HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2017-1)

Protocol Title: Sensory Basis of Speech Motor Learning (R01)

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Version Date: April 15, 2019

(*If applicable*) **Clinicaltrials.gov Registration #:** Click or tap here to enter text.

INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:** 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type "Not Applicable" underneath. 3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

   The studies in Aim 1 will be conducted at McGill University, Montreal and will be reviewed by the Faculty of Medicine IRB at McGill. The studies in Aim 2 and Aim 3 will be conducted at Haskins Laboratories and the Yale University Magnetic Resonance Research Center.

   Aim 1 : To identify brain structures involved in the consolidation of speech motor learning.

   Continuous theta-burst transcranial magnetic stimulation (cTBS) will be used to selectively suppress frontal motor areas and, separately, somatosensory and auditory cortex following speech motor learning to test their causal role in motor memory consolidation. In preliminary studies, we find that cTBS to somatosensory cortex following learning interferes with retention whereas sham cTBS and cTBS to primary motor cortex do not. This suggests that it is somatosensory cortex rather than motor cortex that participates in the consolidation of motor memory.

   Aim 2: These studies test the hypothesis that working memory circuits involving prefrontal cortex contribute to speech motor learning.

   Although memory for articulator configurations is presumably needed for learning, to enable the repetition of correct movements and the avoidance of errors, its contribution to speech motor learning is largely unknown. The proposed studies focus on memory for speech movements and sounds and its relation to learning. Using cTBS, we will suppress activity in a regions of pre-frontal cortex associated with somatic and auditory working memory (Brodmann area 46v) to test their involvement in learning. Preliminary data suggest that suppression of area 46v interferes both with learning and working memory, consistent with its involvement in each.

   Aim 3: To test the hypothesis that somatosensory inputs similar to those normally associated with speech production alter the perception of speech sounds and reveal the presence of a somatic cortical network that participates in speech perception.

   The involvement of the somatosensory system in speech perception presumably arises during speech motor learning as auditory and somatosensory inputs are repeatedly paired. We have created a model of this process to test the idea that the pairing of somatosensory inputs with speech sounds results in experience dependent changes to the perceptual classification of speech. We have developed an MR compatible robot that delivers speech-like patterns of facial skin deformation as participants listen to speech sounds in the scanner. We will use this technique to test the idea that repeated pairing of auditory and somatosensory inputs, as occurs in speech motor learning, engages somatosensory areas in speech perception.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.

   July 1, 2019—June 30, 2023

3. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Brain structures in speech motor memory consolidation. The consolidation of motor memory makes possible the retention of newly learned movements. The behavioral characteristics of motor memory consolidation are well documented in work on upper limb movement, but the neural circuits which enable maintenance and consolidation of motor memories are less certain. There has been little work on the factors and associated brain structures that determine motor memory consolidation in speech. For a convincing demonstration of the involvement of a brain structure in memory consolidation it is necessary to rule out any possible interference by the experimental manipulation with the learning process itself. However, it is difficult to rule out this possibility when, as in previous studies, stimulation is delivered prior to or during training. An alternative approach which we pursue in Aim 1 to assess motor memory consolidation in speech, is to disrupt candidate structures following the completion of training (to block consolidation) and then, following a delay which would normally permit consolidation, assess whether there is an impairment in retention. A small number of arm movement studies have taken this approach. rTMS to M1 following motor learning is found to disrupt retention of a simple ballistic movement task but does not alter retention of a more complex motor task involving altered dynamics. Apart from simple repetitive movements, it is not presently known which areas of the brain are involved in the consolidation of motor memory neither in arm movement nor in speech. It is known that changes to sensory systems occur broadly in association with motor learning, speech motor learning included. Accordingly, changes to sensory systems could possibly play a role in speech motor memory consolidation. If this were the case, then the transient suppression or disruption activity in somatosensory and / or auditory cortex following learning, with the goal of blocking the storage of new sensory targets, should adversely affect the retention of speech motor memory.

Role of sensory working memory in speech motor learning. The need to retain information about prior movements and states is central to motor skill acquisition. This need is particularly clear in speech motor learning which occurs without visual guidance and hence is likely reliant on both auditory and somatosensory working memory. However, apart from a small set of studies on working memory in visuomotor adaptation and sequence learning and our own recent work on reinforcement learning, there has been little work on sensory working memory in the context of motor learning and none that we are aware of in relation to speech motor learning per se.

We expect parts of prefrontal cortex to contribute both to sensory working memory and learning. Prefrontal cortex in general is interconnected anatomically with frontal motor areas and also with areas of the cerebellum and basal ganglia. However, apart from Broca's area in the inferior frontal gyrus, little is known about its role either in movement control or in speech motor learning. Areas within prefrontal cortex have been implicated in somatosensory and auditory working memory, specifically, ventrolateral prefrontal cortex (area 46v). This area is part of a network that receives both auditory and somatosensory inputs and accordingly, we expect that suppression of activity in 46v should adversely affect both sensory working memory and speech motor learning.

Contribution of the somatosensory system to speech perceptual processing. Somatosensory function in speech is normally associated with motor function. However, one intriguing aspect of somatosensory function is that it affects speech perception even in the absence of movement. There are several examples in which somatosensory stimulation affects the auditory perception of speech sounds. Notably, somatosensory inputs due to speech-like skin stretch and orofacial airpuffs both result in changes to the auditory classification of speech. While speech processing is clearly auditory in nature, these studies suggest that the somatosensory system contributes not only to speech motor control, but also to the perceptual processing of speech sounds. Indeed, it raises the possibility that a somatosensory cortical network may participate in the perception of speech.

