SPECIFIC AIMS

Motor learning is a cornerstone of human adaptability that encapsulates the brain's capacity to refine motor actions through practice and experience. From pioneers in motor control, Fritsch and Hitzig laying the foundation for uncovering the brain's role in motor control, to modern research that demonstrates the interplay of corticomotor excitability and inhibition, our understanding of motor learning has evolved significantly. Nonetheless, a crucial gap remains in comprehensive understanding how intracortical inhibition influences neurophysiological changes across learning phases and complexities. This gap hinders our ability to comprehensively understand how motor skills are acquired and mastered, constraining advancements in motor movement interventions and rehabilitation.

Recent studies demonstrate that rapid gains in motor performance in the early phase are paralleled by an increased corticomotor excitability due to the active inhibition of γ-aminobutyric acid (GABA)-mediated inhibitory activity. This resultant increase in corticomotor excitatory activity produces a rapid expansion of functional representations in the primary motor cortex, thereby facilitating in the encoding of new motor memories, synaptic strengthening and learning-dependent neural plasticity. As motor learning transitions into the late phase, the increasing synaptogenesis and motor map reorganization lead to lasting intracortical changes and motor map reorganization reflecting the brain's plastic adaptive responses to learning.

Therefore, my **long-term goal** is to reveal the breadth of inhibition’s role in motor learning, thereby shedding light on the neurophysiological mechanisms underlying skilled motor acquisition and refinement. My **objective** is to dissect the role of intracortical inhibition (ICI) during various learning phases and complexities to determine how ICI influences topographic representations and reorganization within the primary motor cortex (M1). My **central hypothesis** states that decreased ICI during early phase motor learning will facilitate exploration of novel motor strategies, with ICI returning to baseline for task consolidation after a successful motor strategy has been established. The **rationale** for this study is to understand how modulatory inhibition is driven by task parameters and cortical demands in motor learning.

Aim #1: Determining the Role of Intracortical Inhibition in Motor Skill Formation and Consolidation

The first aim will examine changes in ICI, across motor learning phases, under the influence of varying task complexities. During each training period, motor-evoked potential (MEP) from task-relevant muscles will be recorded and resting short-intracortical inhibition (SICI) will be obtained pre- and post-training to identify ICI changes. *We hypothesize that the initial decrease in inhibition is crucial in exploring new motor strategies, while the subsequent increase allows for the exploration of new motor strategies and consolidates effective ones.*

Aim #2: Determine the Relationship between Task Complexity and Motor Map Reorganization

The second aim examines how task complexity impacts somatotopic changes and motor map reorganization post-training. The protocol is the same as Aim #1, however measures of MEP amplitude changes will be recorded for the purpose of simulating neural electric field changes pre- and post-training. *We hypothesize that a complex task induces more selective and nuanced cortical reorganization, due to the importance of task-specific inhibitory control to optimize motor skill acquisition and mastery.*

The expected outcomes of this project include a detailed mapping of intracortical changes and identifying neural correlates of cortical plasticity relative to task complexity. These findings aim to significantly enhance our understanding of motor cortex adaptability, marking a pivotal moment for neurorehabilitation. The project promises to improve the quality of life for millions with motor movement disorders by setting the foundation for novel interventions and neurorehabilitation protocols, potentially offering increased levels of independence to affected individuals worldwide.

RESEARCH STRATEGY

SIGNIFICANCE

A crucial step in advancing the field of motor control is to understand the scope of neurophysiological processes by which motor skill acquisition and adaptation are mediated. Recent studies have delved into motor cortex plasticity and how intracortical inhibition (ICI) actively facilitates motor learning. The interplay between inhibitory and excitatory processes as it relates to motor skill complexity presents a promising opportunity to uncover mechanisms by which motor function is learned and perfected. This study hopes to highlight how inhibitory behavior in various phases of learning, shape corticomotor excitability and reorganization.

