Video Article

Online Transcranial Magnetic Stimulation Protocol for Measuring Cortical Physiology Associated with Response Inhibition

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Abstract

We describe the development of a reproducible, child-friendly motor response inhibition task suitable for online Transcranial Magnetic Stimulation (TMS) characterization of primary motor cortex (M1) excitability and inhibition. Motor response inhibition prevents unwanted actions and is abnormal in several neuropsychiatric conditions. TMS is a non-invasive technology that can quantify M1 excitability and inhibition using single- and paired-pulse protocols and can be precisely timed to study cortical physiology with high temporal resolution. We modified the original Slater-Hammel (S-H) stop signal task to create a "racecar" version with TMS pulses time-locked to intra-trial events. This task is self-paced, with each trial initiating after a button push to move the racecar towards the 800 ms target. GO trials require a finger-lift to stop the racecar just before this target. Interspersed randomly are STOP trials (25%) during which the dynamically adjusted stop signal prompts subjects to prevent finger-lift. For GO trials, TMS pulses were delivered at 650 ms after trial onset; whereas, for STOP trials, the TMS pulses occurred 150 ms after the stop signal. The timings of the TMS pulses were decided based on electroencephalography (EEG) studies showing event-related changes in these time ranges during stop signal tasks. This task was studied in 3 blocks at two study sites (n=38) and we recorded behavioral performance and event-related motor-evoked potentials (MEP). Regression modelling was used to analyze MEP amplitudes using age as a covariate with multiple independent variables (sex, study site, block, TMS pulse condition [single- vs. paired-pulse], trial condition [GO, successful STOP, failed STOP]). The analysis showed that TMS pulse condition ($p<0.0001$) and its interaction with trial condition ($p=0.009$) were significant. Future applications for this online S-H/TMS paradigm include the addition of simultaneous EEG acquisition to measure TMS-evoked EEG potentials. A potential limitation is that in children, the TMS pulse sound could affect behavioral task performance.

Video Link

The video component of this article can be found at https://www.jove.com/video/56789/

Introduction

Response inhibition is the ability to selectively prevent those unwanted actions that can interfere with intended functional goals.[1] The cortico-striatal network is critically involved in response inhibition, which progressively becomes more efficient as children mature but is impaired in numerous neuropsychiatric conditions such as attention-deficit hyperactivity disorder (ADHD), learning disorders, obsessive compulsive disorder, and schizophrenia.[2,3] Motor response inhibition can be examined with different behavioral paradigms such as Go/NoGo (GNG) and Stop Signal tasks (SST).[1,4] Behavioral data alone does not provide information about potentially modifiable, quantifiable biological mechanisms. The overarching goal in the present study was to develop a child friendly method to evaluate motor cortex physiology during the execution of response inhibition, in order to develop a brain-based quantitative biomarker of the neural substrate of this task. Such biomarkers could have wide application in predictive studies of prognosis or treatment of neurobehavioral disorders.

For this purpose, the investigators selected and modified the Slater-Hammel (S-H) task[5]. This is a stop signal task that requires participants to inhibit an internally generated pre-programmed action. This self-paced task consists of both GO and STOP trials. GO trials are initiated by the subject pressing and maintaining pressure on a button, with the instruction to lift finger off the button (i.e. GO action) as close to but before the 800 ms target. In the original paradigm, time is indicated on a clock with a rapidly rotating hand. STOP trials are randomly interspersed amongst GO trials during which the person must inhibit the pre-planned GO action (i.e. prevent finger lift). The stop signal task is more difficult because subjects have to inhibit a response in the context of a pre-programmed GO signal, whereas in GNG task, the decision is whether to initiate or not initiate an action with no prior commands.[6] Furthermore, it may be more accurate to investigate response inhibition by using stop signal tasks because in the GNG task, consistent correlations between signal and responses may result in automatic inhibition.[7] Automatic inhibition is the theory that consistent mapping between signal and response (i.e. GO signal always results in a GO response and vice versa) leads to

an automatic processing throughout the course of the experiment such that the STOP trials are partly processed through memory retrieval and bypasses certain executive controls.[8,9]

