Optimizing Repetitive Transcranial Magnetic Stimulation Protocols for Motor Function

by

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Dedication

This work is dedicated to my grandparents, Isabel and Ralph Goldenkoff and Ina and Robert Mayer, from whom I have inherited my curiosity, passion for science, love of reading, and desire to never stop learning new things.

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Abstract

Humans are incredibly adept at reaching for and manipulating objects – tasks vital for daily activities of independent living. Restoration of motor function after a neurological disorder like Parkinson's disease or stroke is critical to the rehabilitation process. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation method that can affect neural activity and produce lasting changes in cortical physiology, making it a useful tool for studying the brain network that controls motor function. However, the effects of rTMS on the brain and behavior across the lifespan are highly variable and not fully understood, which limits its application in both basic research and clinical settings. This dissertation aims to investigate factors that contribute to the development of optimal rTMS protocols for promoting plasticity in a parietal-frontal network that mediates movement processes. The central hypothesis is that controlling the brain state during repeated, spaced, network-targeted stimulation will improve motor function and performance. I tested the central hypothesis by pursuing the three following specific aims.

Aim 1 examines whether a network-targeted rTMS approach that leverages individual-specific functional parietal-motor pathways of the motor control network for skilled reach-to-grasp actions will maximize stimulation specificity. Aim 2 investigates the impact of stimulation dosage on motor excitability and performance by varying the number of rTMS sessions focused on a defined reach-to-grasp network in the motor system. Aim 3 tests the notion that the functional context of brain activity (i.e., brain state) during parietal stimulation can modulate

interactions with functionally connected motor regions to alter plasticity associated with skilled motor control of hand actions.

The first study describes a multi-focal TMS method to measure and manipulate functional interactions between parietal and motor regions with two coils, providing insight into the cortical reach-to-grasp network connectivity and its alteration at a system level. The second study investigates age-related changes in functional interactions between parietal and motor regions, revealing decreased facilitation of parietal-motor functional connections and its association with age-related decline in the neural control of movement. The third study demonstrates the cumulative dose-dependent effect on excitability in the motor cortex after repeated spaced rTMS to the parietal-motor pathway involved in reach-to-grasp control in young adults. The fourth study examines the application of a multiple-dose rTMS protocol to the parietal-motor pathway in older adults, demonstrating the challenges of augmenting plasticity induction with rTMS for the aging brain. The fifth study investigates how modulating cerebellar activity in the reach-to-grasp control network impacts subsequent stimulation responses downstream in the parietal-motor pathway. Lastly, the sixth study investigates the impact of controlling the brain state during parietal rTMS with a reach-to-grasp task on motor excitability and skilled motor performance, highlighting the potential of behavioral-induced brain states to amplify rTMS effects on functionally specific neural populations and pathways associated with motor function. Together, these studies demonstrate effective, functionally specific, and lasting changes to the parietal-motor network that support motor function. Leveraging these insights can better guide the plasticity mechanisms of motor control and inform the design of targeted interventions that can transition from research settings to widespread clinical practice. These studies could lead to targeted neuromodulation strategies to combat age-related sensorimotor declines and restore neuromotor abilities lost to neurological disorders like Parkinson's disease and stroke.

Chapter 1: Introduction

Humans demonstrate remarkable skill and flexibility when reaching out to grab and manipulate objects; a task performed many hundreds of times every day for eating, grooming, and interacting with the world. These behaviors are crucial for independent living, and relearning motor skills and improving upper limb dexterity are vital for rehabilitation following stroke or neuromuscular disorders that disrupt voluntary movement regions in the brain. Noninvasive brain stimulation (NIBS) — and specifically repetitive transcranial magnetic stimulation (rTMS) — is a powerful tool that can be used to probe the relationship between brain and behavior and even modify the brain's own neural plasticity mechanisms to support motor function (Hallett, 2007; Latorre et al., 2019; Polanía et al., 2018; Ridding & Rothwell, 2007; Rothwell, 2011; Rothwell & Hannah, 2021). However, the mechanisms by which NIBS induces modulatory effects on neural networks, cortico-motor plasticity, and motor control remain unknown (Chervyakov et al., 2015; Chisari et al., 2014; George et al., 2003; Klomjai et al., 2015; Silvanto et al., 2018). There is a critical need to establish how rTMS interacts with dynamic patterns of neural activity to induce lasting plasticity changes in motor networks, as this gap in knowledge hinders the development of interventions for both basic research and clinical applications (M. J. Burke et al., 2019; Cantarero & Celnik, 2015; Cárdenas-Morales et al., 2010; Chen et al., 2008; Cramer et al., 2011; Terranova et al., 2019).

rTMS interventions are FDA-approved for depression and psychiatric disorders, but their efficacy for the treatment of neuromotor impairments is still lacking evidence (Polanía et al., 2018; Raffin & Siebner, 2014). Previous clinical trials have yielded mixed results, indicating that

interpreting rTMS mechanisms of action and their parameter optimization could lead to beneficial plasticity modifications to support improved motor function after injury and movement disorders (Adeyemo et al., 2012; Harvey et al., 2018; He et al., 2020).

However, the more basic questions remain unanswered: 1) Why is there so much variability in the outcomes of studies exploring rTMS as a potential therapy for movement impairments? And 2) how can this promising technique be improved so it can be used clinically for motor control rehabilitation?

Addressing these questions and developing such an understanding is the first step in designing interventions that can effectively enhance the use of rTMS for treating movement impairments and facilitate the translation from basic research to clinical practice. To achieve this, it is necessary to comprehend how rTMS protocols can affect neural networks in various ways throughout one's lifespan. This is because it is well-established that plasticity mechanisms change with age, and older populations tend to have a higher prevalence of neurodegenerative diseases and motor control impairments. (S. Burke & Barnes, 2006; Iriarte & George, 2018; Mahncke et al., 2006; Seidler et al., 2010). This study aims to shed light on the neural mechanisms of rTMS in young and older adults in basic research settings, offering insights into how various rTMS parameters can modulate activity within particular brain networks and be personalized to suit individual patient needs for optimal outcomes. To maximize the effectiveness of rTMS in basic research and therapeutic settings, it is important to identify key rTMS parameters that might impact brain and behavior outcomes.