Earlier works (Pascual-Leone et al.,1994; Ziemann, 2001) have shown motor learning follows a biphasic pattern of excitability. There is an initial period of excitability increase due to the active inhibition of inhibitory activity, followed by a consolidation phase where inhibitory baseline levels are restored. Building on these earlier works and recent studies (Foysal & Baker, 2019; Giboin et al., 2020), we hypothesize that more complex tasks will result in a higher inhibitory baseline which will be reflected in moderate increases in motor-evoked potentials (MEP), whereas a simple version of that task, using the same effectors, will cause greater increases in MEPs. Further, exploring how task complexity might influence motor map reorganization within the primary motor cortex (M1), we seek to advance our models of cortical plasticity. We know that task complexity combined with motor skill practice, elicits differential somatotopic adaptations with simple tasks leading to shifts in the primary motor cortex (M1) representation (Pearce et al., 2000) and complex tasks leading to consolidation in the cortical representation of movement (Adkins & Lee, 2021; Beaulieu & Milot, 2018). This inquiry will clarify how task complexity influences M1 changes and with that, our understanding of plasticity in the M1.

If successful, our research in these aims is expected to advance our understanding of motor learning processes and their application in the field of motor movement disorders and rehabilitation. By unveiling the influence of intracortical inhibition on the acquisition of motor skill and cortical reorganization, along a continuum of task complexity, the development of novel, empirically supported rehabilitation methods can be inspired. This research builds on the theoretical underpinnings of motor control and holds the promise to help increase the motor movement interventions and recovery results.

INNOVATION

This research proposal is innovative as it systematically delves into how task complexity influences ICI and M1 reorganization, diverging from traditional motor learning paradigms that focus more so on types of learning, the process of learning and adaptation and the consequent outcomes, rather than the underlying neurophysiological mechanisms driving changes associated with learning. Our approach seeks to further understand motor control and learning in humans by examining the nuanced interplay between task complexity and its influence on M1 reorganization and cortical alterations. Current literature has examined components of these factors in motor control, however, to our knowledge, there hasn’t been an extensive dive into how the complexity of a task influences intracortical inhibitory behavior, and the subsequent changes observed after task performance plateaus. By integrating neuroimaging, neurostimulation, and electric field simulation techniques, we seek to reveal how task complexity influence ICI, triggering neuroplasticity in the motor cortex, filling a significant gap in existing knowledge. This could overturn long-standing barriers in neuroscience, fostering new research into optimizing novel motor skills training, customizing rehabilitation strategies, and advance the field of neuroprosthetics. Ultimately, our project aspires to elucidate the breadth of inhibition’s role in motor control enhancement. By uncovering how task complexity can be optimized for positive adaptations in the motor cortex, we're paving the way for substantial improvements in functional outcomes and quality of life across diverse populations.

APPROACH

*Introduction*

Physiological changes of topographic specific muscular regions of the primary motor cortex (M1) occur after motor learning and dynamic intracortical inhibitory activity induces structural synaptic changes. The extent of somatotopic representational changes and cortical excitability is influenced by the requirements and complexity of a task (Rosenkranz & Rothwell, 2006; Ziemann et al., 2018). Therefore, the *objective* of the current aims is to delineate the conditions that shape changes in M1 representation and cortical excitability post-training. The *working hypothesis* for our objective is that there will be an initial decrease in intracortical inhibition (ICI), followed by an increase, signifying motor consolidation. Post-training, we *expect* to observe an overall increase in motor-evoked potential (MEP) amplitude, indicated by decreased short-intracortical inhibition (SICI) recruitment after having learned the task, regardless of the complexity of the task. For a highly complex task however, we *expect* to see a dampened version of post-training changes due to the greater inhibitory activity required for successful task performance, resulting in an increase in SICI post-training (Murphy et al., 2020). Our *approach* to testing the hypothesis will be to employ a two-group design that will train on the same task, with one group having an added component to increase complexity of the task. This will allow for a comparative analysis of intracortical activity changes (Aim 1) and M1 reorganization (Aim 2) between the groups. Successfully meeting this aim will broaden our grasp of motor control, especially regarding the temporal dynamics of ICI and the influence of task complexity on neurophysiological changes. Gaining this insight is crucial for demonstrating how inhibitory mechanisms contribute to primary motor cortex structural and functional changes, potentially inspiring new insights into motor movement disorders.

RESEARCH DESIGN AND METHODS

Participants will be screened for MRI and TMS eligibility prior to scheduling and on the day of their MRI, consent will be collected prior to testing, as well as dominant handedness, derived from the Edinburgh Handedness Inventory (EHI). An anatomical scan (T1 and T2-weighted) of the left and right M1 will be acquired and diffusion weighted imaging will be obtained. After the scan, participants will schedule the three visits to the laboratory, separated apart by 24 hours.