Transcranial magnetic stimulation (TMS) is a non-invasive technology that can be used to measure cortical physiology. Using single- and paired-pulse stimulation paradigms, one can quantify cortical excitability and inhibition. Although most published TMS studies investigate cortical physiology at rest, some groups have examined cortical excitability/inhibition during mental preparation for action[10] and during different cognitive states that may be reflected in motor cortex physiology.[11,12,13,14] This functional TMS (fTMS) approach requires online TMS measurements while participants are performing behavioral tasks, thus allowing one to probe cortical changes that are state-dependent with high temporal resolution. Providing real-time information on neurophysiologic changes in such a manner broadens the physiologic investigation of motor control[15,16] and neuropsychiatric conditions[17,18,19,20].

Prior fTMS studies have explored cortical mechanisms of response inhibition in healthy adults using GNG[14] and SST tasks[15,16,21]. Furthermore, one study showed that a single dose of methylphenidate changed motor cortical physiology of healthy adults during an fTMS/GNG experiment.[22] To date, there are two groups that have published pediatric fTMS studies using GNG task to characterize cortical physiology of ADHD[23] and Tourette Syndrome[17]. There is currently no published fTMS study utilizing SST in the pediatric population.

A critical issue in fTMS studies, to a much greater extent than rest-alone TMS studies, is muscle artifact. Standardized surface electromyography (EMG) measures of amplitude and latency from motor-evoked potentials (MEP) must not be contaminated by muscle artifact. So, for example, to study cortical changes in preparation for a movement in a reaction time study, TMS pulses must be precisely timed to occur after a GO signal but prior to an individual's reaction time. Thus in any task, it is critical to ensure that TMS pulses are occurring at a time when the motor response has not yet begun, and that the participant is comfortable and able to maintain the relevant muscle at rest. This can be exceptionally problematic with hyperkinetic children who may naturally have extraneous movements and who may keep their arm and hand tensed throughout a reaction time game.

The aim of the present study is to develop a version of the Slater-Hammel SST that is child-friendly and suitable for studying primary motor cortex (M1) physiology. This task should be 1) easily understandable for children, 2) relatively easy to complete for children and 3) compatible with online TMS.

Protocol

This protocol was approved by the Cincinnati Children's Hospital Medical Center and Johns Hopkins Institutional Review Boards as a minimal risk study in children and adults. Single- and paired-pulse TMS is considered as safe in children 2 years and older per international expert consensus.[24] After explaining the potential risks of TMS to parent/guardian and participant, consent and assent forms are signed if they agree to proceed with the study.

1. Screening and introduction

1. Screen subjects for TMS contraindication(s) using a standardized questionnaire.[25]
2. Demonstrate how TMS works by delivering a magnetic pulse over the operator's own forearm.
3. Deliver a TMS pulse over the participant's forearm so that he/she can feel the pulse.
4. Place earplugs in participant's ears for hearing protection.

2. Surface EMG lead setup and hand positioning

1. Have the subject abduct the dominant index finger to identify the first dorsal interosseous muscle (FDI). Place the negative electrode over the belly of the FDI, then place the positive electrode between 2nd and 3rd metacarpophalangeal (MCP) joints and the ground electrode over the 5th MCP joint.
2. Position the participant's hands with ulnar aspects of both arms and hands resting fully on a pillow, with no anti-gravity effort required (**Figure 1**).
3. Have the participant extend the dominant index finger while the third - fifth fingers are flexed. Then place a game controller pad on the pillow so that the index finger rests on the button used for the racecar S-H task. The rationale for this hand position is that the GO action requires the activation of the FDI to lift the index finger off the button. Therefore, recording EMG tracing of the dominant FDI will probe M1 excitability and inhibition for GO and STOP trials respectively.