The participation of the somatosensory system in speech perceptual processing likely arises over the course of speech motor learning during which auditory and somatosensory inputs are repeatedly paired. We have designed a new experimental model of this process to test the idea that the pairing of somatosensory inputs with speech sounds results in experience dependent plasticity in auditory and somatosensory cortex, which in turn changes the perceptual classification of speech. The idea is that paired sensory experience over the course of speech motor learning results in a paired sensory contribution to speech perception.

4. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths**. Describe the setting in which the research will take place.

   Experimental Participants: Different groups of subjects will be tested in each study of each specific aim. Unless otherwise indicated, subjects will each participate in only one experimental condition. The number of participants per condition is 20 for tests involving behavioral manipulations and 25 for testing involving fMRI. Subjects are randomly assigned to treatment conditions.

   Aim 1: To test the idea that both somatosensory and auditory cortex contribute to the consolidation of speech motor memory. Note that work on this Aim is to be conducted entirely at McGill University in Montreal. The Methods and Expectations which are given below are provided for completeness.

   Methods: Subjects will train using either altered somatosensory feedback or altered auditory feedback (different groups of subjects). Immediately following adaptation, cTBS will be applied to either auditory or somatosensory or motor cortex with the goal of blocking consolidation of motor memory. Stimulation sites we be identified from fMRI behavioral localizer scans run on a separate day. The logic of applying cTBS to both sensory areas is to test the hypothesis that both areas are involved in motor memory consolidation regardless of whether adaptation to altered auditory or altered somatosensory feedback is tested. Subjects leave the laboratory following cTBS and return 24 hours later to assess retention of learning. In retention tests related to somatosensory feedback, subjects will be connected to the robot and required to read words aloud one at a time that are displayed on a computer screen. To test for retention of altered auditory feedback, subjects also read words aloud one at a time but are not connected to the robot. After-effect trials under null conditions followed by re-learning trials will be tested in each case.

   As a control, we will test for the possibility that any observed effects of cTBS on retention are due to current leakage from sensory cortices into motor cortex. Subjects in a further control group will undergo the same procedures using sham TMS in which the stimulating coil over somatosensory or auditory cortex is turned sideways. These subjects will also return 24 hours later to test for retention of learning. In preliminary data cTBS to M1 did not interfere with the consolidation of motor memory. Assuming this is replicated in the proposed studies, it would rule out the possibility of a non-specific effect of cTBS. However, if necessary we will add another control group, in which cTBS is applied to visual cortex.

   Note that sham TMS is used to assess the possibility of placebo effects of TMS stimulation. Participants are not informed of this deception as knowledge of potential sham stimulation may introduce cognitive factors into subjects' performance, for example, if participants believe they are possibly being tricked, this could bias how they perform the task and make the basic sensorimotor effects under study difficult to interpret. The specific information that is withheld in the sham TMS procedure is that fact that the stimulating coil is turned sideways so that while the subjects feels vibration on the scalp, the brain is not being magnetically stimulated.

Participants in the sham TMS condition will be debriefed after participation, in which an explanation of the sham TMS procedure will be given and the reason for deception will be explained. During the debriefing session, subjects will have the opportunity to ask questions and they will be given the opportunity to withdraw from the study or have their data removed.

Expectations and Interpretations. We expect that cTBS to S1 (and also to A1) will block consolidation of learning as assessed in after-effect and re-learning trials 24 hours after initial training. We do not expect that cTBS to M1 will interfere with retention, nor will sham TMS. If obtained, these results would be consistent with the idea that auditory and somatosensory cortex contribute to the consolidation of speech motor memory.

Aim 2.1: To test the hypothesis that individual differences in auditory and somatosensory working memory predict speech motor adaptation.

Methods: We will assess the relationship between sensory working memory and speech motor adaptation using a between subjects design. Participants will be assigned to one of two groups. Each group will undergo both auditory and somatosensory working memory tests as well as a test for digit span memory. One group will adapt to altered auditory feedback and the other group will adapt to altered somatosensory feedback. Memory testing and adaptation tests will be balanced for order, with half of the subjects doing the memory tests first and the other half doing the adaptation first.

Adaptation to Altered Somatosensory Feedback. These studies will involve the application of mechanical loads to the jaw using a Phantom robot (Figure 1). The robot is connected to an acrylic and metal dental appliance that is attached to the mandibular teeth with a dental adhesive. The connector together with the robot permit completely unrestricted jaw motion in 3D when forces are not being applied.

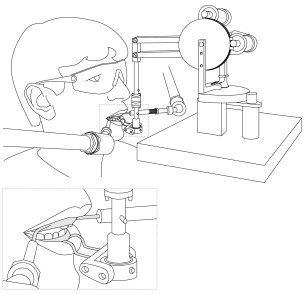


Figure 1 Adaptation to altered somatosensory feedback.

A computer monitor positioned in front of the subject will display stimulus items in random order. Subjects are instructed to read aloud the words that are presented on the screen. The subjects' task is to produce the words "head", "ted", "said", "bed". These same stimuli are used in tests of adaptation to altered auditory feedback. Subjects will be tested both in the absence of load (null condition, 200 trials) and with forces applied in the protrusion direction (200 trials). The strength of the force-field will be incremented gradually over the course of training to minimize subject awareness of the perturbation and the involvement of cognitive strategies in adaptation.

Adaptation to Altered Auditory Feedback. These studies involve the alteration of auditory feedback in real-time during speech production. A computer monitor displays the stimulus items and subjects are instructed to read each word aloud when it is presented. We use the Audapter software to selectively alter the first formant frequency of vowels within the stimulus words. We increase the volume of the signal that is played back to subjects. The volume change, along with masking noise, help to minimize any airborne or bone-conducted unaltered feedback the subject might receive other than through the earphones. Subjects will be tested both with unaltered feedback (null condition, 200 trials) and with gradually introduced frequency shifts

(200 trials) to minimize cognitive strategies in correcting for the perturbation. As in other work, the shift magnitude will be between 20 and 25% of the F1 value.

