detailed description of how nrTMS SCM can be performed to obtain reliable speech-specific results is provided. After gaining practical experience, the suggested protocol can be tailored to best fit the patient- and site-specific demands. The protocol can be further expanded to certain targets, such as speech production (speech arrest)[18,19] or visual and cognitive functions[20].

Protocol

This study was approved by the Hospital District of Helsinki and Uusimaa ethics committee. Informed consent to participate was obtained before the procedure from each subject.

1. Preparation of the structural images

1. Record a high-resolution T1-weighted structural MRI of the whole head for each subject (preferably with a 0 mm slice gap and 1 mm slice thickness). Acquire the images as specified in the neuronavigation system's instructions.
2. Upload the MR images to the navigation system in its preferred format (typically DICOM or NifTI).
3. Go through the MR images, and check for any errors (e.g., blurry cardinal points, noise disturbances, or misplacements in the 3D model reconstruction).
4. Find the cardinal points (i.e., the middle of the ridge in each earlobe and the nasion) in the axial, sagittal, and coronal MRI planes, mark them by pressing the crosshair function in the planes, and choose the exact spot by clicking the left button of the mouse. Then, press the "add landmarks" button with the mouse.
5. Insert parcellations of the brain areas of interest (e.g., pinpointed by other functional methods [MEG, fMRI, PET] or based on MRI databases or atlases)[21]. Choose the "overlay image" function.

2. Preparation for neuronavigation

1. Check that the subject does not have any metal items (e.g., earrings) in the head and neck area, and ensure that there are no absolute contraindications such as intracranial metal clips.
2. Place the subject in the patient chair. Adjust the chair so that the subject is sitting comfortably, with the neck, hands, and legs relaxed. Adjust the chair height so that the operator can comfortably stimulate the whole hemisphere under investigation.
3. Place the head tracker so that it is stabilized during the stimulation session (with a sticker or a strap) and does not block the TMS coil from being moved freely over the head, especially over the temporal areas. The tracker may be situated slightly right on the forehead if the left hemisphere is stimulated and vice versa if the right hemisphere is stimulated to ensure that the anterior frontal lobe areas can be stimulated.
4. Co-register the subject's head to the MRI-reconstructed 3D head model. Use a digitizing pen on the participant's head to mark the cardinal points (nasion, pre-auricular points) that were selected on the MRIs. Digitize additional

points over the whole skull surface to reduce the final registration error. Place the digitizing pen over each highlighted spot on the 3D head model, and press the left pedal when the spot starts blinking on the navigator screen.

5. Validate the registration, even if the overall error is acceptable (below 4 mm). Touch the subject's head with the tip of the digitizing pen. Double-check visually that the pen is at the analogous place on the surface of the 3D MRI-based model. If its position does not correspond to the point in the MRI, repeat steps 2.1-2.4.

6. Ensure that both the subject and the operator wear ear protection before starting the stimulation.

3. Defining the hot spot and motor threshold for M1 stimulation

1. For determining the resting motor threshold (rMT), choose a distal hand muscle (e.g., the abductor pollicis brevis [APB]) from the right hand.

   NOTE. The motor threshold is used to define the initial stimulation intensity, which may be subsequently changed as explained below. Thus, any distal hand muscle can be used for this purpose.

2. Place a single-use gel electrode (diameter: ~30 mm) over the right APB (the belly of the muscle), and another on the middle of the thumb (tendon). Place the ground electrode near the wrist (or follow the manufacturer's guidelines).

3. Connect the electrodes to the electromyography (EMG) amplifier, and verify that the APB is at rest by observing the continuous EMG signal. Change the position of the hand if the recorded muscle cannot be easily relaxed.

4. Find the cortical hot spot for determining the APB motor threshold. Starting from the motor hand knob area[22], deliver a few TMS pulses, and continue by moving and rotating the coil until APB motor evoked potentials (MEPs) appear.

   NOTE: Usually, motor representations of the thumb are located perpendicular to the lateral wall of the hand knob.

   1. Choose a TMS intensity that evokes MEPs of around 200-500 μV. Optimize the coil location and orientation by slightly changing its angle to evoke the maximum MEPs.

