Video Article

Neuronavigation-guided Repetitive Transcranial Magnetic Stimulation for Aphasia

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) is widely used for several neurological conditions, as it has gained acknowledgement for its potential therapeutic effects. Brain excitability is non-invasively modulated by rTMS, and rTMS to the language areas has proved its potential effects on treatment of aphasia. In our protocol, we aim to artificially induce virtual aphasia in healthy subjects by inhibiting Brodmann area 44 and 45 using neuronavigational TMS (nTMS), and F3 of the International 10-20 EEG system for conventional TMS (cTMS). To measure the degree of aphasia, changes in reaction time to a picture naming task pre- and post-stimulation are measured and compare the delay in reaction time between nTMS and cTMS. Accuracy of the two TMS stimulation methods is compared by averaging the Talairach coordinates of the target and the actual stimulation. Consistency of stimulation is demonstrated by the error range from the target. The purpose of this study is to demonstrate use of nTMS and to describe the benefits and limitations of the nTMS compared to those of cTMS.

Video Link

The video component of this article can be found at <http://www.jove.com/video/53345/>

Introduction

Repetitive transcranial magnetic stimulation (rTMS) non-invasively activates neuronal circuits in the central and peripheral nervous systems.¹ rTMS modulates brain excitability² and has potential therapeutic effects in several psychiatric and neurological conditions, such as motor weakness, aphasia, neglect, and pain.³ The target sites for rTMS other than the motor cortex are conventionally identified using the International 10-20 EEG system or by measuring distances from certain external landmarks.

However, inter-individual differences in size, anatomy, and morphology of the brain cortex are not taken into account, making optimal target localization challenging.³ Another critical issue for rTMS applications is the discordance between placement of the magnetic coil and the cortical region of intended stimulation.

Optically tracked navigational neurosurgery has expanded its applications to encompass the cognitive neuroscience field including rTMS for guidance of the magnetic coil. The neuronavigational system assists in identifying the optimal target structures for rTMS.^{4,5} Such divergence in coil positioning on the target area frequently occurs with the conventional method adopting the 10-20 EEG system, and this is expected to be overcome by neuronavigation.

This study protocol demonstrates a method to induce virtual aphasia in healthy subjects by neuronavigational rTMS targeting Broca's area, using individual anatomical mapping. The degree of virtual aphasia in terms of change in reaction time to picture naming is measured and compared with those from the conventional stimulation method. The neuronavigation-guided method has higher accuracy for delivering magnetic pulses to the brain, and is thus expected to demonstrate greater clinical change than that of the conventional method. The goal of this study was to introduce a more precise and effective method of stimulation for patients with aphasia in clinical setting.

Protocol

Ethics statement: This study was approved by the institutional review board of a blinded hospital.

1. Preparing Materials (Table 1)

1. Use TMS equipment with maximum output of 3.0 Tesla and a power supply of 200-240 Vac 50/60 Hz 5A at a pulse width of 350 μ sec.

2. Acquire resting motor threshold (RMT) in each subject by electromyography (EMG) to determine the motor evoked potential (MEP) using the TMS system and the active electrode (see step 3.1 for details). Set the RMT as individual intensity for the actual TMS study protocol (**Figure 1**).
Note: The neuronavigational system includes a computer screen, subjective tracker, coil tracker, pointer, calibration block, camera, and TMS chair seating system. (**Figures 2-4**)
3. Use the Superlab program to set up the picture naming task and present the stimulus to the subjects to test the degree of induced virtual aphasia.
4. Record reaction time for each picture using a voice recording system, described in more detail in step 4.
5. Analyze latency and duration of the picture naming response by a voice analysis system, described in more detail in step 4.

2. Checking the Study Design

1. Use rTMS to Induce Virtual Aphasia.
 1. Ask the subject to perform the picture naming task, described in more detail in step 4. Picture naming task.
 2. Apply either neuronavigation-guided rTMS (nTMS) or conventional rTMS (cTMS) during the picture naming task. The details of cTMS are described in steps 5.3.2 and 5.5.
2. Measure reaction time and error rate for picture naming and compare the results under both conditions, as described in more detail in step 4.