1.1 Overview of the human motor control network

Proprioceptive and tactile information about the limb position is encoded in the

somatosensory cortex (S1) while visual information about the object's location and properties are processed by the visual cortices (VC; Kandel et al., 2021). The posterior parietal cortex (PPC) then integrates this information to inform subsequent action intentions and motor commands (Vesia & Crawford, 2012). Briefly, the PPC is involved in visuomotor transformations that convert the abstract goal movement into explicit motor commands. The PPC and associated frontal cortical areas have designated substreams to process distinct reach-and-grasp information. The dorsomedial pathway, which connects the medial intraparietal sulcus and parietal area V6A to the dorsal premotor cortex (PMd), facilitates smooth coordination of movement by integrating the hand and finger grasping movement with the arm reaching movement (Fattori et al., 2010; Turella & Lingnau, 2014; Vesia & Crawford, 2012). Meanwhile the dorsolateral pathway, which shares information from the anterior intraparietal sulcus to the ventral premotor area (PMv),

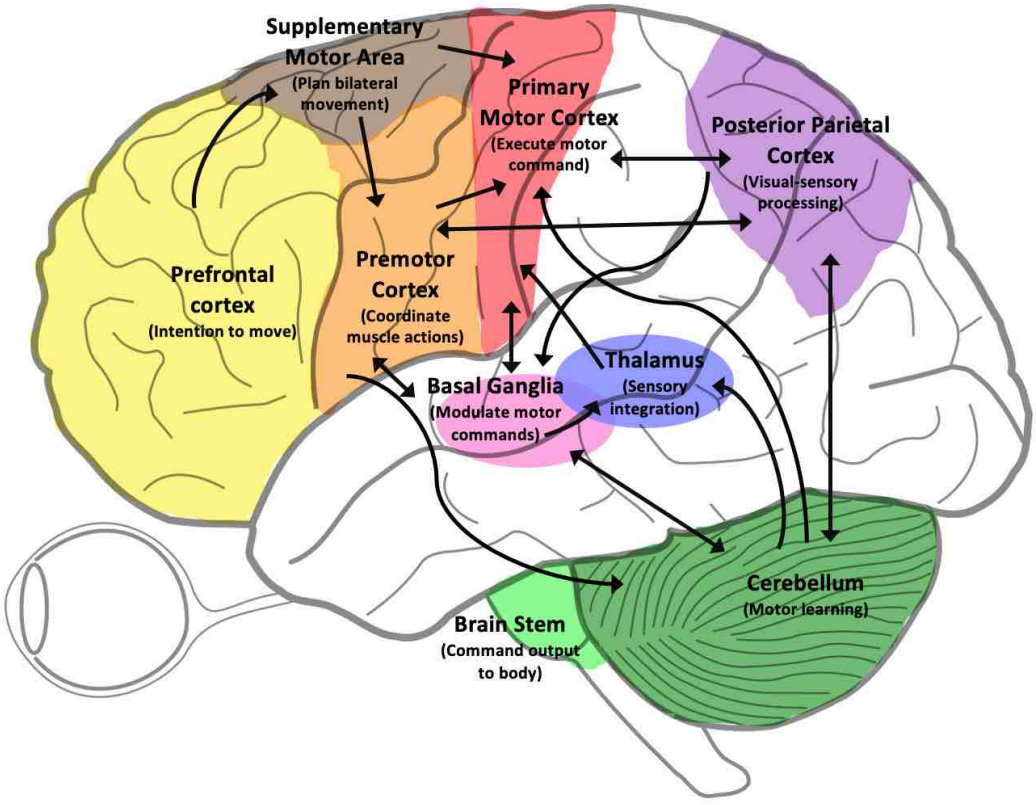

Figure 1-1 A simplified overview of the visually guided reach-to-grasp pathway within the motor control network. Arrows indicate directions of information transference between distinct brain regions.

encodes complex visual and contextual information about the object's properties to allow for hand shaping adjustments (Fattori et al., 2017; Turella & Lingnau, 2014; Vesia & Crawford, 2012). Motor planning continues in areas of the frontal cortex; premotor areas select appropriate, context-specific grasp responses, including hand and finger shaping, based on spatial information and the supplementary motor area (SMA) coordinates complex sequences of movement and bimanual tasks (**Figure 1-1**; Andersen & Cui, 2009; Davare et al., 2008, 2011; Gallivan & Culham, 2015; Olivier et al., 2007).

Once the motor response is selected, the primary motor cortex (M1) generates movement commands which are sent to different muscles. An action potential generated in M1 will travel down the corticospinal tract, synapse onto a lower motor neuron, and innervate muscle fibers causing a muscle contraction and generating movement (Kandel et al., 2021).

Because there is a delay in the transmission of visual and somatosensory information to the cortex, spatial and temporal inconsistencies can arise during the execution of a grasping movement. To account for this, the parietal cortex develops predictive models about body movement and potential changes to the target object's form or location. A feedback loop between PM and PPC continuously assesses mismatches between hand-conformation and intrinsic object properties, and support any necessary adjustments (Olivier et al., 2007; Vesia & Crawford, 2012). The cerebellum (CB) has reciprocal connections with motor, premotor, and parietal areas, providing it with sensory information and motor plans (Allen et al., 2005; Bernard et al., 2012; Bostan et al., 2013). These feedback loops allow the CB to compare intended output with actual effects, modulate future actions, and facilitate skilled motor learning (Kandel et al., 2021). The CB also receives feedback throughout the grasping process and can help modulate the pressure and grasp force (**Figure 1-1;** Olivier et al., 2007).

1.2 Basic principles of transcranial magnetic stimulation

1.2.1 Equipment

Transcranial magnetic stimulation (TMS) is a type of non-invasive brain stimulation where the cortex is stimulated over the intact scalp and skull with minimal discomfort. A TMS device has both a pulse generator, which supplies electrical current, and a coil (B. Wang et al., 2021). The pulse generator controls the temporal characteristics of the induced electric field, while the coil's properties define the special characteristics of the e-field in the brain (Peterchev & Riehl, 2021; B. Wang et al., 2021). Within the pulse generator, there is a capacitor and a switch that controls the discharge of current into the coil (Peterchev & Riehl, 2021). The properties of the voltage discharge (e.g., time duration, intensity, current waveform shape, direction of current flow within coil) can often be defined by the operator depending on the specific stimulator device used (Peterchev & Riehl, 2021). The studies presented in this dissertation use two primary stimulation devices: a Magstim Bistim² (Magstim) for single and paired-pulse stimulation and a MagPro x100 with MagOption (MagVenture Inc.) for theta burst stimulation protocols.

A TMS coil contains multiple loops of wire. As several thousand amps of current are discharged from the pulse generator flows through the windings in the coil for ~100μs, a magnetic field, approximately 1-2 Tesla in strength, is generated perpendicular to the coil, which can penetrate the scalp and skull (Ilmoniemi et al., 2021; B. Wang et al., 2021). This magnetic field generates an exogenous low-frequency electric field in the brain. The electrical field can depolarize neuronal membranes to create action potentials in targeted neurons (Ilmoniemi et al., 2021). The research studies discussed here utilize figure-of-eight shaped coils that have two "wings" of wire loops with current flowing in opposing directions in each wing (Ilmoniemi et al.,

2021). This produces a stronger and more focal electric field at the center of the coil that can stimulate superficial cortical regions about 2-3cm in depth (Ilmoniemi et al., 2021). The D70^2 (Magstim), D50 Alpha B.I. (Magstim), and MCF-B70 (MagVenture Inc.) are the primary TMS coils used in the following studies.