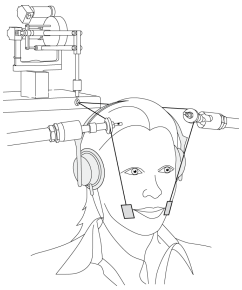


Figure 2 Facial skin stretch.

Sensory Working Memory. We will test both somatosensory and auditory working memory. In the somatosensory working memory test, small plastic tabs will be attached to the lower lip using two-sided tape and connected with thin wire to a robotic device (a variant of the setup shown in Figure 2). On each trial, the robot will apply small (<1 N) loads to the lips in each of six different outward directions (memory set, Figure 3, panel a) followed by a test trial which half of the time corresponds to a direction in the memory set and half of the time is a lure. The subject is required to make a yes/no response on a keyboard to indicate whether the test direction was in the memory set or not. Items in the memory set will spaced at approximately 30 degree intervals and individually jittered on a trial by trial basis to introduce variability in direction for the items in the memory set. Subject responses will be classified, as a function of lag between the item in the memory set and the test movement, as hits, misses, correct rejections and false alarms. A test of auditory working memory will be conducted in the same fashion, with movements produced by the robot replaced by the sounds that are composed of three pure tones (Figure 3, panel b). Subjects are not connected to the robot for this test. The pure tone combinations are presented through headphones and as can be seen in Figure 3b, the stimuli have the basic structure of vowels.

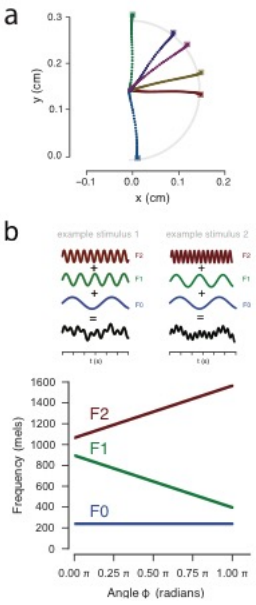


Figure 3. Stimuli for somatosensory (panel a) and auditory (panel b) working memory tests.

As in the somatosensory tests, subjects are presented with a memory set of six items followed by a test item which is an item in the memory set 50% of the time. Subjects will be required to indicate on a keyboard whether the test sound was in the memory set or not. We will use total proportion of hits summed over all lags minus the proportion of false alarms as an aggregate dependent measure of sensory working memory for both auditory and somatosensory stimuli. As a control, we will conduct tests of verbal working memory using a standard digit span task (memory for a sequence of digits) to address the possibility that the auditory and somatosensory memory tests described above involve a cognitive strategy in which subjects use a non-sensory working memory to perform the memory task. In these tests subjects will be presented individual digits visually as memory set items, followed by a test digit which is in the memory set 50% of the time.

Expectations and Interpretations. As in work on human arm movement, we expect that individual differences in sensory working memory will predict differences in speech motor adaptation. We expect, based on previous evidence of sensory preference in speech motor adaptation, that the benefits of sensory working memory will be selective. Specifically, we expect that subjects that show greater auditory working memory performance will also display greater amounts of adaptation to altered auditory feedback. In contrast, we expect that differences in somatosensory working memory will not predict differences in altered auditory feedback adaptation. Similarly, we expect that differences in somatosensory working memory (and not auditory working memory) will predict adaptation to altered somatosensory feedback. We do not expect measures of digit span memory to correlate with auditory or somatosensory measures of memory or with

either adaptation measure. If obtained, the results would point to the involvement of sensory working memory in speech motor adaptation and would likewise provide a measure of the specificity of the working memory contribution to adaptation.

Aim 2.2: To test the participation of ventrolateral prefrontal cortex in speech motor learning.

Methods: Other than for Broca's area, little is known about the role of prefrontal cortex in human motor learning. We have chosen to focus on it here because of its known involvement in working memory and its anatomical connectivity with frontal motor regions. We will focus specifically on ventrolateral prefrontal cortex (area 46v) as it has been implicated in somatosensory working memory and also auditory working memory and is hence a likely candidate for involvement in speech motor adaptation. Using different groups of subjects (one for adaptation to altered auditory feedback and one for adaptation to altered somatosensory feedback), we will use cTBS to disrupt neural activity in this area to test its involvement in adaptation. One set of tests will focus on the effects of cTBS on both auditory and somatosensory working memory (all subjects will do both tests of sensory working memory). A second set of tests will focus on the effects of cTBS on speech motor adaptation, testing the effects on adaptation to altered auditory feedback and altered somatosensory feedback in different groups of subjects. Although it would be preferable to conduct both working memory and adaptation tests with the same subjects during the same test session, the duration of theta-burst suppression (60 to 90 minutes) is unlikely to permit this. Accordingly, two sessions per subject balanced for order will be required, one to test for the effects of 46v suppression on working memory and a second to test for the effects of 46v suppression on adaptation. In the working memory tests, the experimental sequence will be: working memory test I, cTBS, working memory test II. In the motor learning test, the sequence is: baseline utterances, cTBS, adaptation testing, baseline utterances. For each of the behavioral manipulations, groups of control subjects will be tested using sham TMS with the coil turned sideways (sham cTBS + working memory and sham cTBS + adaptation).

Continuous Theta-Burst Stimulation. cTBS will be delivered using the BrainSight neuronavigation system to register the position of the stimulating coil to participant's brain. cTBS is delivered using a Magstim 70 mm coil that produces highly focal stimulation. We will use two variants of this sequence—3 pulses at 50 Hz delivered five times a second, or 3 pulses at 30 Hz delivered 6 times a second, in each case for a total of 600 pulses. We will adopt Ridding's procedure in which the cTBS sequence is applied twice with a 10-minute intervening delay. The stimulation intensity for cTBS will be 70% of the resting motor threshold for the lip muscle orbicularis oris (Figure 4). The stimulation procedure takes 11 and a half minutes in total, including the 10-minute delay between the two 40 second cTBS sequences.