3. Preparation of the TMS Protocol

1. Determine RMT
 1. Place the active electrode on the left first dorsal interosseous (FDI) muscle.
 2. Deliver 10 consecutive stimulations to the right M1 area at a 4-6 sec interstimulus interval, checking the contraction of the left FDI muscle.
 3. Determine subject's RMT using the minimum TMS intensity at which a peak-to-peak MEP amplitude greater than 50 μ V is produced at least five times.
2. TMS Mapping
 1. Obtain a high resolution T1-weighted magnetic resonance (MR) anatomical images using a 3-T MR scanner of the subject for use of the neuronavigational system. The parameters for the MRI scan are summarized in **Table 1**.
Note: Transfer the brain MR images to the neuronavigation program, which reconstructs the brain curvilinear and skin of each individual using anatomical guidance of the anterior commissure (AC) and posterior commissure (PC), as shown in **Figure 5**.
 1. Reconstruct the skin structure
 1. Obtain the file of the subject's brain MR image in standard Digital Imaging and Communications in Medicine (DICOM) format. Convert the MR image by selecting "convert study". Set the search directory from which the file is transferred to the neuronavigation computer. Convert type should be selected by DICOM type to be used in the neuronavigation program.
 2. Transfer the DICOM file to the computer in which the neuronavigation program is installed. Implement the navigation program. The default icon is "Anatomical." For a new patient record, select one of the DICOM image files.
 3. Click "Atlas spaces". This step is to set the reference point to reconstruct each image. Press "new" in the dropdown and set the reference anatomical structure by clicking "manual (AC-PC box)".
 4. Find the patient's AC of the corpus callosum, just the midline of two hemispheres placed in front of the columns of the fornix. Mark AC on the MR image and click "set AC".
 5. Find the patient's PC, the midline of the two hemispheres in the dorsal aspect of the upper end of the cerebral aqueduct. Mark PC on the MR image and click "set PC".
 6. Click "Reconstructions" to make the skin structure. Press "new" in the dropdown to select "Skin". Set the range for reconstruction on the MR images. Be sure to include the whole skull with the nasal tip and both ears.
 7. Click "compute skin" in the new structure. Wait until the process is done. After completion of skin construction, skin morphology should be displayed.
 2. Select "Full brain curvilinear" in the "Reconstruction" section to reconstruct the brain curvilinear following 3.2.1.1. Similar to the previous step, set the range for reconstruction on the MR images containing the nasal tip. Click "compute curvilinear". Full brain curvilinear should be displayed after construction is completed.
 2. Mark the nasion, nasal tip, and both tragus to register the anatomical landmarks. This step is to match the anatomical point between the patient and the reconstructed skin structure for configuration of the relative position of the target on the brain cortex (**Figure 6**).
 1. Click the "Landmark" icon. To configure the landmark, mark the nasion (point between the forehead nose, at the junction of the nasal bones) on the computed skin structure. Register it by clicking "new" and store it as "Landmark 1"
 2. Mark the nasal tip after registering nasion as landmark 1. Register the nasal tip by clicking "new" and store it as "Landmark 2"
 3. Mark each tragus on the skin structure. The tragus is the small pointed eminence of the external ear, situated in front of the concha. Register each tragus after marking and clicking "new" landmarks. For this protocol, the right tragus is registered as "Landmark 3" and the left is registered as "Landmark 4".
 3. Put the head strap with the subjective tracker on the participant's head. Calibrate the coil tracker with the calibration block of the navigational seating system at every session for each subject. Make sure the navigational camera detects and displays all of the tracking system of the subject, the chair, the coil, and the pointer on the computer screen before proceeding.
 1. Calibrating the coil with the seating system.

1. Calibrate the coil tracker before every nTMS stimulation. At the main computer menu, select "Window". Click "TMS coil calibration" in the dropdown. Click "new calibrate". At the second session, select the coil name used the first time and click "Re-calibrate".
2. Place the TMS coil on the standard point posterior of calibration block. Be sure the coil is horizontally placed. Check that the camera is detecting both the calibration block and coil tracker (shown in green). Then, click "Begin calibration countdown", and a 5 sec of countdown will start. Hold the coil still during the countdown.