3. Baseline TMS data acquisition

1. Set the recording parameters for MEP recording - low and high pass filters of 100 and 1000 Hz, sampling rate of 2 kHz.
2. Obtain baseline TMS measurements using a 90 mm circular TMS coil positioned tangentially to the skull over the vertex with the handle pointing towards the occiput at the optimal position and orientation for producing an MEP in the right FDI by following standard protocol.[26] This coil position and orientation should produce an induced posterior-to-anterior current over M1.
    1. Use a wax pencil to mark the scalp location once the hotspot was located to ensure that the TMS pulse delivery occurs at the same cortical region.
3. Perform twenty trials[27] of baseline single-pulse (sp) TMS induced FDI MEPs with both hands at rest using an intensity of 120% of RMT.
4. Perform twenty trials of baseline paired-pulse TMS measures of M1 short-interval intracortical inhibition (SICI) at rest using inter-stimulus interval of 3 ms, 60%*RMT as the conditioning pulse intensity and 120% RMT as the test pulse intensity to quantify M1 inhibitory $GABA_A$-ergic interneuronal activity.[28,29,30] Set the inter-trial interval for baseline measurements at 6 ± 0.3 seconds.

4. S-H behavioral task

1. Display the Racecar S-H response inhibition task on a monitor directly in front of the subject. Start the experiment by first training subjects on the behavioral task. Tell the subject that the car on the left side of the monitor will begin to move after the button is pressed by adduction of the dominant index finger (**Figure 2A**).
2. Tell the participants that the goal for GO trials is to lift the finger as close to but before the 800 ms target as depicted by a vertical line on the screen. The screen will display "Good Job" if finger lifts occurs between 700 and 800 ms, otherwise it will display either "Too Early" or "Too Late". Have the participant practice 10 GO trials.
3. Provide training for the STOP task by telling participants that the second set of trials involves the car randomly stopping before the 800 ms target.
    1. Tell the child to keep his index finger on the button without lifting the finger whenever the car randomly stops. To succeed in these STOP trials, the finger must remain on the button until a checker flag is seen which is programmed to appear 1000 ms after the start of each trial. Inform the participant that if stop signal is presented and finger is lifted before the checker flag, a "Too Early" message will appear. Tell the child that a "Great" message will be displayed after successful STOP trials.
    2. Have the child practice 10 STOP trials.
    NOTE: The program has a dynamic tracking algorithm. In the actual experiment after training, the first STOP signal occurs at 500 ms. If the participant fails one STOP trial, then the next STOP trial will be easier (i.e. the STOP signal will shift 50 ms away from the 800 ms target). However, if the STOP trial was successful, then the next STOP trial will be more difficult (i.e. the STOP signal will shift 50 ms towards the target). This dynamic tracking process ensures that by the end of the entire experiment, approximately 50% of the STOP trials will be successful while the other half would be failed trials. The STOP signal is programmed to adjust between 300 and 700 ms after start of trial.
4. After the participants practice GO-only and STOP-only trials, tell them that the next practice block contains a mixture of GO and STOP trials. Have the child perform 20 trials of mixed GO and STOP as a final practice.

5. Online S-H/TMS experiment

1. Before starting online S-H/TMS experiment, remind the participant to adduct (push down) the dominant index finger to start the trial, to abduct (lift off) finger for GO trials and keep finger on the button for STOP trials. The index finger adduction was chosen to initiate and maintain car movement during each trial because at the time of the TMS pulses (**Figure 2A and 2B**), the antagonistic first dorsal interosseous (FDI) muscle, where the EMG lead is placed, would be resting, thus reducing the likelihood of motion artifact in the FDI tracing.
2. Tell the participant that TMS pulses will be delivered during the S-H task. Instruct the subject that there will be 3 blocks of online S-H TMS trials (3 GO: 1 STOP trial ratio).
NOTE: During GO trials, TMS pulse is programmed to be delivered at 650 ms after the start of each trial. This timing is initially chosen based on prior TMS study showing that increase in M1 excitability associated with movement preparation can be captured in this range.[10] For STOP trials, TMS pulse is delivered 150 ms after the stop signal. In successful STOP trials, the index finger does not lift off the button therefore the captured M1 excitability reflects cortical activity related to response inhibition rather than motor preparation or execution.
3. Place the 90 mm circular coil over the vertex using previous wax pencil mark to preferentially stimulate dominant M1 and set the conditioning pulse intensity to 60%*RMT and test pulse to 120%*RMT. Begin the online S-H/TMS experiment. The time required children to finish 120 trials is generally 30-40 minutes.