5. Save the optimal coil location in the neuronavigation software by right-clicking over the pulse number corresponding to the hot spot site and choosing the option to repeat the stimulus. Repeat the stimuli, and apply an automatic threshold hunting algorithm[23] by right-clicking on the hot spot and choosing the option of motor threshold from the neuronavigation software.

6. If these options are not available, apply the rule that a TMS pulse needs to evoke 10 MEPs (≥50 μV) out of 20 trials[24].

4. Baseline naming of images

1. Familiarize the subject with the images before the baseline object naming task[11,12]. Print the images (or show them in digital format), and let the subject practice before the session starts (the subject could also practice at home).

   1. Use properly standardized normalized color images (e.g., from the Bank of Standardized Stimuli[25]; **Supplementary Figure 1**).

2. Use only images that are frequently seen in an everyday environment, have a minimal number of synonyms, and have high name agreement.

2. If available, attach an accelerometer on the skin above the larynx and the vocal cords to record the speech onset, as explained in Vitikainen et al.[26].

3. Show the images to the subject one by one and ask them to name the images aloud without stimulation.

   1. Present the images to the subject on a screen placed at a 0.5-1 m distance.

   2. Use a display time of 700-1,000 ms per image.

4. Adjust the inter-picture interval (IPI) to make the task slightly challenging for each subject (e.g., start with 2,500 ms, and vary between 1,500-4,000 ms).

   1. If many errors occur during the baseline naming task, increase the IPI in steps of 200-300 ms. If the task is too easy, decrease the IPI in steps of 200-300 ms.

5. For the actual speech mapping session with nrTMS, omit the images that during the baseline testing were not trained adequately, not named correctly, not named clearly, not articulated correctly, named with delay or hesitance, or seemed difficult for the subject.

6. Run the baseline naming task three times, and repeat steps 4.3-4.5 if performance is not satisfactory.

5. Speech cortical mapping

1. Vary the stimulation intensity by increasing/decreasing it in steps of 1% of the stimulator's output so that each target area receives the same induced electric field (E-field), as defined for the rMT of the hand muscles at the cortical hand motor hotspot. Usually, higher intensities need to be applied for parietal than for frontotemporal targets to reach similar cortical E-fields as for the rMT hotspot.

   1. Lower the intensity when stimulating cortical structures located closer to the head surface (E-field above the pre-defined rMT E-field).

2. Check before starting the stimulation that the induced E-field values are approximately similar (with a 2-3 V/m difference) in the different speech-related areas in both hemispheres.

   1. Adjust the cortical depth (peeling depth) if needed.

   2. Ensure that the coil center is not in the air.

3. Start with a default picture-to-TMS interval (PTI) of 300 ms, or use a 0-400 ms PTI; a PTI above 150 ms is preferred to optimize the overlap of stimulation with language processing.

4. Start with five pulses at a 5 Hz stimulation rate. Start from a cortical area not related to speech processing so that the subject gets used to the sensation induced by the stimulation. Then, move the coil to the expected speech-related areas.

5. Keep the coil in the same position until the pulse train is over and the subject's naming is completed.

6. Focus on the subject's performance as described below.

   1. If no error is observed, move on to the next locus.

   2. If an error, or even a hesitation, is observed, continue stimulating that site for an additional two to three nrTMS trains, and then move on. Keep the site in mind for possible later re-stimulation.

   3. Make small coil adjustments when even a slight error is detected (e.g., minor hesitation or a louder voice

during the naming due to an increased effort) to provoke clearer errors.

4. Avoid repeating stimulation on the same site for more than five consecutive trains. Continue with other cortical sites, and revisit the site later.
5. If repeated errors appear at several stimulated locations, lift the coil in the air above the scalp, and check if errors still occur.
6. If errors still occur, take a break, and wait until the naming returns to normal.
   NOTE. Repeated naming errors unrelated to the stimulation may be common if speech-related areas are affected by a tumor or other lesion.
7. Stimulate in blocks of 7-10 min (maximum) continuously, and have 2-5 min breaks in between.
   NOTE: Errors become more common with long stimulations and if the subject is tired.