4. Picture Naming Task

1. Set the picture naming program to present each stimulus for 3,000 msec before automatically moving onto the next picture.
2. Ask the participant to name the presented picture as accurately and quickly as possible.
3. Measure reaction time (latency from pop up of the stimulus on the screen to the first sound made by the participant) for each picture by detecting the sound made by the subject through the headset microphone using the freeware voice analysis program.
 1. Forty pictures matched in name length and segments of two to three from the picture database of the Korean version of the Boston Naming Test (K-BNT) are presented on the screen pre- and post stimulation, as in the study by Kim *et al.*, (2014).

5. TMS Mapping Protocol

1. Deliver 1 Hz stimulation at an intensity of 90% of RMT for 10 min, with a total of 600 TMS pulses.
2. Hold the figure-eight coil tangentially to the skull with the coil perpendicularly oriented to the target.
3. TMS Mapping (**Figure 7**)
 1. Identify the anatomical inferior frontal gyrus (IFG) based on the surface of the normalized brain, for nTMS.
 1. Register the IFG as the nTMS target.
 1. Click "Target" and press "Configure targets". Mark the IFG on the window displaying the brain curvilinear. Detailed target setting is achieved by targeting each transverse and sagittal MR images. Save the point as "Trajectory".
 2. Register landmarks with the subjects scalp.
 1. Click "Sessions" for mapping. Create a new session by selecting "Online session" in the new dropdown. A "Session 1" window is created, within which the default icon is "Targets". Select the target name saved in step 3.2.2.2. (Select "Trajectory 1"). Click the "Add" button, and move to the next step.
 2. Click "Registration". This step is to match the reconstructed brain curvilinear with the subject. The registered landmark in step 3.2.2.1. is used for matching the anatomical point with the real anatomical structure.
 3. Make sure the camera identifies both the pointer and the subject tracker, displayed in green color. Point to the subject's nasion with the pointer. Click "Sample % Go to Next Landmark". Point to the subject's nasal tip and sample it. Repeat until all four landmarks are matched.
 2. Place the coil on F3 of the 10-20 international EEG system⁷ for cTMS.
4. Look at the screen to ensure the coil is on the desired target and is maintained throughout the nTMS procedure. The screen should display the subject's brain surface, intended target, and the coil, as well as the error range as the coil moves away from the target shown by the bull's eye (**Figure 8**). Referring to the screen, the operator adjusts the coil on the target as it is moved away.
 1. Perform nTMS over the registered target
 1. Click "Perform" on the screen after registering the subject's landmarks as described in step 5.3.1.1. To change the default setting of the camera to detect the pointer, choose the coil name saved during step 3.2.3.1. at the bottom of the "Driver" dropdown. Make sure the camera identifies both the subject tracker and coil tracker.
 2. Check that the screen displays the relative distance and angle of the TMS coil from the registered target (IFG). If the coil moves away from the target, the distance is marked in red, whereas it is marked in green when the coil is within the intended target range. Try to obtain the angle between the coil and the target as a bull's eye as much as possible.
5. Turn the screen away from the operator for the cTMS procedure to blindly deliver the TMS. The coil is maintained as it was at the beginning of the session.

6. Topographic Data Acquisition

1. Record coil location per stimulation by manually pressing the "record" button on the remote control.
2. Upon recording each stimulation, acquires Talairach coordinates in the x, y, z for the designated target and actual stimulated area.
3. Depict the coordinates on a single normalized brain using the freeware image processing program (MRIcro, <http://www.mccauslandcenter.sc.edu/micro/micro/index.html>).
4. Acquire corresponding anatomical brain areas, including the Brodmann area, the gyrus, lobe, and hemisphere region labels to the talairach coordinates using a freeware labeling program (Talairachclient, <http://www.talairach.org/client.html>).

Representative Results

Kim *et al.* demonstrated a more superior effect of TMS with neuronavigational system guidance compared to the non-navigated conventional method by less dispersion of stimulus and more focal stimulation to the right M1 area,⁸ as shown in **Figure 9**. Further evidence to support incorporating the neuronavigational system with TMS is demonstrated by a randomized crossover experiment to induce virtual aphasia in healthy subjects by targeting Brodmann area 44 and 45 for nTMS and F3 of the International 10-20 EEG system for cTMS.⁹

Kim *et al.* compared cTMS and nTMS in 16 healthy subjects by following measures; reaction time for a picture naming task measured before and after each session of stimulation, the mean Talairach space coordinates of localization of stimulation, and the error range relative to the target (**Figures 10-12**). **Figure 10** shows only the nTMS induced a significant delay in reaction time compared with baseline, and greater consistency of localization of stimulation with the target in demonstrated in **Figure 11**. **Figure 12** shows a narrower error range relative to the target for the nTMS compared with that of cTMS.