Because the cortical volume stimulated by TMS is quite focal, approximately 5mm x 5mm x 5mm, it is important to ensure accurate targeting of neural tissue (Goetz & Kammer, 2021). Neuronavigation systems that use frameless stereotaxy can enable precise delivery of TMS pulses based on anatomical or functional magnetic resonance imaging (MRI). This is done by co-registering the participant's head to a computer model of their head anatomy generated from their MRI scan and simultaneously tracking the TMS coil's position and orientation relative to the pre-determined target (Goetz & Kammer, 2021). Using frameless stereotactic neuronavigation allows the participant free movement of their head and neck while ensuring the researcher can stimulate the same location for each bout of TMS. This increases the specificity and reliability of TMS effects (Goetz & Kammer, 2021). The Brainsight 2 system (Rogue Research Inc.) is used in the TMS experiments presented in this dissertation. In situations where we did not obtain the participant's own MRI scan, a template brain was used for the neuronavigation to ensure reliability in the target location across TMS sessions.

1.2.2 Neurophysiology

1.2.2.1 Measuring neuronal activity (single and paired pulse TMS)

A single TMS pulse to M1 can depolarize the underlying neurons that control muscle force production and generate descending volleys in the spinal cord. This, in turn, can activate the spinal motor neurons that innervate peripheral muscles contralateral to the stimulation site. The resulting stereotyped muscle twitch called a motor evoked potential (MEP), can be recorded

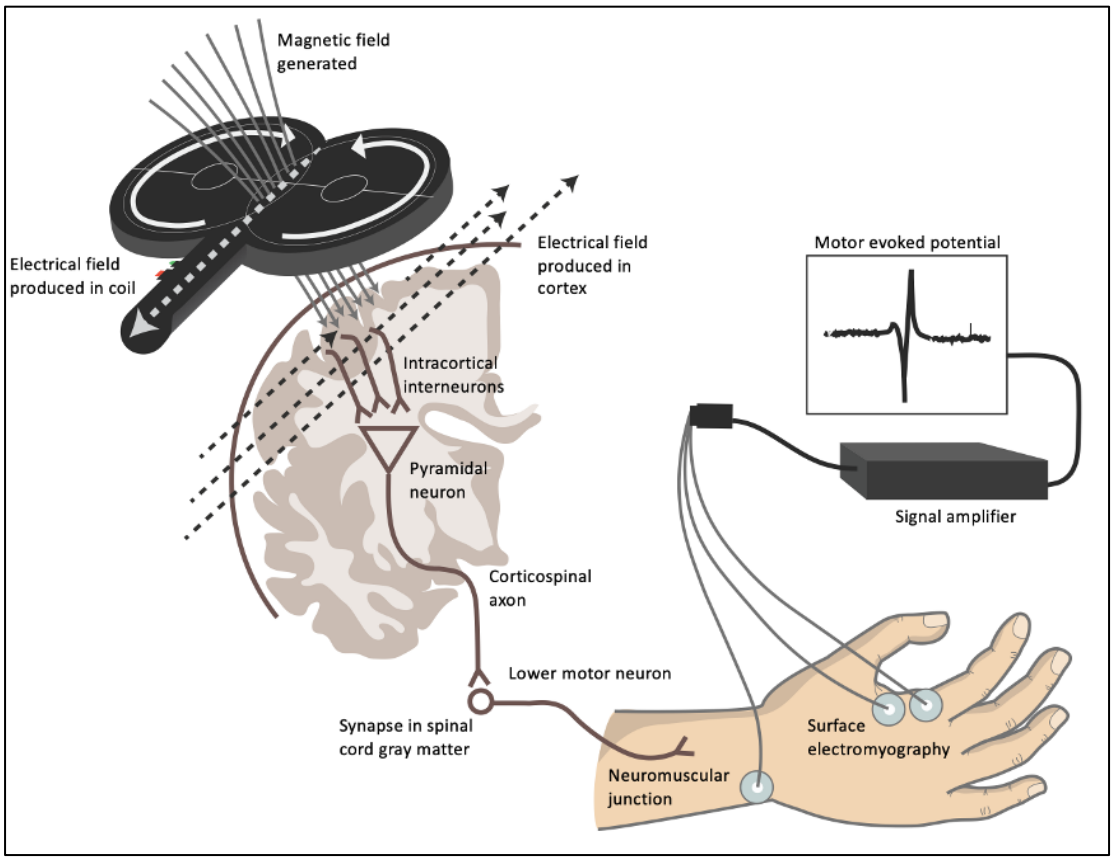

Figure 1-2 Diagram depicting how the magnetic field generated by a TMS coil activates neural tissue and generates an action potential and muscle contraction.

with surface electromyography (EMG) and provide neurophysiological readouts for changes in the motor system before and after interventions (**Figure 1-2**). The resultant MEP's peak-to-peak amplitude is measured and monitored over time. The intensity and location of stimulation required to produce an MEP varies by individual and muscle being targeted. Therefore, a baseline intensity referred to as a motor threshold (MT) is determined to standardize protocols across individuals (Hallett, 2007). TMS intensity is usually reported as a percentage of maximum stimulator output (MSO) to account for disparities across machines. It is more challenging to threshold the proper stimulation intensity for areas outside the motor cortex. A fixed intensity is often used for all participants, or the MT is adjusted based on distance from the scalp to the target brain area (Stokes et al., 2005).

Single-pulse TMS and diagnostic paired-pulse TMS can be used to assess cortical excitability and excitatory and inhibitory circuits within the brain. TMS applied to the representation of the hand area of the motor cortex produces a stable and quantifiable response in the hand muscles. This provides an opportunity to study brain function in both healthy individuals and those with injuries or diseases, as well as measure the impact of interventions on plasticity and cortical excitability (Bestmann & Krakauer, 2015; Di Lazzaro & Rothwell, 2014).

Delivering pairs of pulses in quick succession is a useful way to measure connectivity between separate brain regions (Lafleur et al., 2016). Briefly, it is possible to use a paired-pulse, multi-focal TMS paradigm to investigate causal interactions between motor and non-motor regions or across cerebral hemispheres with two coils. By comparing the MEP response from a single pulse (test stimulus) to the response from a paired-pulse (conditioned-test stimulus) at various intervals and intensities, one can gauge the excitability of cortical circuits (for more information on using the dual-site TMS paradigm, see **Chapter 2.3.5**).

1.2.2.2 Manipulating neuronal activity (repetitive TMS)

When TMS pulses are applied repetitively (rTMS), induced brain and behavioral changes can occur that outlast the stimulation period (Berardelli et al., 1998; Beynel et al., 2020; Huang et al., 2011; Klomjai et al., 2015). This makes rTMS a useful tool to understand mechanisms of healthy or aberrant brain plasticity as well as modulate brain activity to support neurorehabilitation and motor learning (Chou et al., 2015; Dionísio et al., 2018; He et al., 2020; Mally & Stone, 1999).