7. Stimulate all the possibly related anatomical areas (e.g., IFG, STG, SMG, middle temporal, precentral, postcentral, and angular gyri, and the prefrontal cortex) to obtain as many control responses as possible.
8. If feasible and/or clinically supported, stimulate both hemispheres. Stimulate carefully inside and around the tumor region or the estimated location of the lesion even if those regions do not belong to the classical speech-related areas (for tumor and epilepsy patients).
   1. Investigate cortical areas that are located away from the lesion site to identify possible spatial shifts in the language areas due to plastic changes or the mass effect, especially in patients with large lesions.
9. Reduce the TMS intensity in steps of 2%-5% of the maximum stimulator output if the mapping induces pain or discomfort.
10. Stop the measurement if the induced pain or discomfort are not tolerated by the subject.

6. Strategy when no naming errors occur

1. Terminate the stimulation, and change stimulation parameters.
2. Decrease the IPI in steps of 200 ms from the default value (e.g., from 2,500 ms to 2,300 ms).
3. Change the frequency of pulse delivery from 5 Hz to 7 Hz. Change the interval between the onset of the presented image and the rTMS (currently, there is no consensus on whether to increase or decrease it). Increase the stimulation intensity (without evoking discomfort).

7. Off-line analysis of the evoked naming errors

1. Collaborate with an expert (e.g., a neuropsychologist), who should optimally be present in the operating room.
2. Double-check the evoked naming errors by observing the coil positioning and possible pain interference from the video recordings.
3. Classify the errors according to Corina et al.[27] (e.g., anomia, semantic and phonological paraphasia, performance errors).
   1. If a particular type of error repeats itself in the baseline video, do not consider it as an error when analyzing the stimulation session videos.
4. If an object is named after the rTMS train, consider this as a delay or a no-error; check also for possible discomfort of the subject during the pulse delivery.

5. If the subject cannot name a given object although the tongue, lips, and jaws are moving, record a no-response error.
6. If an image is named differently in each session, discard it.
7. If unsure, control the performance of the neighboring stimulation site or the effect of the stimulation of the other hemisphere with the same image.

Representative Results

A navigated transcranial magnetic stimulation system with integrated screens and cameras was used. **Figure 1A-C** highlights the different TMS-evoked naming errors in one subject during the task at different PTIs (180 ms, 200 ms, and 215 ms). The effect of the timing of the TMS pulses on the number of errors evoked is evident. In other words, TMS-related changes in performance were detected in different areas at different PTIs. The number of errors varied depending on the timing of the TMS pulses even at the same cortical sites, in accordance with MEG studies demonstrating the variation in the timing of activation in different speech-related cortical areas[28]. A comparison of the results between extraoperative DCS mapping and nrTMS with a fixed PTI at 300 ms in a patient with intractable epilepsy is shown in **Figure 2**. The data were obtained from a previous publication focusing on epilepsy[29].