We will determine the motor threshold for orbicularis oris using single-pulse TMS. Single pulse TMS will be delivered to the left side of the scalp using BrainSight for registration. A resting motor threshold is determined by finding the stimulation intensity that 5 times out of 10 gives a peak to peak MEP of 50 μV. Figure 4 shows MEPs recorded from orbicularis oris superior and inferior. The latency of the evoked response is 6 ms.

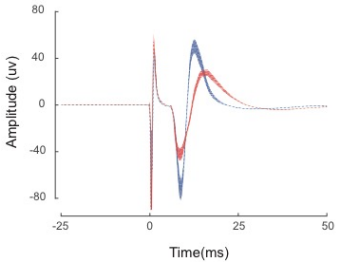


Figure 4 Orbicularis oris superior (blue) and inferior (red) MEPs.

We will apply cTBS to ventrolateral prefrontal cortex (Brodmann area 46v) which will be identified using a high-resolution anatomical scan. Area 46v is in the middle frontal gyrus, above the ascending sulcus that separates pars opercularis and pars triangularis (areas 44 and 45). In preliminary tests, we are readily able to localize 46v directly from anatomical

scans. A T1 weighted structural image (MPRAGE, 1 mm slice thickness, 192 slices, 2300 ms TR, 2.98 ms TE, 9 deg flip angle, iPAT GRAPPA x2 acceleration) will be obtained with a 3 Tesla Siemens Prisma scanner with a 32-channel head coil. A member of the research team will accompany the participant to the MRRC and remain there for the duration of this phase of the experiment.

Expectations and Interpretations: As in preliminary data, we expect cTBS to 46v to lead to decreases in working memory and, also to decreases in adaptation. This would support the idea that these somatic and auditory regions in prefrontal cortex, which support sensory working memory, are also involved in speech motor adaptation. The magnitude of the performance reduction will provide a measure of the relative involvement of 46v in both kinds of adaptation and working memory. Given the extensive connectivity of 46v to other somatic regions of the brain, we predict that the impairment in both somatosensory working memory and somatosensory adaptation will be greater.

Aim 3.1: To test the hypothesis that the repeated pairing of somatosensory inputs with speech sounds, such as occurs during speech motor learning, results in changes to the perceptual classification of speech sounds.

Methods: We will assess changes to the perceptual classification of speech sounds that are related to repeated pairing of somatosensory and auditory inputs (as would occur during speech motor learning). Paired auditory-somatosensory stimulation will be divided into 4 blocks of 100 stimulus pairs each. The auditory stimulus will be the word "*head*". Somatosensory stimuli (facial skin stretch), matched on timing and duration will be presented as in Figure 2 with the auditory stimulus. Before and after the training, base-line and post-training auditory perceptual performance will be examined in the absence of somatosensory stimulation, in order to evaluate the effects of the pairing on speech perception. Follow-up perceptual tests will be conducted 24 hours and 7 days later to assess the persistence of the perceptual change. In the baseline perceptual tests, auditory stimuli, on a continuum between "*head*" and "*had*", will be presented one at a time in random order. Subjects will be assigned to one of three experimental groups, in which the somatosensory stimulation in the pairing task is in either the upward, downward or backward direction. A control group will follow the same testing sequence without somatosensory stimulation during the training session.

Expectations and Interpretations: Based on pilot data, we expect that repeated pairing of auditory and somatosensory stimuli will alter the offline perceptual classification of speech sounds when somatosensory stimulation occurs in speech relevant directions (for these sounds) but not when the skin stretch direction is inconsistent with that experienced during normal speech production (backward). As in work on human arm movement, we expect the perceptual effects to be retained at later re-test. Retention of the perceptual change would suggest consolidation of perceptual learning following auditory-somatosensory pairing. Altered perceptual classification would be consistent with the idea that the repeated pairing of auditory and somatosensory inputs during speech motor learning results in persistent changes to the perceptual classification of speech sounds that are mediated by the somatosensory system.

Aim 3.2: To test the idea that somatosensory cortical areas participate in speech perception.

Methods: We will use task-based fMRI scans involving both auditory and somatosensory stimulation to test for somatosensory involvement in speech perception. A second experiment will use resting state fMRI to identify areas whose functional connectivity is strengthened off-line as a result of paired auditory-somatosensory stimulation such as that which normally accompanies speech motor learning. A member of the research team will accompany the participant to the MRRC and remain there for the duration of the experiment.

The task-based scan will use both speech and non-speech stimuli. In the speech condition, the word, "*head*" will be used in combination with downward facial skin stretch. In a non-speech condition sets of pure tones, matched in loudness and duration to the speech condition, will be paired with somatosensory stimuli. In total, there will be two auditory-somatosensory conditions [Multi: M-1(speech vs soma) and M-2 (non-speech vs soma)], two auditory alone conditions [Aud: A-1(speech) and A-2(non-speech)], and one somatosensory alone condition (Soma). The five stimulus conditions along with a rest condition will be tested in a randomized block design (Figure 5). Subjects are instructed to attend to the stimuli.

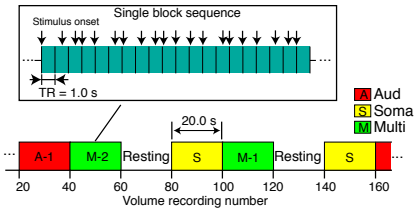


Figure 5 Scanner skin stretch protocol.