At the cellular level, plasticity changes underlying learning and memory are mediated by the process of long-term potentiation (LTP, increasing synaptic strength) and long-term depression (LTD, reducing synaptic strength; Malenka & Bear, 2004). High-intensity and high-

frequency synaptic stimulation for brief periods can induce lasting changes to synaptic connectivity (Kandel et al., 2021). Interestingly, these processes are input specific as changes can be localized to specific synapses without affecting others (Bliss & Cooke, 2011). The temporal proximity of novel stimuli strongly influences how associative plasticity occurs. Pairing a pre-synaptic stimulus with a post-synaptic stimulus (i.e., neuron A causing firing in neuron B) repeatedly at a low frequency leads to long-term changes in the larger neural network in a Hebbian-like manner. The stimulation of two cortical areas in rapid succession the stimulation of two cortical areas in rapid succession, termed spike-timing dependent plasticity (STDP), facilitates the development of functional neuron assemblies and fine-tunes synaptic connections (Feldman, 2012; Kandel et al., 2021).

Researchers and clinicians can take advantage of this naturally occurring physiological process with NIBS. Patterns of stimulation from a single coil can inhibit or excite activity by

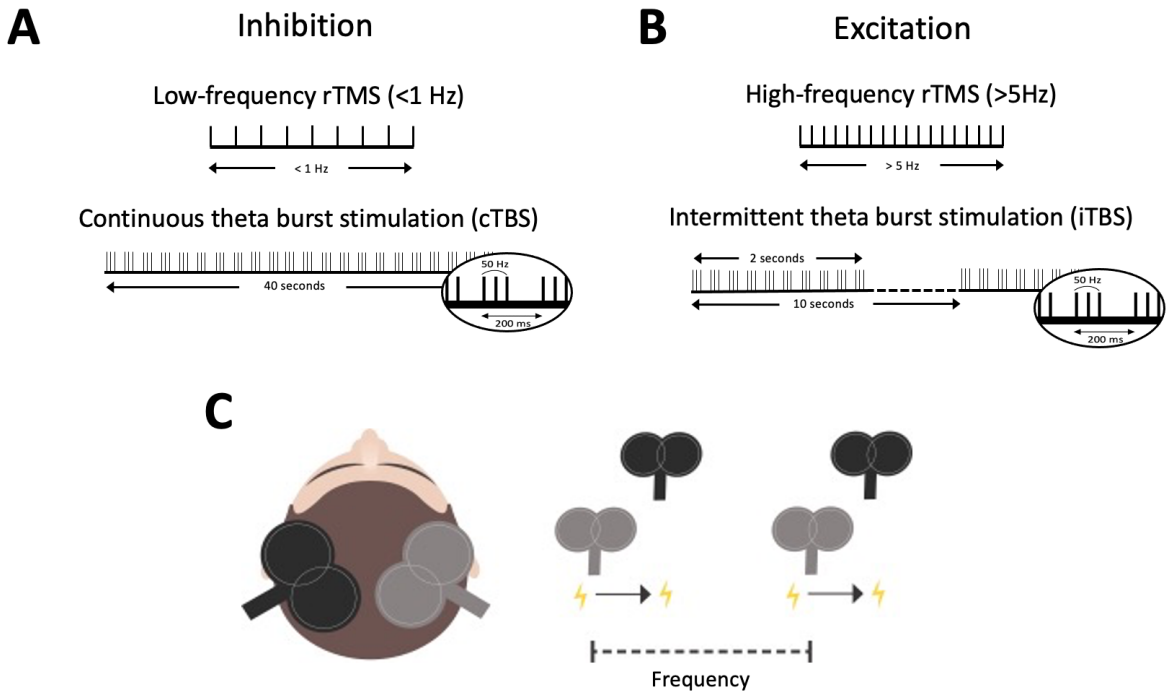

Figure 1-3 Modulating neural plasticity with repetitive transcranial magnetic stimulation to cause (**A**) inhibitory effects, (**B**) excitatory effects or (**C**) network strengthening effects.

inducing homosynaptic plasticity (**Figure 1-3**). Intermittent theta burst stimulation (iTBS) is characterized by bursts of high-frequency stimulation applied in short intervals (e.g., 3 pulses at 50 Hz every 200 ms) for 2 seconds repeated every 10 seconds for a total of 190 seconds (600 total pulses). iTBS is believed to produce excitatory effects on the brain regions it targets (Cárdenas-Morales et al., 2010; Huang et al., 2005). In contrast, continuous theta burst stimulation (cTBS) involves a continuous train of stimulation bursts (3 pulses at 50 Hz every 200 ms) without rest periods for 40 seconds (600 pulses total) (Cárdenas-Morales et al., 2010; Huang et al., 2005). cTBS is generally understood to produce inhibitory effects on the brain region where it is applied. Steady repetitive stimulation can also have modulatory effects over time. Low-frequency stimulation (<1 Hz) is generally inhibitory while higher-frequency stimulation (>5 Hz) is excitatory (Chen et al., 1997; Klomjai et al., 2015).

Cortical paired associative stimulation (cPAS) is a type of rTMS that induces Hebbian-like plasticity between two cortical areas to transiently enhance synaptic efficiency between them (Goldenkoff et al., 2020; Koch et al., 2013; Veniero et al., 2013). Using principles of heterosynaptic plasticity, two coils are used to repeatedly deliver near simultaneous stimulation to distinct brain regions to strengthen the functional connectivity (i.e., synaptic efficiency) between them (Goldenkoff et al., 2020; Koch et al., 2013; Veniero et al., 2013). In this manner, cPAS can be an effective tool to restore functional connectivity patterns that underlie declines in function resulting from injury, disease, or the natural aging process (Freitas et al., 2013; Kohl et al., 2019). For more information on cPAS, see Hallett et al., 2017; Koch, 2020; **Chapter 2.3.7**).

1.3 Variability of brain and behavioral responses to rTMS

Many rTMS studies in the motor system yield inconsistent results, with high inter- and intra-subject variability in neurophysiological and functional responses supporting motor control

(Corp et al., 2020; Fox et al., 2012; Ozdemir et al., 2021; Rocchi et al., 2018; Terranova et al., 2019; Ziemann & Siebner, 2015). Researchers have found that a considerable number of healthy control subjects are 'non-responders' or 'opposite-responders' and demonstrate unanticipated neuroplasticity effects, especially with regard to iTBS and cTBS protocols (Hamada et al., 2013; McCalley et al., 2021). Additionally, variability arises from subject-specific and intervention-specific factors, including neuroanatomical and neurochemical determinants, psychological and physiological factors, and differences in subject populations, stimulation duration, intensity, and target localization (Karabanov et al., 2016; Peterchev et al., 2012; Polanía et al., 2018; Raffin & Siebner, 2014).