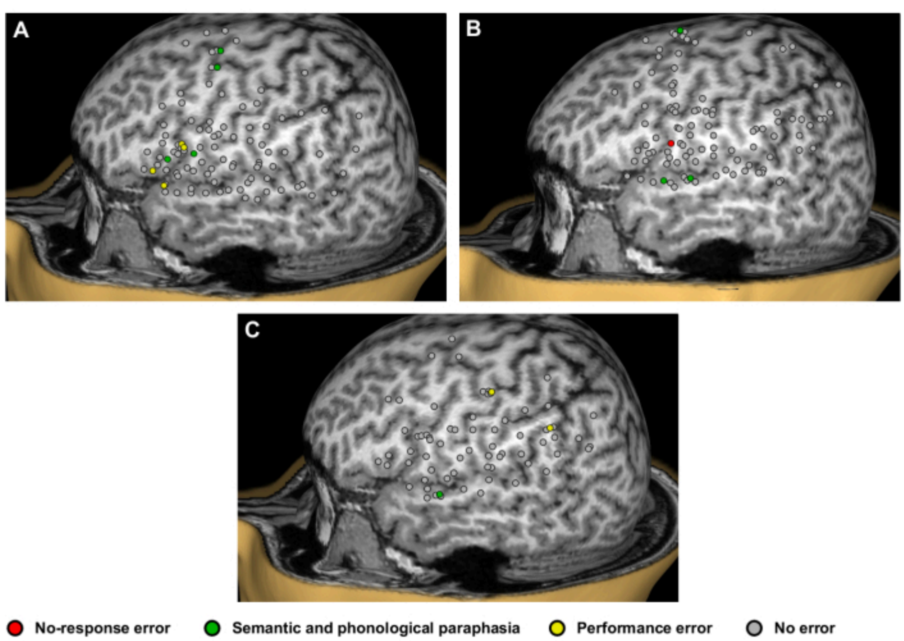

Figure 1: Results of an nrTMS SCM illustrated over a 3D MRI-based model from a healthy volunteer. (**A**) PTI of 180 ms. (**B**) PTI of 200 ms. (**C**) PTI of 215ms. In addition to the major speech-related areas, the pre-supplementary motor area (pre-SMA) was stimulated as described in the protocol (step 5.7). Most of the errors were evoked in the classical speech

areas (IFG, STG, SMG), but also along the path connecting the pre-SMA and Broca's area (the close-to-midline green spots in **A** and **B**). Please click here to view a larger version of this figure.

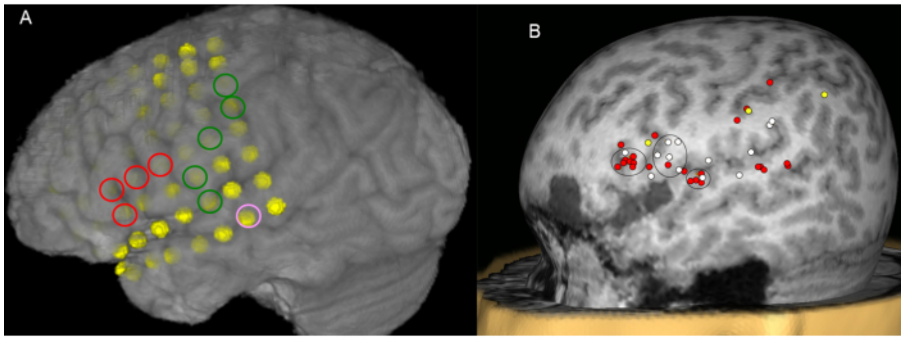

Figure 2: Comparison of the results between extraoperative DCS mapping and nrTMS with a fixed PTI at 300 ms in a patient with intractable epilepsy. (**A**) Extraoperative grid mapping at the age of 13. The yellow spheres represent all the electrodes on the cortex. The sites of electrode stimulation (2-5 mA) that induced motor responses of the hand and mouth (green circles), naming arrest (anomia; red circles), and interrupting sentence repetition (pink circles) are shown. (**B**) nrTMS SCM of the same patient at the age of 15. The sites of nrTMS-induced anomias (red dots), semantic and phonological paraphasias (yellow dots), and hesitations (white dots) are shown. The areas with highly reproducible and reliable error induction are circled. The data for this image were taken from the study of Lehtinen et al.[29]. Please click here to view a larger version of this figure.

Supplementary Figure 1: Examples of images presented in the nrTMS SCM experiment (in Finnish in parentheses). (**A**) Hanger (Henkari). (**B**) Scissors (Sakset). (**C**) Strawberry (Mansikka). Please click here to download this File.

Discussion

Here, a protocol is presented for nrTMS SCM, which enables practically complete cortical noninvasive mapping of the most important hubs of the speech and language network. Its main advantage is that it can non-invasively simulate the DCS mapping during awake craniotomy[30] or extraoperatively[29] (see **Figure 2**). Moreover, it can be applied to language cortical network studies in healthy populations[31] and in patients with diseases that are not amenable to surgery[32]. nrTMS for SCM may also be applied to develop neurorehabilitation strategies such as target selection (e.g., after stroke). The induction of plasticity in speech-related cortical representations by DCS prior to surgery has been studied[33] to increase the extent of resection[34]. The possibilities of nrTMS SCM in such studies should be examined.

In the present results, a relatively large area, including classical speech-related areas and the pre-SMA, was repeatedly stimulated at three different PTIs. Each PTI showed different sensitivity and specificity to errors, but also demonstrated the well-known response variability in non-invasive brain stimulations[35]. Most errors were induced by the stimulation of the IFG, STG, pre-SMA, and along the frontal aslant tract[36]. This highlights the power of nrTMS SCM; specifically, in comparison to DCS, the stimulation can be quite flexibly targeted to several areas. We have observed that changing the PTI and recording many sessions does not clearly speed up the reaction times[26,29], which would be associated with a learning effect.