On the first visit to the laboratory, the participants will fill out a TMS screening form and will be offered the opportunity to ask any questions prior to the setup. The participant will be fitted with BrainSight headband and will be registered to the simulated brain that was derived from the MRI scan to ensure accurate representation. On the participant’s dominant arm, optimal electrode placement will be determined for the Abductor Pollicis Brevis (APB) and the Flexor Digitorum Profundus (FDP), additional electrode placement will be against the participant’s C7 to pick up TMS artifact and the ground electrode will be placed on the non-dominant styloid process. After electrode placement and quiet activity is observed in the EMG traces, TMS ‘hotspotting’ will be administered. This procedure involves applying five consecutive stimuli with the peak-to-peak amplitude monitored, this is repeated up to five different locations along the M1. The site that elicited the strongest and most consistent motor-evoked potential (MEP) was determined to be the hotspot and was marked in Brainsight. The maximum voluntary contraction (MVC) of the participant’s FDP will be obtained using a force transducer to take 3 maximum contractions with a break of 2 minutes between to ensure accurate representation. Participants will be asked to maintain 20% of their MVC and the active motor threshold (AMT) was defined as the intensity producing 50 uV more EMG activity than the constant contraction in at least 5 of 10 consecutive trials. The SICI recruitment curve will be determined, followed by baseline SICI levels.

Participants will be seated with support for both wrists and elbows and freedom of hand movement ensured for the optimal positioning for both tonic contraction and dynamic movement tasks. The task will be explained to the participant by the researcher and a practice round of 3 shortened trials will be administered so that the participant understands the task. Depending on the which cohort the participant was randomized to, they will either complete the *Simple Task* or the *Complex Task.* In the simple task, participants will maintain contact with a force transducer with their APB and FDP placed on seperate buttons and use their thumb to perform tapping sequences in response to on-screen stimuli while maintaining FDP contact to the transducer the entire time. This task emphasizes timing and coordination over a 5-minute duration. A failure to accurately time the downward thumb movement, will be noted and the participant will be allowed to continue from that point until the pre-designed 5-minute stimulus ends. Building on the simple task's foundation, the complex task introduces the addition of force modulation which requires the participant to modulate the force applied to the button by their FDP, where greater force correlates to higher obstacles. Obstacle height will be set relative to a range of maximal voluntary contraction (MVC) levels. As in the simple task, failures will be noted and gameplay will resume until the end of the round. A total of 6 rounds will be completed, afterwhich SICI will be measured again. On day 2, baseline SICI levels will be measured, followed by 6 rounds of gameplay, and follow-up SICI will be measured. Day 3 will follow the same procedure as day 2, however after the follow-up SICI is obtained, an end-of-training SICI recruitment curve will be acquired.

Overview of Methods

Baseline AMT and short-intracortical inhibition SICI measurements will be established using a TMS protocol (Kujirai et al., 1993). Participants will undergo training sessions every other day, with SICI measurements recorded post-session. Additionally, individualized electric field models will be generated using simNIBS software, leveraging MRI scans to accommodate inter-individual and group-level analysis (Thielscher et al., 2015).

Equipment

Electromyography (EMG): Surface sensors will monitor muscle activity, with data extraction tailored to task requirements to measure cortical excitability during each visit to the lab. Participants will be seated comfortably with hands and forearms in a supported and relaxed posture. A 2-line surface electrode will be placed on the muscle belly for the APB and FDP of the dominant hand and a ground electrode on the nondominant ulnar styloid process. Participants will be asked to flex the recorded muscles to evaluate sensor placement. This procedure will be repeated as necessary to ensure data quality. Participants will then be asked to maximally contract muscles and hold the contraction for 4-5 seconds to measure the MVC. This procedure will be repeated three times, with rest periods between each contraction to ensure participant comfort. During some behavioral testing, and all brain stimulation sessions, EMG will be recorded and will be used to measure when muscles are activated during behavioral responses and to assess the excitability state of the motor system when combined with brain stimulation. Individuals with irritated skin or open wounds in the areas where EMG recordings will be taken will be excluded from the study

Transcranial Magnetic Stimulation (TMS): TMS will be utilized to examine corticospinal pathway inhibition, with paired pulse protocols adjusting for optimal sensitivity to inhibition. Coil placement will follow guidelines sensitive to inhibitory measurement. At each TMS session, the optimal TMS coil position for eliciting a response in the EMG of a targeted muscle will be located on the scalp and marked in the Brainsight neuronavigation program. Participants will be asked to maintain a muscle contraction at 20% MVC while the intensity of TMS is gradually adjusted gradually to determine the AMT, i.e. the intensity that produces a muscle response of at least 50 µV in the EMG on 5/10 attempts. An inhibition recruitment curve procedure will be performed to determine individual sensitivity to TMS during a low-level of activity.