Variability in experimental outcomes may also stem from methodological factors. Conventionally, rTMS protocols target only the primary motor cortex (M1) and apply stimulation to an unregulated brain state when the participant is behaviorally and mentally disengaged (Bergmann, 2018; Chiappini et al., 2018; Romei, Thut, et al., 2016; Silvanto et al., 2018). As a result, the effects of stimulation on spontaneous neuronal activity can unintentionally propagate to other areas, causing undesired changes in brain plasticity and behavior. Failure to control for the brain state of subjects to limit the spread of current can also contribute to variability across studies (Karabanov et al., 2016).

In the following chapters of this dissertation, I suggest exploring different methods of using rTMS within the motor control network. By targeting multiple brain regions with rTMS, spacing out repeated rTMS sessions, and considering the brain state during stimulation, we could enhance plasticity and behavioral responses. This could result in more precise and effective outcomes for stimulation.

1.4 Network-based rTMS stimulation

At the site of stimulation, rTMS can alter LTP- and LTD-synaptic plasticity mechanisms, modify blood flow and metabolic processes in the region, and affect the levels of available neurotransmitters and brain-derived neurotrophic factor (Chervyakov et al., 2015; Duan et al., 2018; **Figure 1-4A**). rTMS can also transiently induce "virtual lesions" by temporarily disrupting the function of the targeted focal brain region (M. J. Burke et al., 2019). For example, stimulating the parietal area can disrupt eye movements and reach-and-grasp tasks (Leib et al., 2016; Vesia et al., 2010).

However, the effects of the induced current from rTMS are not confined to the stimulated area (Liew et al., 2014; Siebner et al., 2009). The stimulation can spread a) directly via axonal projections to other brain areas and alters synaptic plasticity patterns in anatomically connected regions (**Figure 1-4B**) and b) indirectly by modulating neural oscillatory activity and homeostatic mechanisms throughout the whole brain (**Figure 1-4C**). Therefore, it is important to

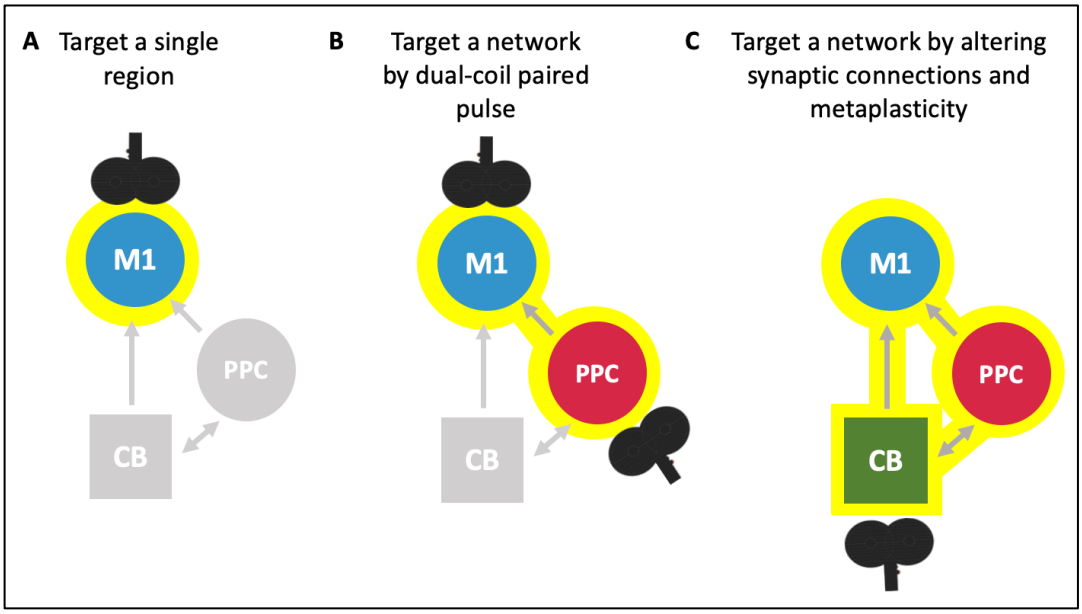

Figure 1-4 Approaches to target the motor network: (**A**) homosynaptic plasticity, (**B**) circuit activation with dual-coils and (**C**) heterosynaptic plasticity and distal metaplastic effects.

consider how stimulation alters whole-brain network interactions as well as how large-scale network dynamics may influence the effects of stimulation. Functional neuroimaging studies have indicated that following rTMS to M1, changes to cerebral blood flow occur within M1 as well as interconnected cortical and subcortical regions such as sensorimotor cortices, supplementary and premotor areas, and the thalamus (Liew et al., 2014). Furthermore, changes to motor excitability and behavioral performance correlate with changes to functional connectivity within the motor network (Liew et al., 2014). Not only can these effects occur within and between cerebral hemispheres, but cerebellar TBS has also been shown to modulate functional connectivity within cerebral networks and alter cortical temporal dynamics (Farzan et al., 2016; Halko et al., 2014; Rastogi et al., 2017). In this manner, cognitive and behavioral functions that are not directly dependent on the stimulated brain area can be altered with rTMS (Hebscher & Voss, 2020).

While many conventional rTMS protocols often only target M1, this may not be the most effective way to induce consistent and lasting behavioral changes because M1 is part of a larger motor network that is responsible for more complex and precise movements (Plow et al., 2015). Targeting areas that influence M1 and have projections to the spinal cord may serve as better intervention targets (Rathelot et al., 2017). The regions in the frontal lobe, such as SMA, PMd, and PMv, and parietal lobe are usually more intact following a typical stroke and have descending motor tracts down the spinal cord which can control motor function and compensate for weakened M1 projections (Cunningham et al., 2015; Grefkes & Fink, 2011; Plow et al., 2015; Silasi & Murphy, 2014). Stimulating higher-order areas in the motor network may be able to improve recovery from neurological injury because these regions have a lower probability of

being damaged by a stroke than M1 and have high adaptive remapping potential (Plow et al., 2015).

In addition, stimulating M1 with another node within the parietal-frontal network may enhance the intended modulatory effects (Raffin & Siebner, 2014). Using a multifocal approach and targeting multiple nodes within the motor control network may better localize the current spread and induce more precise and intended neurophysiological and behavioral outcomes (Fischer et al., 2017).

1.5 Dosing quantities of rTMS stimulation

As previously mentioned, the manner in which electromagnetic stimulation affects the human brain depends on the characteristics of the generated electromagnetic field, brain tissue and skull anatomy, individual physiological determinants, and a variety of external environmental factors (Peterchev et al., 2012). When dosing NIBS – essentially deciding on the electromagnetic properties, temporal and spatial distribution of the pulses, and the overall intervention characteristics – it is necessary to consider all relevant factors in order to generate a reproducible biological effect (Peterchev et al., 2012). Most of these considerations are beyond the scope of this dissertation. Here, the relevant chapters are focused on the number of stimulation sessions delivered during an rTMS intervention.