6. Racecar Slater-Hammel Behavioral Data

1. For GO trials, determine the reaction time as the finger-lift time relative to the beginning of each trial. Average each block. For STOP trials, the finger-lift time determines success, whereas the car stop signal time (i.e. Stop Signal Delay; SSD) is the time interval from the start of the trial to the point where the car randomly stops. Due to the dynamic tracking process, the stop signal time converges towards a ~50% success/fail average.
2. Calculate the Stop Signal Reaction Time (SSRT) by subtracting the average car-stop time from the average finger lift time on GO trials (SSRT = average GO reaction time – average stop signal time [i.e. SSD]). Average all the SSD by block and calculate an SSRT for each block.

7. TMS Data Processing

1. Quantify TMS during each trial produced an MEP using peak-peak amplitude measured in millivolts. Exclude trials for movement artifacts (EMG areas under the curve greater than 70 microvolts over 100 ms) prior to the TMS pulse.

Representative Results

Regression analysis is performed using a commercial statistical software package to analyze behavioral and neurophysiologic data separately. The representative data is from 23 typically developing children from Cincinnati and 15 from Baltimore (25 male, 13 female). Age did not differ between site (10.3 ± 1.3 years for Cincinnati and 10.4 ± 1.2 years for Baltimore; t test p=0.74)

We used a regression model to analyze SSRT with age as a covariate along with sex, site (Cincinnati vs. Baltimore) and trial block as independent variables. Interactions between these variables were also explored. This analysis revealed that age was the only variable with a significant effect on SSRT (p=0.005).

The TMS neurophysiologic data was characterized using peak-to-peak MEP amplitude as the dependent variable for regression analysis. During movement preparation, M1 excitability increases before actual movement occurs. TMS studies have shown that this excitability increase occurs 100 - 140 ms before muscle contraction.[10,11,31,32] In this S-H task, the time between TMS pulse and finger-lift for successful STOP trials is always greater than 150 ms (i.e. latest possible TMS pulse occurs at 850 ms and finger lift occurs > 1000 ms after initiation of trial). In our analysis, we are interested in comparing cortical excitability and inhibition related to motor response inhibition. Since we are interested in comparing all three different task conditions (GO, successful STOP, failed STOP), we analyzed data from trials when the time between TMS pulse and finger lift is at least 150 ms because MEP amplitude beyond this time frame is not affected by movement preparation.[10,11,31,32] Therefore this time latency was not included in the regression model as a covariate. For our regression model, we included age as a covariate because it affects MEP amplitude in childhood.[33] Independent class variables for the model included sex, site, trial block, TMS pulse condition (single- vs. paired-pulse) and trial condition (GO, successful STOP, failed STOP). The primary interaction of interest is between TMS pulse condition and trial condition because we are interested in how M1 excitability (single-pulse TMS) and inhibition (paired-pulse TMS) differ between different task conditions.

For MEP amplitudes, the independent variables sex, site and trial block were not significant in the regression model. Age was not significant as a covariate in the regression model ($p=0.28$). The TMS pulse condition ($p<0.0001$) and its interaction with trial condition ($p=0.009$) were significant. **Figure 3** shows representative neurophysiologic data in different trial conditions using least squares mean estimates calculated from the regression model with error bars representing standard errors. All pair-wise comparisons of single-pulse MEP amplitudes between the three task conditions were insignificant (false discovery rate [FDR] adjusted $p>0.05$). However, for the inhibitory paired-pulse MEPs, the differences between GO vs. failed STOP (FDR adjusted $p=0.009$) and successful vs. failed STOP (FDR adjusted $p=0.03$) were significant. The comparison of paired-pulse MEP amplitudes between GO and successful STOP trials was not significant (FDR adjusted $p=0.56$).