A second imaging study focusing on resting-state connectivity will be conducted using only the multisensory condition from Aim 3.1. The experimental sequence is [Resting State Scan 1] → [Task-based scan during paired auditory-somatosensory stimulation, three 10-minute scans] → [Resting State Scan 2]. Skin stretch will be restricted to the downward direction. In a control condition, there will be two resting state scans, but in place of the paired stimulation, the subject will rest quietly while being scanned but there will be no task. A task-based scan, in which participants repeat aloud words presented auditorily, will be run at the end of the session. This will be used to obtain seed-regions to assess changes in functional connectivity associated with paired somatosensory auditory stimulation.

Somatosensory stimulation in the scanner will involve the use an MR-compatible ultrasonic motor manufactured by Shinsei Co USR60-E3N (see Figure 6). A product description can be found at http://www.shinsei-motor.com/English/product/nonmagnetic.html. The actuator is connected to 2 cm x 3 cm plastic tabs which are attached bilaterally to subject's face using double-sided tape. fMRI data will be acquired using a 3 Tesla Siemens Prisma scanner with a 32-channel head coil. Both resting-state data and task based localizers will be acquired using a T2*-weighted multi-band EPI sequence with x6 acceleration (2 mm isotropic voxels, 72 slices, 950 ms TR, 30 ms TE, 60 deg flip angle, iPAT off). The functional images will be superimposed on a T1 weighted anatomical image (1 mm slice thickness, other parameters as given above). Gradient field-maps will be collected to correct for B0 field inhomogeneity.

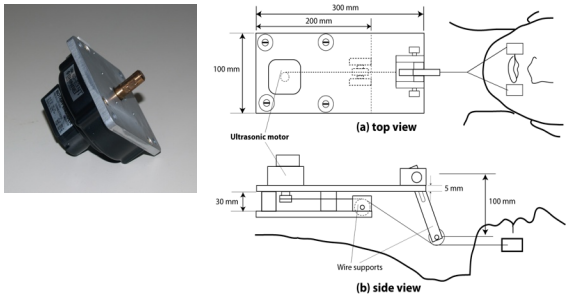
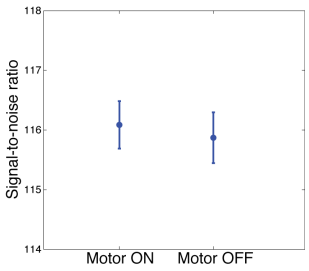


Figure 6. Ultrasound motor (left) and skin stretch system for MRI recording with ultrasound motor (right).

In a preliminary study, we verified the practical feasibility of using the ultrasonic motor in the MR scanner without degrading the quality of the MR image. Although the feasibility of using the ultrasonic motor, in terms of the MR signal-to-noise ratio (SNR), has been demonstrated previously (Izawa et al. 2005, Suzuki et al. 2007), we verified the electromagnetic interference with our planned setup in a 3T MR scanner at the Montreal Neurological Institute. Functional MR images were recorded with the motor activated, but in the absence of a connection between the motor and the facial skin. The motor ON and OFF were alternated every



10 volume recordings. In total, 100 volumes were recorded in each condition. The SNR was calculated as the ratio of the average intensity in the center region to the average of the standard deviation of the intensity at the four corners of the image as done in Suzuki (2007). The accompanying figure shows the obtained SNR in the motor ON and motor OFF conditions. Error bars show standard errors across 100 trials. We found the SNR was comparable to that reported previously by Suzuki et al. (2007). Importantly, there was no significant difference in the SNR between the ON and OFF conditions ($p > 0.1$). In visual inspection, there was no indication of noise on the MR image. We thus concluded that the proposed experimental configuration with the ultrasonic motor will permit functional MR imaging even when the motor is active during MR volume recording.

Expectations and Interpretations: It is expected that auditory speech stimuli will produce activity in both auditory and somatosensory regions of the brain and somatosensory stimuli will also activate auditory and somatosensory cortical regions. We expect that this pattern of reciprocal activation will only be seen for speech. This would be consistent with the idea that somatosensory cortex participates in speech perception. In a second study for this aim, we expect a strengthening of functional connectivity between auditory and somatosensory cortex offline in the resting brain. This would be consistent with the idea that, independent of motor outflow, the auditory somatosensory pairing that normally accompanies speech motor learning engages both auditory and somatosensory circuits in speech perception.

Additional Procedures: EEG and fMRI

Electroencephalography: In studies involving EEG recording, participants will be asked to repeat aloud words presented auditorily or on a computer monitor, or to listen to pre-recorded speech material or sounds. The procedure involves one session lasting approximately 150 minutes.

EEG data will be obtained using the non-invasive BioSemi recording system. Subjects will wear a 64-channel electrode cap. Water-soluble electrode gel will be placed in each electrode gap in the cap, in order to create a conductive path from the scalp to the electrode. If necessary, a wooden Q-tip will be inserted into the gel and twisted lightly against the scalp to ensure that the gel reaches through the hair all the way to the scalp. Data will be sampled at 1024 Hz and analyzed off-line with open-source software. After the experiment subjects will have the choice of either cleaning the gel out of their hair themselves, or having an experimenter assist in removing the gel from their hair. 3D representations of the scalp locations of the electrodes will be recorded in a separate procedure in which a plastic stylus that contains a small magnetic coil is placed at each of the 64 electrode locations.

Speech Motor Learning and fMRI: Subjects will be asked to complete one session lasting approximately 120 minutes in which they will complete an fMRI while participating in behavior tasks.

We will obtain fMRI measures to assess changes in functional connectivity that occur in conjunction with speech motor learning. The fMRI data will be acquired with multi-band neuroimaging sequences (x6 acceleration) using the scanners at the Yale University MRRC. The resting-state data will be acquired using a T2* weighted EPI sequence using a 32-channel head-coil channel. The functional images will be superimposed on a T1 weighted anatomical image. Each session typically involves resting-state scans, task-based scanning, field-map acquisition and a T1-weighted high-resolution anatomical scan.