Recent research has suggested that increasing the amount of stimulation delivered during an rTMS intervention increases persistent motor excitability (Nettekoven et al., 2014; Nyffeler et al., 2006; Peinemann et al., 2004). However, the magnitude and duration of this effect depend on the interaction between the stimulation and homeostatic mechanisms of metaplasticity within the brain; the beneficial effect of multiple doses of stimulation is likely modulated by the interval

time between the stimulation trains (Gamboa et al., 2010; Nyffeler et al., 2006; Thomson & Sack, 2020). Adding breaks in between multiple sessions applied in a single day can improve the reliability and lengthen the duration of neuroplastic and behavioral aftereffects (Terranova et al., 2019). Studies have shown that spacing out the delivery of rTMS doses can lead to longer-lasting LTP-like responses compared to massed delivery. This method also prevents the targeted brain area from returning to its baseline activation state and producing spontaneous activity, which could interfere with the rTMS-induced synaptic modifications (Nyffeler et al., 2006). Within the motor cortex, an interval of 50-60 minutes between rTMS doses appears optimal to promote cumulative plasticity effects and enhance motor function. The interval corresponds with the spaced training effects that enhance motor learning (Smolen et al., 2016; **Figure 1-5**).

In addition to increasing the number of rTMS sessions delivered per day, evidence suggests that for cognitive and mood disorders, rTMS interventions with multiple days of

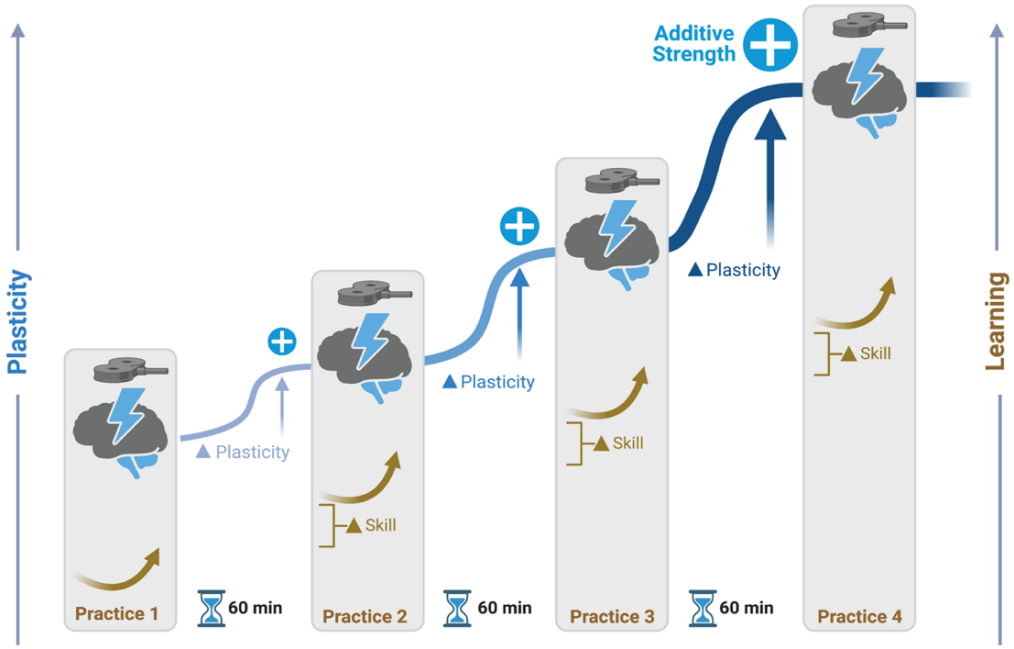

Figure 1-5 Conceptual model demonstrating how spaced learning and spaced delivery of modulatory rTMS protocols can induce additive effects on neuroplasticity and motor learning.

stimulation are more effective at inducing the desired behavioral result than single-day protocols (Kim et al., 2020; Pettorruso et al., 2020; Song et al., 2019; J. X. Wang & Voss, 2015). However, there have been few studies on long-term trials that have specifically focused on the motor network (K. E. Brown et al., 2014). Using a multi-day rTMS approach could be an effective strategy for treating neuromotor impairments because of its potential to induce more persistent plasticity changes and support motor function.

1.6 Controlling the brain-state during rTMS stimulation

The human brain is a highly dynamic and complex system with rapidly fluctuating internal brain states. Brain states can vary temporally on a scale of nanoseconds to minutes, and are spatially defined at the local, network, and global level (Bergmann, 2018). Conventionally, rTMS studies apply stimulation while the subject is sitting at rest, which leaves the brain state unconstrained. Yet, applying stimulation to an unregulated brain state when the subject is behaviorally or mentally disengaged, as well as not accounting for the effects of stimulation on spontaneous neuronal activity, can cause unwanted changes in brain plasticity and behavior (Bergmann, 2018; Fox et al., 2012; Romei, Thut, et al., 2016; Siebner et al., 2009; **Figure 1-6A)**. There are multiple ways to adjust stimulation protocols to endogenous brain activity previously or concurrently measured by electroencephalography (EEG), magnetoencephalography (MEG), or fMRI. Additionally, the brain state can be exogenously controlled either by preconditioning from a prior rTMS stimulation protocol or by being constrained during the rTMS intervention by a cognitive or motor task (**Figure 1-6B**). For example, it is possible to manipulate the brain state during stimulation by engaging the participant in a task that activates the target brain network (Romei, Chiappini, et al., 2016; Romei, Thut, et al., 2016).

The transmission of neural activity along axons and across synapses is highly state-dependent (Di Lazzaro et al., 1999). Controlling the functional state of the cortex with a cognitive or motor task can change the responsiveness of distinct neuronal subpopulations responsible for that task (Romei, Thut, et al., 2016; Siebner et al., 2009). Preconditioning subpopulations can prime neurons to make them more sensitive to stimulation and alter their response to external stimuli. This can be achieved by exogenous manipulation of brain activity with rTMS and using behavioral adaptation to activate a network (Fiori et al., 2018; Silvanto et al., 2018; Suppa et al., 2008). In fact, recent work has shown that a perceptual adaptation can