Magnetic Resonance Imaging (MRI): Participants will undergo a brain imaging session at the Lewis Center for Neuroimaging (LCNI) that will include T1, T2, and diffusion-weighted scans, to support structural analysis and simNIBS model generation. LCNI standard operating procedures (SOPs) will be used for this protocol. Brain imaging data will be compared with behavior and TMS measures of motor excitability. Anatomical scanning for both T1 and T2 will take about 20 minutes and the diffusion scanning about 45 minutes for a total scan time of about 1.5 hours, including setup time.

BrainSight: A Brainsight neuronavigation system that records the locations of TMS stimulation. The Brainsight system uses a stereo camera to track the position of the TMS coil relative to the participant’s head. The participant wears a headband, or glasses fitted with markers that are visible to the camera, and the participant’s head can be co-registered to an anatomical MRI image using the Brainsight software. The TMS coil is also tracked by the camera, allowing the experimenter to use the Brainsight system to visualize the positioning of the TMS coil relative to anatomically defined targets. Additionally, the coordinates of the location of the TMS pulses relative to the MRI image are recorded using Brainsight software to provide a record of where the TMS was administered relative to individual participant anatomy.

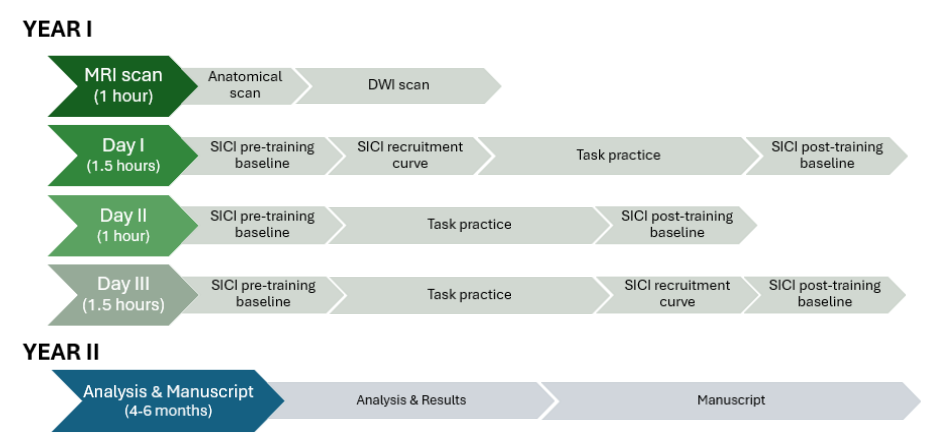
SimNIBS: Employs MRI-derived models to simulate electric field propagation induced by TMS, facilitating detailed analysis of stimulation effects and cortical excitability changes. Using the coordinates of the position of the stimulation relative to the participant MRI, we will be able to create a 3D mesh head model, calculate the electric field stimulation, visualizing and post-process the results on the individual and group level (Thielscher et a., 2015).

Participants: Based on prior motor learning studies (Dayan & Cohen, 2011), 20-22 healthy adults aged 18-35, will be recruited from the University of Oregon Human Subject Pool. Participants will be screened for TMS and MRI eligibility, with no history of meeting TMS and MRI screening criteria. The cohort will be randomly divided into control (simple task) and experimental (complex task) groups.

Expected Outcomes: This study anticipates the ability to delineate the nuanced interplay of functional, structural, and temporal intracortical changes during motor learning, as modulated by task complexity.

Potential Problems & Alternative Strategies: Addressing potential issues, such as TMS coil orientation effects on MEP responses, the study will employ alternative strategies to ensure robust detection of group differences, maintaining the integrity of the investigation into complex task-induced inhibitory mechanisms (Rossini et al., 2015).

STUDY TIMELINE



All behavioral testing, video, TMS, and EMG procedures will be conducted in the Action Control lab on the third floor of Gerlinger Hall. All brain imaging procedures will be conducted at the LCNI.

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