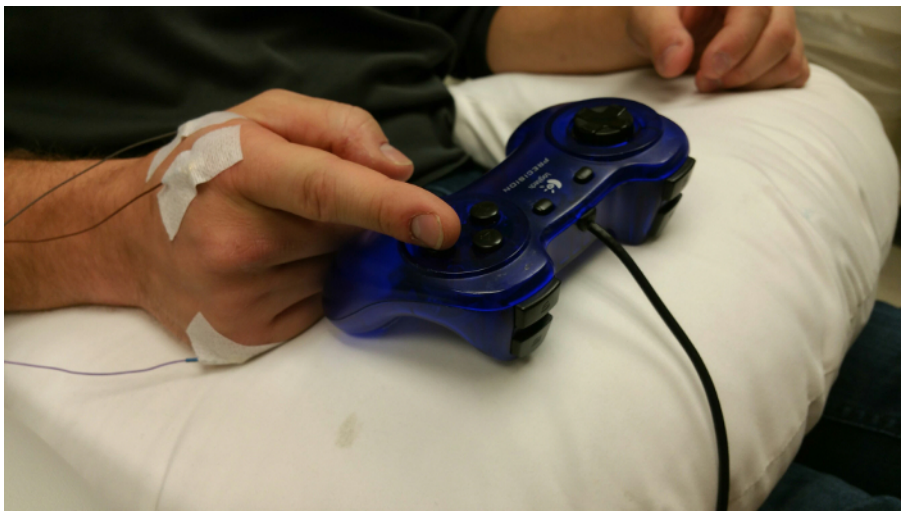

Figure 1: Hand and finger position during racecar S-H task. Both hands are rested on the pillow. Dominant index finger is extended and rests on a game controller button. Adduction of the dominant index finger depresses the button and activates each trial. Please click here to view a larger version of this figure.

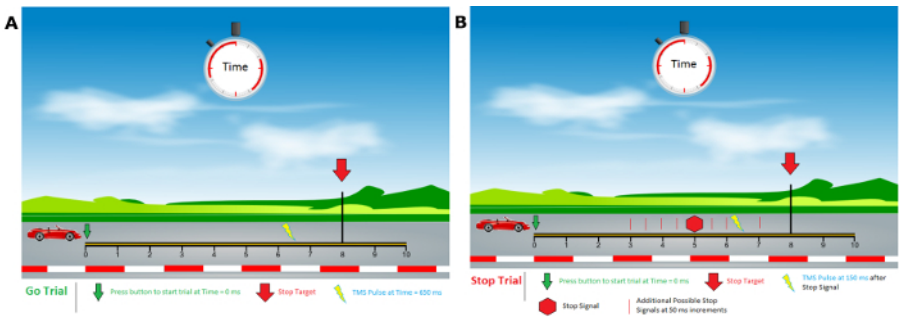

Figure 2: Trial schematics.
(A) GO trial schematic. Dominant index finger adduction onto a button activates the car to move across the screen. Participants are expected to lift the finger between 700 - 800 ms after start of the trial to stop the car close to but before the 800 ms target. TMS pulse is given at 650 ms after trial onset.
(B) Interspersed among GO trials are STOP trials during which participants were instructed to prevent finger-lift in response to a stop signal (i.e. car suddenly stops at some point before the 800 ms mark). TMS pulses were delivered 150 ms after the stop signal. Please click here to view a larger version of this figure.