Additional On-Line Procedures: Subjects will be recruited by Prolific, an on-line testing website, to participate in variants of currently approved studies of speech motor learning and perception. The motor learning studies involve adaptation to altered auditory feedback (described above in Aim 2.1). The speech perception task is a variant of the task in Aim 3.1.

The experiment will involve both a listening task and a word-reading task. Participants will need a computer or mobile device that has a microphone and they will also need headphones to participate. In the listening task, speech sounds will be played through their headphones (at comfortable listening levels) and participants will be required to indicate which of a number of alternatives they heard by pressing a key. In the reading task, words will be presented on their device screen and they will have to read them aloud. They will be required to wear their headphones for both parts of the experiment.

5. **Genetic Testing** **N/A ☒**
   A. Describe

6. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

   We will test healthy right-handed adults (21-40 years) that will be recruited in equal number from both sexes. All participants will be native English speakers. We will screen for handedness using the Waterloo Handedness Questionnaire.

7. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐Children	☒ Healthy	☐Fetal material, placenta, or dead fetus
☐Non-English Speaking	☐ Prisoners	☐Economically disadvantaged persons
☐Decisionally Impaired	☐ Employees	☐Pregnant women and/or fetuses
☐Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?
Yes ☐ No ☒

8. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

   The subjects will be normal right-handed adults of both sexes between the ages of 21 and 40. The subjects will have no known physical or neurological abnormalities. Subjects will be naive as to the objectives of the experiments. The experimental procedures will be performed one subject at a time.

   Subjects will be excluded from these studies which involve MRI and TMS (including cTBS) if they report any of the following pre-existing conditions: cardiac pacemaker, surgical clips or values on the heart, implants, metal or metallic fragments in any part of the body, cochlear implants, claustrophobia. They are additionally excluded if they have a personal or family history of epilepsy, or are taking antipsychotic drugs, antidepressant drugs or antianxiety drugs.

9. How will **eligibility** be determined, and by whom? Write here

   Potential participants will complete a questionnaire in which exclusion criteria are identified. The screening will be conducted by a trained team member. For on-line experiments, subjects will be recruited and screened by Prolific for age, handedness and psychoactive medication. Pre-screening for these categories is provided during Prolific recruitment.

   Commented [GG1]: Describe how Prolific screen participants? Do they have a pool of participants form where they choose form?

10. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

    The principal potential risk is injury caused by the robotic manipulator. However, injury is very unlikely, and we have implemented a range of safety precautions (see below) that are widely used for the prevention of injury in studies of human motor control involving robots. There are no known risks associated with any of the other behavioral tasks.

    Continuous theta-burst transcranial magnetic stimulation (cTBS) may cause mild adverse effects such as mild headache, non-specific discomfort, mild discomfort due to cutaneous sensation and neck muscle contraction. There have been three cases of seizure. One ten years ago in a healthy adult was reported in Oberman and Pascual-Leone (2009). More recently, two seizures occurred in conjunction with cTBS to insular cortex (2019) in which a double-cone coil designed for deep brain stimulation was used.

    There have been no reports of seizure with single pulse TMS. The main risk with single pulse TMS is syncope. There may be presently unknown risks of TMS to a fetus however none have been reported to date. In my laboratory at McGill University we have tested about three hundred subjects using this same cTBS protocol. We have had four cases of syncope with single pulse TMS and no serious adverse events with cTBS.

    One further rare risk is damage to hearing. A single incident of permanent threshold shift was reported in 2005 in which a highly non-focal H-shaped coil was used for stimulation.

    The use of magnetic resonance imaging may cause discomfort due to the need to remain still during the experiment and the noise that is generated by the MRI when images are being acquired. Subjects may also feel a certain sense of stress or anxiety or a sense of claustrophobia. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste or feel tingling sensations or muscle twitches.

    There is a risk of an allergic reaction to the electrode gel used on the EEG cap, and/or to the adhesive tape used to secure the EMG electrodes. Turning the Q-tip against the scalp to spread the electrode gel is a painless procedure but may result in slight tugging of the hair that gets wrapped around the Q-tip.

    The on-line study has no known risks.

11. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

    A number of safety precautions have been implemented. In addition to minimizing the applied force in studies involving robotic devices, we test for forces at the endpoint. If forces exceed 10 N all forces are immediately set to zero. Additional vendor supplied algorithms limit the workspace over which forces may be applied. Moreover, all experimental protocols are tested in full prior to introducing the subject into the setup. In studies over the past fifteen years using this set up we have not had a single incident of injury. In the event of an injury, the subjects will receive treatment as necessary.

The precautions for neuroimaging and brain stimulation studies are as follows: Before participating either in an MRI or TMS session participants must complete detailed screening forms so as to detect any contraindications, for example, a cardiac pacemaker, an aneurysm clip, a metal prostheses or cardiac valve replacement, the presence of metal in an eye or any part of the body, tattoos, body piercing, certain dental work, cochlear implants and claustrophobia. Additional screening for cTBS includes personal or family history of epilepsy, psychopharmacological agents (antipsychotic drugs, antidepressant drugs, antianxiety drugs). Verification of the presence of contraindications will be strictly enforced.

Another risk in MR imaging studies is the possibility of metal objects being pulled into the magnet and hitting the subject. To lower this risk, all people involved with the study must remove all metal from their clothing and all metal objects from their pockets. All people involved with the study will be asked to walk through a detector designed to detect metal objects. No metal will be brought into the magnet room at any time. Once the participant is in the magnet, the door to the room will be closed so that no one from outside accidentally goes near the magnet.

There are no reported cases of single-pulse TMS triggering seizures. For cTBS, there have been only three reports of seizure, ten years ago in a healthy adult, reported in Oberman and Pascual-Leone (2009), and more recently, two in the same study in which cTBS was delivered to insular cortex with a double-coned coil specifically designed for deep brain stimulation (Lenoir et al., 2019). Seizure risk will be migitated in the present studies by strictly adhering to the exclusion criteria below. In the event of seizure, standard first responder procedures for dealing with aware, unaware and generalized seizures will be followed.