The protocol highlights different parameters that can affect the accuracy of nrTMS SCM. The results can be sensitive to the choices made by the TMS operator; the present paper aims to provide a standard guideline with well-tested stimulation parameters. High specificity results from an appropriate choice of several different parameters, including the ISI, PTI, coil location, and rTMS frequency. These parameters affect the specificity of the induced errors, which reflect the functions in the underlying cortical areas; the parameter selection needs to be based on current knowledge on the neurobiology of language.

The images for the naming task should be selected so that they do not induce erroneous naming by themselves (**Supplementary Figure 1**). Here, the images were chosen from a standardized image bank and controlled for various naming parameters[25,37]. For example, the pool of images was restricted to items with similar complexity and frequency in everyday use, as well as high name agreement. The choice of images can vary based on the needs of each surgical center[38], the population under investigation[39], the native language of the tested subject[40,41] and the used task[42]. As presented in the protocol, the baseline image selection is finally individualized for each subject, as on-spot naming is subjective.

The stimulation frequency needs to be defined individually, because it may determine the distribution of errors during navigated transcranial magnetic brain stimulation[43]. The presented choice, 4-8 Hz, is based on the rTMS work by Epstein et al.[44]. The initial stimulation frequency is set to 5 Hz. If no errors are detected, the stimulation frequency is increased to 7 Hz. Higher frequencies may reduce nrTMS-induced pain and increase the specificity of naming errors[45]. Higher frequencies also have the advantage of limiting the pulses to a short and more specific time interval. They may, however, affect functions related to, for example, speech motor execution[44,46], which are not the main target of the present protocol.

It is recommended to vary the PTI between 150-400 ms. This is an important time window for word retrieval during the object naming task[28,47]. The protocol aims at speech specificity by avoiding the interference of basic visual processing, which occurs during the first 150 ms after image presentation and may affect object naming but is unrelated to speech production. The recommended upper limit for the PTI is based on typical response latencies in picture naming in the same subject[28,48], and individual variation in the optimal values between subjects can be expected (see **Figure 1**). The PTI selection should ideally be based on personalized measures, although this may be logistically demanding in a clinical setting. Helsinki University Hospital protocols usually start with a 300 ms PTI. It may also be useful to change the PTI based on the stimulated area[12,13,49], as indicated by several language studies[28,47,50]. Nevertheless, PTIs outside the above-mentioned window may also induce naming errors that are useful for presurgical evaluation (for a comparative study, see Krieg et al.[49] using PTIs of 0-300 ms).

The cortical speech network is widespread and varies among individuals, particularly in patients with tumors and epilepsy[29,30,39]. nrTMS induces language disturbance with great variability across individuals, analogous to those observed during awake craniotomy stimulations[27,51]. The information obtained from fMRI[50], DTI[52,53,54], and MEG[55] can direct the nTMS user and result in a procedure that is tailored for each individual and is, thus, more specific and accurate. The objective in nrTMS SCM is to increase the specificity, reduce the number of non-responders, guide the DCS reliably, or replace it when the resources and conditions do not allow a team of highly specialized experts to perform it. In the future, multilocus TMS (mTMS) could be applied in the procedure to stimulate different parts of the cortex without physically moving the stimulation coil[56].

The present protocol can be performed with several types of naming tasks[42,57] or other cognitive tasks (calculations, decision making, etc.)[58]. The video recording can disclose crucial features of the task performance (e.g., grimaces by the subject indicating that no motor speech arrest is induced) that can go unobserved during the stimulation. The setup also allows for asking the subject about the nrTMS-induced experiences and sensations by jointly viewing the video recording. This can help in distinguishing pain-induced errors from the true effects of nrTMS. Finally, the protocol can be easily modified to different subject groups (e.g., bilingual individuals[31]) and to serve the needs of each surgical or research team.

Disclosures

P.L. has been a consultant to Nexstim Ltd. for motor and speech cortical mapping.

Acknowledgments

Pantelis Lioumis has been supported by an HUS VTR grant (TYH2022224), Salla Autti by the Päivikki and Sakari Sohlberg Foundation, and Hanna Renvall by the Paulo Foundation and Academy of Finland (grant 321460).

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