These significant differences in the nTMS group were induced by the high precision of the TMS pulse delivery to the intended target by narrowing the distance between the target and the coil when guided by neuronavigation, thereby producing more significant results compared to those of the conventional method. Exact placement of the coil on the target is absolutely critical for producing clinically effective results. Above results support use of neuronavigational guidance when applying rTMS.

Figure 1: Transcranial Magnetic Stimulation (TMS) System and Electromyography (EMG) Machine to Acquire Resting Motor Threshold (RMT)

Right M1 area is stimulated with the active electrode on the left first dorsal interosseous muscle to determine RMT [Please click here to view a larger version of this figure.](#)

Figure 2: Equipment Setting for the Navigation System. Transcranial magnetic stimulation (TMS) chair, mobile camera, and computer screen with TMS equipment are included. [Please click here to view a larger version of this figure.](#)

Figure 3: Preparing Materials. Picture of coil tracker, pointer, and subjective tracker. [Please click here to view a larger version of this figure.](#)

Figure 4: Calibration Block with Coil Tracker. This allows the program to detect the relative position of the transcranial Magnetic stimulation (TMS) coil. [Please click here to view a larger version of this figure.](#)

Figure 5: Reconstructed Brain Curvilinear by the Neuronavigation Program. Once the brain magnetic resonance MR images are transferred to the neuronavigation program, the brain curvilinear and skin are reconstructed using anterior commissure (AC) and posterior commissure (PC). [Please click here to view a larger version of this figure.](#)

Figure 6: Anatomical Landmarks for Navigation Transcranial Magnetic Stimulation (TMS). Anatomical landmarks, nasion, nasal tip, and both tragus are marked using a pointer. [Please click here to view a larger version of this figure.](#)

Figure 7: Transcranial Magnetic Stimulation (TMS) Mapping. Inferior frontal gyrus for the navigation-guided TMS (left) and F3 of the International 10-20 system for conventional TMS (right) are set to stimulate the target. [Please click here to view a larger version of this figure.](#)

Figure 8: Neuronavigation Display during Navigation-guided Transcranial Magnetic Stimulation (nTMS). Screen displays subject's brain surface, intended target, coil, and error range. [Please click here to view a larger version of this figure.](#)

Figure 9: Less Dispersion of the Stimulus and More Focal Stimulation with the Navigation. Comparison of the non-navigated conventional method (left) with navigational guidance (right) demonstrates less dispersion of the stimulus and more focal stimulation of the right M1 area using navigation-guided transcranial magnetic stimulation (nTMS). Modified from reference⁹. [Please click here to view a larger version of this figure.](#)

Figure 10: Comparison of the Ability to Induce Virtual Aphasia between Navigation-guided Transcranial Magnetic Stimulation (nTMS) and Conventional TMS (cTMS) in 16 Healthy Subjects. Mean picture naming time (in msec) is significantly increased ($p < 0.001$) with nTMS whereas no change is made with cTMS ($p = 0.179$). Bars represent mean reaction time with corresponding standard errors. Modified from reference⁹. [Please click here to view a larger version of this figure.](#)

Figure 11: Drawing of Mapping Area and Stimulation ($n = 16$). The areas stimulated for the conventional method (green) are more widely distributed with the coordinates scattered more upward relative to the target (red) compared to those of the navigation method (purple). Modified from reference⁹. [Please click here to view a larger version of this figure.](#)

Figure 12: Mean Error Ranges for Navigation-guided Transcranial Magnetic Stimulation (nTMS) and Conventional TMS (cTMS) ($n = 16$). The distance from the actual stimulation site relative to the target is closer with nTMS than cTMS. The error range is narrower for nTMS than that for cTMS. Bars represent means and standard errors. Modified from reference⁹. [Please click here to view a larger version of this figure.](#)