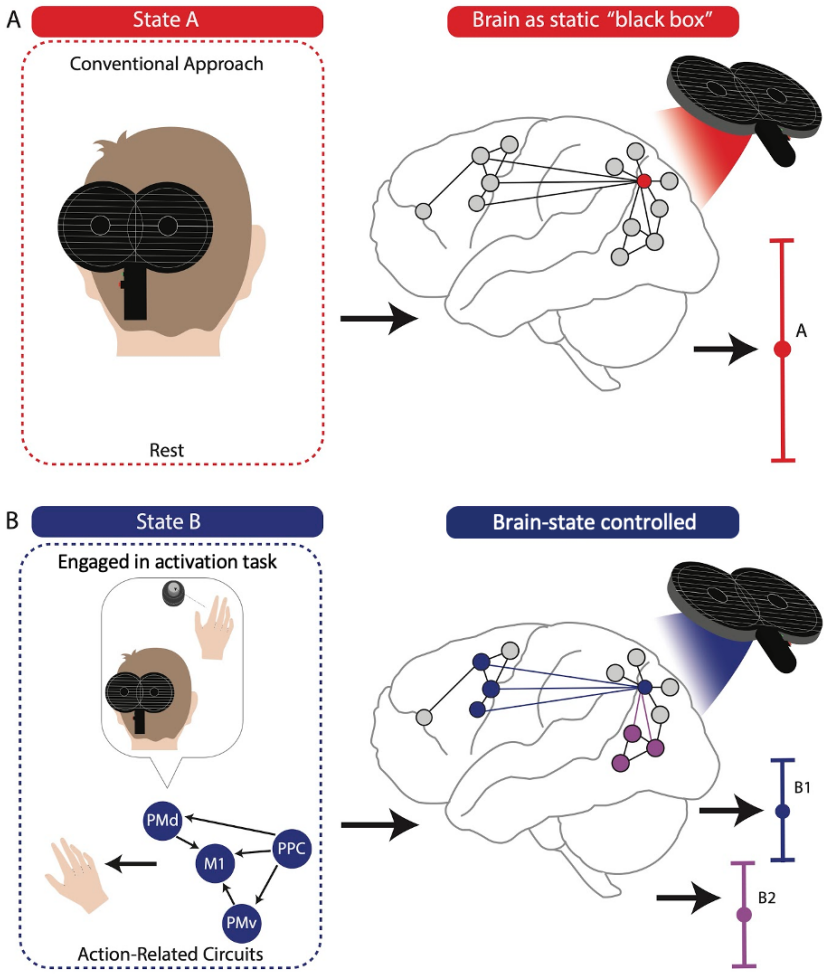

Figure 1-6 Model of (**A**) the conventional rTMS approach where the brain state is uncontrolled and (**B**) a brain-state controlled approach where the participant is engaged in a network-activating task.

augment the TMS-induced neural representation of observed motor behavior (Rotenberg et al., 2014). It is possible that selective neural representations and pathways underlying the perceptual and behavioral processes are more susceptible to stimulation when primed or concurrently engaged (Pasley et al., 2009; Romei, Thut, et al., 2016; Rotenberg et al., 2014; Silvanto et al., 2007, 2018). Therefore, manipulating the brain state during rTMS by engaging the participant in a reach-and-grasp task may induce more persistent and intended plasticity changes within the targeted motor control circuit by selectively conditioning a specific neuronal population (Chiappini et al., 2018; Romei et al., 2016). This approach is especially useful for targeting action-related circuits that involve multiple brain regions because stimulation to one location can remain constrained within the pre-activated functionally connected circuits.

1.7 Summary

The studies presented in this dissertation explore factors for applying rTMS within the motor control circuit that could produce more effective, functionally specific, and lasting changes to the parietal-motor network that supports motor function. The dissertation also probes the effects of rTMS on older adults, as aging brains may respond differently to stimulation than younger brains. Here I investigate three primary aims. Aim 1 examines whether a network-targeted rTMS approach that leverages individual-specific functional parietal-motor pathways of the motor control network for skilled reach-to-grasp actions will maximize stimulation specificity. Aim 2 explores the impact of stimulation dosage on motor excitability and performance by varying the number of rTMS sessions applied to a defined reach-to-grasp network in the motor system. Aim 3 tests the notion that the functional context of brain activity

(i.e., brain state) during parietal stimulation can modulate interactions with functionally connected motor regions to alter plasticity associated with skilled motor control of hand actions.

In **Chapter 2** (Goldenkoff et al., 2020), I describe a multi-focal TMS method to probe and modulate interregional brain connectivity with two coils. Investigating functional interactions between parietal and motor regions allows for the nuanced understanding of the causal dynamics of cortical reach-to-grasp network connectivity and its alteration at a system level. **Chapter 3** (Goldenkoff et al., 2021) assesses age-related changes in the parietal-motor network involved in reach-to-grasp actions. This study demonstrates that facilitatory inputs from parietal to motor regions are altered by age and may influence age-related decline in the neural control of movement.

In **Chapter 4** (Goldenkoff et al., under review), the focus transitions to dose-dependent factors of rTMS variability and examines the impact of administering multiple doses of rTMS in young adults. I investigate how repeated, spaced bouts of stimulation to the parietal-motor pathway involved in reach-to-grasp control produce cumulative effects on motor plasticity. Additionally, given the reduced capacity for plasticity in older adults, I explore in **Chapter 5** (Goldenkoff et al., in prep) whether the benefits of multiple rTMS doses observed in younger individuals extend to older adults. The chapter demonstrates the challenges of augmenting plasticity induction with rTMS for the aging brain.

I then shift to probe the influence that brain state has on rTMS effects on motor plasticity. **Chapter 6** (Goldenkoff et al., in prep) examines the concept of exogenously manipulating the brain state through a prior bout of "priming" rTMS stimulation. Specifically, I explore how modifying cerebellar activity with rTMS affects a subsequent multi-focal rTMS plasticity induction protocol with two coils in the downstream parietal-motor pathway. Finally, **Chapter 7**

(Goldenkoff et al., 2023) delves into the impact of controlling brain state during parietal stimulation through behavioral engagement on the brain and behavior. This study shows that a behavioral-induced brain state can enhance motor excitability and improve motor skilled performance during parietal rTMS.

Together, these studies demonstrate effective, functionally specific, and lasting changes to the parietal-motor network that support motor function. These research studies underscore that individualized rTMS approaches that consider age, stimulation dose, and target nodes in the reach-to-grasp motor network are crucial for successful neuromodulation. Leveraging these insights can better guide the plasticity mechanisms of motor control and inform the design of targeted interventions that can transition from research settings to widespread clinical practice. The work presented in these studies could lead to targeted neuromodulation strategies to combat age-related sensorimotor declines and restore neuromotor abilities lost to neurological disorders like Parkinson's disease and stroke.

Chapter 2: Measuring and Manipulating Functionally Specific Neural Pathways in the Human Motor System with Transcranial Magnetic Stimulation

2.1 Abstract

Understanding interactions between brain areas is important for the study of goal-directed behavior. Functional neuroimaging of brain connectivity has provided important insights into fundamental processes of the brain like cognition, learning, and motor control. However, this approach cannot provide causal evidence for the involvement of brain areas of interest. Transcranial magnetic stimulation (TMS) is a powerful, noninvasive tool for studying the human brain that can overcome this limitation by transiently modifying brain activity. Here, we highlight recent advances using a paired-pulse, dual-site TMS method with two coils that causally probes cortico-cortical interactions in the human motor system during different task contexts. Additionally, we describe a dual-site TMS protocol based on cortical paired associative stimulation (cPAS) that transiently enhances synaptic efficiency in two interconnected brain areas by applying repeated pairs of cortical stimuli with two coils.