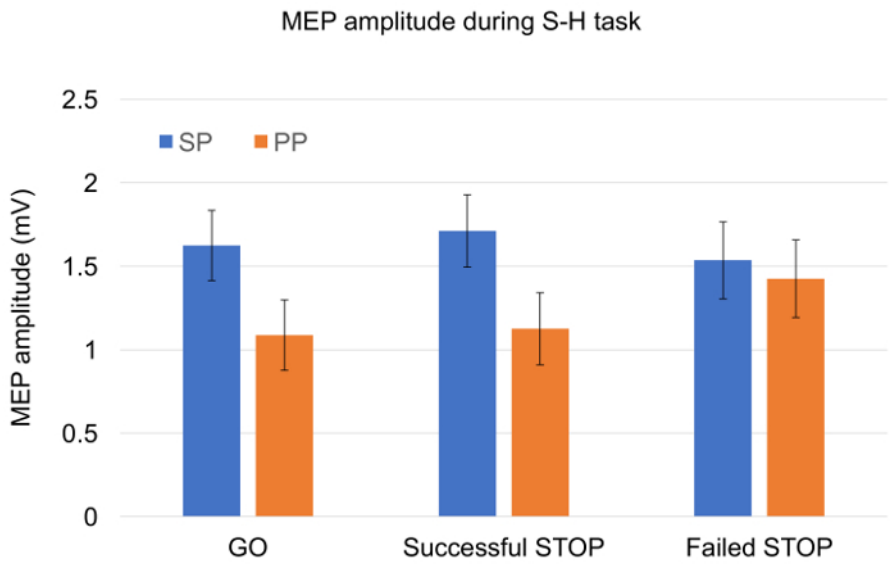

Figure 3. MEP amplitudes during racecar S-H task. MEP amplitudes (in millivolts) for M1 single- and paired-pulse TMS measurements are plotted for different conditions of this online S-H/TMS task (GO, successful STOP, failed STOP). Least squares mean estimates calculated from the regression analysis were used for this figure. Error bars represent standard errors calculated from the regression model. Please click here to view a larger version of this figure.

Discussion

This protocol is a novel child-friendly method of combining a stop signal task and TMS to examine event-related cortical inhibition. Clinical observation of motor inhibitory deficits and poor performance in stop signal tasks have been demonstrated in numerous neuropsychiatric conditions.[3] Relatively few investigators have used online fTMS to examine cortical excitability and inhibition during response inhibition tasks. Some groups have successfully used TMS during GNG task to show differences in cortical physiology in children and adults.[14,23,34] However, GNG task should ideally be conducted at a relatively fast pace to elicit prepotent motor response throughout the task so that inhibitory control can be adequately examined in Nogo trials.[35,36] From methodological standpoint, a fast-paced GNG task imposes difficulties for online fTMS experiments as device capacitors require time to recharge for the next stimulation pulse. For example, our monophasic pulse generating TMS device needs at least an inter-trial interval of 4 seconds thus limiting fast-paced online TMS/GNG experiments. Furthermore, underlying neuropsychiatric or developmental disorders can affect children's ability to complete a fast-paced GNG task. One feature of the Slater-Hammel task is that it is self-paced and thus allows for integration of TMS to conduct online physiologic measurements.[16] Coxon *et al.* used an online fTMS/clockhand S-H task in healthy adults to show that cortical inhibition, as measured by SICI, is more robust during STOP than GO trials. A separate online fTMS/SST study showed similar results in that M1 excitability decreases significantly after STOP cue in successful STOP trials.[15]Compared to the Coxon fTMS/S-H protocol[16], we made two significant modifications. First, we created the "racecar" version of S-H stop signal task which is more engaging for pediatric participants. Using this design, typically developing children (**Figure 3**) and those with ADHD (unpublished data) were able to complete at least 120 trials. The other feature we built into the online fTMS/S-H task is the dynamic tracking algorithm to adjust the timing of STOP signal such that STOP trial success rate is ~50% at the end of the entire experiment. This is important because it allows comparisons of the cortical inhibition during successful vs. unsuccessful STOP trials and also eliminates task performance as a confounding variable.