In light of unknown risks to a fetus, the consent form indicates that if a participant thinks there is a possibility she might be pregnant, she will be excluded. To guard against possible damage to hearing participants will be tested wearing earplugs.

12. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Greater than minimal risk
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? n/a
    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for
        i. Minimal risk
        ii. Greater than minimal

1. Personnel responsible for the safety review and its frequency:

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator or the IRB have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed greater than minimal for the following reasons:

1. We do not view the risks associated with the TMS as minimal risks since syncope is a side-effect and in one case reported in 2009 a seizure was reported in a healthy adult.
2. Given the now established safe use of this procedure in our prior work, we do not view the proposed studies as high risk.

Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

3. Attribution of Adverse Events:

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator David Ostry according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

5. Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events:
In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death;
2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR
5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to

consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

6. Plan for reporting UPIRSOs (including Adverse Events) to the IRB

The principal investigator will report the following types of events to the IRB: Any incident, experience or outcome that meets ALL 3 of the following criteria: Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized. Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented**.** In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

7. Plan for reporting adverse events

For the current study, the following individuals, funding, and/or regulatory agencies will be notified:

All Co-Investigators listed on the protocol, National Institutes of Health, Yale HIC

The principal investigator David Ostry will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

d. For multi-site studies for <u>which the Yale PI serves as the lead investigator</u>:
   i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed? *Write here*
   ii. What provisions are in place for management of interim results? *Write here*
   iii. What will the multi-site process be for protocol modifications? *Write here*

13. **Statistical Considerations:** Describe the statistical analyses that support the study design.

Performance will be quantified for each subject on a trial-by-trial basis. Statistical analyses will be conducted using analyses of variance followed by Bonferroni-corrected post-hoc tests. The analysis of neuroimaging data is also described above. We have chosen sample size based on power analyses using our preliminary data. We estimated the required sample size necessary to detect the hypothesized effects using Bonferroni corrected tests with α = 0.01 and β = 0.2 (power = 0.8). For our behavioral studies involving sensorimotor adaptation, including cTBS, we

will need 20 subjects per group to obtain an estimated power of 0.8. Based on our preliminary fMRI results, 25 subjects per condition would provide 80% power (α=0.01) to detect changes in connectivity following learning.

The following tables give a breakdown on subjects in each experimental condition.

	Experimental Condition	Number of Subjects
Aim 1	Adaptation to altered auditory feedback + cTBS to somatosensory cortex	20
	Adaptation to altered auditory feedback + cTBS to auditory cortex	20
	Adaptation to altered auditory feedback + cTBS to motor cortex	20
	Adaptation to altered somatosensory feedback + cTBS to somatosensory cortex	20
	Adaptation to altered somatosensory feedback + cTBS to auditory cortex	20
	Adaptation to altered somatosensory feedback + cTBS to motor cortex	20
	Adaptation to altered auditory feedback + sham TBS	20
	Adaptation to altered somatosensory feedback + sham TBS	20

	Experimental Condition	Number of Subjects
Aim 2.1	Auditory and somatosensory working memory + adaptation to altered auditory feedback	20
	Auditory and somatosensory working memory + adaptation to altered somatosensory feedback	20

	Experimental Condition	Number of Subjects
Aim 2.2	Auditory and somatosensory working memory + adaptation to altered auditory feedback + cTBS to 46v	20
	Auditory and somatosensory working memory + adaptation to altered somatosensory feedback + cTBS to 46v	20
	Auditory and somatosensory working memory + adaptation to altered auditory feedback + sham TBS	20
	Auditory and somatosensory working memory + adaptation to altered somatosensory feedback + sham TBS	20

	Experimental Condition	Number of Subjects

Aim 3.1	Auditory training paired with upward skin stretch	20
	Auditory training paired with downward skin stretch	20
	Auditory training paired with backward skin stretch	20
	Auditory training paired without skin stretch	20

Aim 3.2	Auditory + somatosensory + paired exposure + task-based fMRI	25
	Resting state scans + paired auditory-somatosensory stimulation task-based scans	25
	Resting state scans + no task control condition	25

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

B. DRUGS/BIOLOGICS ☒N/A

4. Use of Placebo: ☒Not applicable to this research project

B. DEVICES ☐N/A

The study includes the following devices, but these devices are not the subject of the investigation and are widely used in laboratories around the world in research studies/studies involving magnetic brain stimulation. The research is not testing the safety and/or effectiveness of these devices.

cTBS will be delivered using the BrainSight neuronavigation system.

Somatosensory stimulation in the scanner will involve the use an MR-compatible ultrasonic motor manufactured by Shinsei Co USR60-E3N (see Figure 6). A product description can be found at http://www.shinsei-motor.com/English/product/nonmagnetic.html.

The safety of the brain stimulation devices in research with humans is described in detail in the following publication:

Rossi S, Hallett M, Rossini PM, Pascual-Leone A; Safety of TMS Consensus Group (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 120: 2008-2039.

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

a. Targeted for enrollment at Yale for this protocol: 275 (additional on-line enrollment: 150)

b. If this is a multi-site study, give the total number of subjects targeted across all sites: 435

2. **Indicate recruitment methods below.** Attach copies of any recruitment materials that will be used.