Parameters	Values or descriptions
Field of view	
Anterior to posterior (mm)	256
Right to left (mm)	256
Foot to head (mm)	175
Voxel Size	
Anterior to posterior (mm)	1
Right to left (mm)	1
Foot to head (mm)	1
Reconstruction matrix	
Slices	175
Slice orientation	Transverse
Fold-over direction	Right to left
Scan mode	Three dimensional
Technique	Fast field echo
Contrast enhancement	T1
Fast imaging mode	Turbo field echo
Shot mode	Multishot
Flip angle (degree)	8
Repetition time (ms)	8.1
Echo time (ms)	4.6
Acquisition matrix (MIP)	
Acquisition matrix (MIP)	256×256
Acquisition voxel	
Measurement (mm)	1
Phase (mm)	1
Slice (mm)	1
Reconstructed voxel	
Measurement (mm)	0.5
Phase (mm)	0.5
Slice (mm)	1

Table 1: Three-dimensional T1-weighted Magnetic Resonance Imaging (MRI) Parameters for this Study

Discussion

TMS is widely used both in clinical practice and basic research.¹⁰ Valuable therapeutic effects are offered by the physiologic influence of rTMS, including an inhibitory neuromodulatory effect on cortical excitability with low frequency rTMS for treatment of aphasia.¹¹ Transient disruption of neural processing or virtual lesioning induced by rTMS can change behavioral performance.¹² However, the desired effect of rTMS may be diluted or even not occur with the coil misplaced on the target. Mis-targeting between the originally intended target and the actual stimulated cortical area can occur due to minor differences in coil placement and orientation; hence, significantly affecting the magnetic field created in the brain.⁷ Therefore, such sources of variability should be minimized when applying TMS, and delivering magnetic pulses accurately to the desired cortical area is mandatory to deliver the maximal clinical rTMS effect.

To solve this critical issue of problematic coil placement on the target cortical region, adopting optically tracked rTMS using a neuronavigational system optimizes coil stability.¹³ The neuronavigation program utilizes individual MR images, thereby providing online visual feedback of the coil positioning with respect to the target area, allowing real-time adjustments in coil position by correcting the misdirected coil-head relationship.¹³ A focused magnetic field stimulation within a range of several millimeters is achieved due to the high precision of neuronavigation, enabling more strong rTMS pulses to reach specific anatomical structures.

This protocol tests the effects of neuronavigation-guided TMS on language function in terms of reaction time to picture naming by inducing virtual aphasia in healthy subjects and comparing the results with those obtained from the conventional TMS method using the EEG landmark, and relating the results with the actual stimulated area of the brain by each method.

Precise target determination is critical because accurate stimulation of the target is guaranteed once use of the navigational system is decided. In this protocol, targets for stimulation of IFG are registered based on anatomical mapping of individual brain cortical surfaces, and this can differ from that of the F3 of the 10-20 EEG system, corresponding to Brodmann area 44 and 45,⁶ where F3 is more posterior and superior relative to the IFG, and stimulating the IFG produced significant virtual aphasia, whereas blind stimulation of F3 did not.⁹ The consistency of stimulation on the specific brain region is maximized with the navigation system; thus, enhancing the physiological effects of rTMS. These results are supported by the dramatic shifts in TMS-induced performance due to small changes in the stimulation location.¹⁴

However, the findings and interpretations of the nTMS protocol used by Kim *et al.* (2014) have limitations. It demonstrated a greater inhibitory effect in healthy subjects by inducing significant virtual lesioning, but whether it has the same facilitative effect in patients with aphasia has not

been tested. This can be confirmed by performing this protocol in actual patients with aphasia, such as those with post-stroke aphasia. Speech function is artificially suppressed in normal subjects for our protocol, whereas it must be facilitated with different frequencies for patients with aphasia in whom speech function is already suppressed. Also, recognizing the IFG on the brain surface on anatomical bases can be quite challenging as location and contours may differ among subjects.

Optically tracked neuronavigational system elicits more profound virtual lesions than those of the conventional non-neuronavigated method. This protocol demonstrates that using nTMS, compared to cTMS, can produce more robust neuromodulation of Broca's area which is critical for treatment of post-stroke aphasic patients.

Disclosures

All authors declare no conflict of interest.

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