Single-pulse trials in this protocol allow the study of cortical excitability during movement preparation. However, in the context of the stop signal response inhibition task, we are also interested in quantifying M1 SICI during STOP trials. For SICI quantification, the subthreshold conditioning pulse stimulation intensity is an important experimental parameter. Prior studies have documented the dosing effect of the conditioning pulse intensity on SICI.[37,38] These studies show that a stronger conditioning pulse elicits more profound SICI. However, our laboratory historically used 60%*RMT as the conditioning pulse intensity to detect SICI differences in pediatric case-control TMS studies.[19,20] Since this conditioning pulse intensity also elicits significant M1 SICI[29], we used 60%*RMT for conditioning pulse in this fTMS/S-H task.

Another factor to consider in SICI quantification is the single-pulse induced MEP amplitude. The average single-pulse induced MEP amplitude is used as the denominator for calculation of SICI ratio. This baseline amplitude is dependent on different states such as rest, motor observation/imagery, motor preparation as well as test pulse stimulation intensity.[10,39,40] In this online fTMS/S-H task, MEP amplitudes are typically 3 to 4 times greater during the task compared to baseline rest condition (data not shown). In the original SICI study[28], the authors stated that SICI is less with a stronger test stimulus. However, raw data supporting this conclusion was not shown in the manuscript. Subsequent studies have examined a range of baseline rest MEP amplitudes (0.2, 1 and 4 mV) and showed that baseline MEP amplitude did not affect SICI.[41,42] Another study examined the effects of motor condition (rest, ipsilateral/contralateral isometric contractions) and test pulse stimulation intensities (90 - 150%*RMT) on SICI.[37] SICI is less during isometric finger contraction and varied depending on test pulse stimulation intensity. However, repeated-measures ANOVA did not identify a statistically significant interaction between condition and test pulse stimulation intensity. Post-hoc analysis showed that SICI during contralateral isometric contraction was significant for a range of test pulse stimulation intensities (110, 120, 130 and 140% of RMT). Due to naturally high motor thresholds in children[33], it is ideal to keep the test pulse intensity as low as possible due to potential TMS hardware limitations and participants' comfort. For these reasons, we chose 120%*RMT as the test pulse intensity. However,

this online S-H/TMS task might be applicable to even younger children were we to lower the test pulse intensity to 105-110%*RMT for future experiments.

One potential limitation of this protocol is that stronger, louder TMS pulses necessary for children may affect their S-H task performance. It is also possible that the average increased intensity of the TMS pulses could disrupt cortical circuits such that response inhibition is affected. Another possibility is that the stronger pulse is louder and could distract children during the task. For future experiments, this can be tested by re-doing the Slater-Hammel task with TMS pulses delivered at similar intensities over a region not involved in motor response inhibition, or using a sham TMS coil. Another limitation is the low number of STOP trials. This fTMS task requires the participants to complete 120 trials, of these only 30 are STOP trials. Our dynamic tracking algorithm should result in a ~50% success rate; therefore, there are only 15 successful and 15 unsuccessful trials for analysis. If significant motion artifact is detected in some of these trials, then tracing is not included for analysis and statistical power is decreased. This is likely true if the data are represented as each individual's mean MEP amplitude for each trial type (REST, GO, STOP). Using a repeated measures statistical model that estimates trial-type MEPs based on all trials, as we have done, may allow for more meaningful results.

In conclusion, we developed a noninvasive, well-tolerated and interactive method for quantifying cortical inhibition to detect differences during response inhibition task. This can be applied further to neuropsychiatric conditions to study cortical inhibition in children. There are numerous methods of expanding on this fTMS protocol. Recent studies have used two-coil paired-pulse TMS paradigms to study cortical connectivity during behavioral task in adults.[43,44] Using neuronavigation, this approach can be extended to the pediatric population to examine the effects of prefrontal nodes on response inhibition. Repetitive TMS (rTMS) provides another option to modulate brain regions that are critical for inhibition of motor responses.[43,45,46] Moreover, another potential future application is combining this protocol with simultaneous EEG to quantify TMS-evoked cortical potentials in non-M1 regions[47] to characterize cortical physiology associated with motor response inhibition.

Disclosures

The authors have nothing to disclose.

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