☒ Flyers	☐ Internet/web postings	☐ Radio
☐ Posters	☐ Mass email solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center website	☐ Television
☐ Medical record review*	☒ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☐ Web-based clinical trial registries	☐ Clinicaltrails.gov
☐ YCCI Recruitment database	☐ Social Media (Twitter/Facebook):	
☒ Other: Prolific		

* **Requests for medical records should be made through JDAT as described at**
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. **Recruitment Procedures:**

a. Describe how potential subjects will be identified. Response to flyers, Departmental and Internet postings, Prolific participants. Prolific recruits participants primarily via social media (Facebook, Twitter, Reddit, blog posts) and via poster/flyer campaigns at universities, and through referrals from researchers and participants already using the site. Participants create an account on Prolific and are then notified of future studies they are eligible for based on the demographic information they provide.

b. Describe how potential subjects are contacted. Email or phone or Prolific contact participants eligible for our study

c. Who is recruiting potential subjects? Trained team member or recruited through Prolific participation.

4. **Assessment of Current Health Provider Relationship for HIPAA Consideration:**

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐Yes, all subjects
☐Yes, some of the subjects
☒No

If yes, describe the nature of this relationship. *Write here*

5. **Request for waiver of HIPAA authorization:** (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study
☒ For recruitment/screening purposes only
☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data: *Write here*

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: Because pre-screening information may be collected over the phone and signed consent by phone is not possible.

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

   A trained team member will verify eligibility and obtain consent at the laboratory prior to the start of the experiment. An oral description of the experiment will be offered with an opportunity for the subjects to ask questions as needed. Moreover, care will be taken to ensure that the subjects are fully informed about the risks and discomforts that may be involved.

   In online studies, Prolific notifies participants, who based on initial screening are eligible to participate in our study. The text of the consent is presented to the subject electronically prior to them commencing study procedures.

7. **Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

   Only healthy adults will be tested. If the trained member assigned to obtain consent has any doubt about a potential participant's capacity to provide informed consent, testing will be postponed and the PI will make this determination by talking with the team member and if necessary the potential participant.

   In on-line studies, in the consent process, participants must indicate that they have read the consent form (or have had it read to them) and that the nature of their involvement in the study has been explained to their satisfaction.

8. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.
   n/a

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☐ NO ☐

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. **Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study.** If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐Not Requesting any consent waivers

☒Requesting a waiver of signed consent:

☒ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☒ Entire Study (Note that an information sheet may be required.) Applies to on-line studies only. Prolific does not allow subject identifiers (participants are only identified by their Prolific ID). Participants provide consent by clicking on "I consent" button after reading and agreeing to information in consent form. Participants will be told that they have the option of taking a screen-shot or printing the consent if they wish. The waiver of consent does not apply to any of the procedures to be conducted at Haskins Laboratories or Yale MRRC.

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☐ NO ☐
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☐ NO ☐

OR

- Does the research pose greater than minimal risk? YES ☐ NO☒
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☒

☐ Requesting a waiver of consent:

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

The following protected health information will be collected only as part of recruitment and screening: Any of the following pre-existing conditions: cardiac pacemaker, surgical clips or values on the heart, implants, metal or metallic fragments in any part of the body, pregnancy, claustrophobia. Additional protected health information

that will be used to screen potential subjects includes: a personal or family history of epilepsy, or are taking antipsychotic drugs, antidepressant drugs or antianxiety drugs.

In on-line experiments, participants are fully anonymized by Prolific. We will screen for antipsychotic drugs, antidepressant drugs or antianxiety drugs.

2. How will the research data be collected, recorded and stored? *Write here*

Data will be collected and stored on laboratory computers. fMRI data (brain activation and structural images) will be collected to permit proper placement of the brain stimulation coil.

In online experiments, Prolific provides participants a link to a Yale virtual machine that is hosted by Amazon WebS Services. The participants download an application to their device that runs the experiment. When finished, they click on a button to upload the data to Storage@Yale, after which the data are deleted from their device.

3. How will the digital data be stored? ☐CD ☒DVD ☐Flash Drive ☒Portable Hard Drive ☒Secured Server ☒ Laptop Computer ☒Desktop Computer ☐Other

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

Data will be de-identified at the earliest reasonable time after data collection, meaning we will replace identifying information with a code. A link to personal information will be kept for 6 years, after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form indefinitely. No names will appear in any publication or be mentioned in any public place in connection with this project.

Data from on-line studies are identified only by the Prolific ID of the participant.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

De-identified data will be retained indefinitely. Identifying links to individuals will be maintained by the PI for 6 years following data collection, after which the link will be destroyed by the PI.

6. If appropriate, has a Certificate of Confidentiality been obtained?

This study has been granted a Certificate of Confidentiality by the NIH, although no sensitive information is collected.

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

The individual subjects receive no direct benefits to health or well-being and are fully aware of this before participating. The principal benefits that may develop from the research are related to the development of an understanding of the sensory changes that accompany motor learning.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

   Not applicable

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

   Participants will receive $15/hour monetary compensation for behavioral studies, $20/hour for studies involving EEG and $25/hour for participation in the experiments involving fMRI or magnetic brain stimulation.

   Participants in on-line studies receive $4 from Prolific for completion of a 30-minute experiment.

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

   The participants need to provide their own transportation to Haskins Laboratories.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

   a. Will medical treatment be available if research-related injury occurs? Yes
   b. Where and from whom may treatment be obtained? Emergency help will be provided including transport to the emergency room if needed.
   c. Are there any limits to the treatment being provided? The treatment is limited to the injury sustained as a result of the experimental procedure.
   d. Who will pay for this treatment? Haskins liability insurance will cover the cost of emergency medical treatment.
   e. How will the medical treatment be accessed by subjects? The laboratories will contact emergency medical personnel.

Deleted: 20

Deleted: 50

Deleted:

IMPORTANT REMINDERS

Will this study have a billable service? **Yes ☐** **No☒**

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? **Yes ☐ No ☒**

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? **Yes ☐ No ☐**

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? **Yes ☐ No ☐**

c. Will a novel approach using existing equipment be applied? **Yes ☐ No ☐**

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. **By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.**