These methods can provide a better understanding of the mechanisms underlying cognitive-motor function as well as a new perspective on manipulating specific neural pathways in a targeted fashion to modulate brain circuits and improve behavior. This approach may prove to be an effective tool to develop more sophisticated models of brain-behavior relations and improve diagnosis and treatment of many neurological and psychiatric disorders.

2.2 Introduction

Noninvasive brain stimulation is a promising assessment tool and treatment for many neurological disorders, such as Parkinson's disease, Alzheimer's disease, and stroke (Hallett et al., 2017; Hummel & Cohen, 2006; Koch, Martorana, et al., 2020; Ni & Chen, 2015). There is accumulating evidence establishing the relationship between the behavioral manifestations of neurological diseases and abnormalities of cortical excitability, neuroplasticity, cortico-cortical and cortico-subcortical connectivity (Caligiore et al., 2016; Grefkes & Fink, 2011). Therefore, basic knowledge about brain network dynamics and plasticity in neurological conditions can provide invaluable insight into disease diagnosis, progression, and response to therapy. Functional magnetic resonance imaging (fMRI) is a useful tool to understand the complex relations between brain and behavior in both healthy and diseased brain networks and has the potential to improve treatment based on a network perspective (Calhoun et al., 2014; Fox et al., 2012, 2014). However, fMRI is correlational in nature and cannot provide a causal link between brain function and behavior, nor manipulate functional connectivity to restore abnormal neural circuits associated with behavioral impairments in patients (Bolognini & Maravita, 2007; Pascual-Leone et al., 2000, 1999). Transcranial magnetic stimulation (TMS) can both causally measure and modulate human brain function and behavior in health and disease (Chouinard & Paus, 2010; Hallett et al., 2017; Lafleur et al., 2016; Rothwell, 2011).

TMS is a safe, noninvasive method to stimulate the human brain (Chen, 2000; Hallett, 2000) and can be used to induce and measure plasticity (Udupa & Chen, 2013). This method can advance our understanding of causal relationships between individual brain areas and behavior (Bolognini & Maravita, 2007; Pascual-Leone et al., 2000, 1999; Walsh & Rushworth, 1999) and their specific functional interactions with other nodes of a brain network (Bestmann, Ruff, et al.,

2008; Dayan et al., 2013; Sack, 2006; Siebner et al., 2009). To date, most studies have focused on the human motor system, given that TMS to the hand area of the motor cortex (M1) can produce motor evoked potentials (MEPs) as physiological readouts for changes associated with motor behavior (Bestmann & Krakauer, 2015), allowing examination of different inhibitory and excitatory circuits at the system level in the human brain (Vesia & Davare, 2011). Recent advances using a conditioning test TMS approach with two coils show that it is possible to measure functional interactions between different cortical areas. In the motor system, dual-site TMS experiments show that inputs from cortical areas interconnected with M1 can change with task demands, age, or disease (Cantarero & Celnik, 2015; Lafleur et al., 2016). Seminal work by Ferbert and colleagues has found that applying a conditioning stimulus to M1 prior to a test stimulus of the other M1 can result in inhibition of the MEP amplitude, a phenomenon known as short interval interhemispheric inhibition (SIHI) (Ferbert et al., 1992). A number of TMS studies using this approach have also shown that M1 is strongly interconnected with the contralateral M1, ventral premotor cortex (PMv), dorsal premotor cortex (PMd), supplementary motor area (SMA), pre-SMA, primary sensory cortex (S1), dorsolateral prefrontal cortex (DLPFC), and posterior parietal cortex (PPC) at rest (Bäumer et al., 2009; M. J. N. Brown, Goldenkoff, et al., 2019; M. J. N. Brown, Weissbach, et al., 2019; Cattaneo & Barchiesi, 2011; Civardi et al., 2001; Ferbert et al., 1992; Groppa et al., 2012; A. N. Karabanov et al., 2013; Koch, Del Olmo, et al., 2007; Koch et al., 2009, 2011; Koch, Franca, et al., 2007; Mochizuki et al., 2004; Ni et al., 2009; Shirota et al., 2012; Ziluk et al., 2010). Interestingly, the effect of stimulation from these cortical areas on motor cortical excitability are anatomically, temporally, and functionally specific to the ongoing brain activity during the preparation of a movement (state- and context-dependent; Byblow et al., 2007; Davare et al., 2008, 2009, 2010, 2011; Fujiyama et al., 2016; Groppa et al.,

2012; Hasan et al., 2013; Isayama et al., 2019; A. Karabanov et al., 2012; Koch, Cercignani, et al., 2010; Koch, Del Olmo, et al., 2008; Koch et al., 2006; Koch, Versace, et al., 2010; Koch & Rothwell, 2009; Lago et al., 2010; Mackenzie et al., 2016; Mars et al., 2009; O'Shea et al., 2007; Picazio et al., 2014, 2016; Rizzo et al., 2009; Schintu et al., 2016; Vesia et al., 2013, 2017, 2018). However, very few studies using dual-site TMS have characterized patterns of functional cortico-cortical connectivity with motor and cognitive impairments in patients with brain disorders (Arai et al., 2011; Fiori et al., 2018; Koganemaru et al., 2009). This affords opportunities to develop new methods for assessing and treating motor and cognitive disorders.

Using this technique, it also has been found that repeated pairs of cortical TMS applied to cortical areas interconnected with M1 such as contralateral M1 (Koganemaru et al., 2009; Rizzo et al., 2009, 2011), PMv (Bonnì et al., 2013; Murase et al., 2004; Nelson et al., 2010), SMA (Arai et al., 2011), and PPC (Di Lorenzo et al., 2016; Koch et al., 2008; Ponzo et al., 2016) can induce changes in synaptic efficiency in specific neural pathways based on the Hebbian principle of associative plasticity (Koch et al., 2019; Palomar et al., 2013; Udupa et al., 2016; Ugawa et al., 1995) and enhance behavioral performance (Chiappini et al., 2018; Fiori et al., 2018; Romei, Chiappini, et al., 2016). Still, few studies have used this approach to study circuit and plasticity dysfunction in neurological disorders (Bergmann et al., 2016; Bonnì et al., 2013; Di Lorenzo et al., 2016; Johnen et al., 2015; Keel et al., 2001; Koch et al., 2008, 2008, 2019; Koch, Martorana, et al., 2020; Murase et al., 2004; Palomar et al., 2013; Ponzo et al., 2016; Rossi et al., 2011; Santarnecchi et al., 2018; Tremblay et al., 2016; Veniero et al., 2013; Zittel et al., 2015). It remains to be shown whether strengthening functionally specific neural pathways with TMS can restore activity in dysfunctional circuits, or whether the prospective strengthening of intact circuitry can augment resilience (Rossini et al., 2015) in brain networks supporting motor and

cognitive function across the lifespan and in disease. The lack of fundamental understanding of the neural mechanisms underlying neurological disorders and effects of stimulation on interconnected dysfunctional brain networks limits current treatment.

Despite its capability, TMS has yet to become a standard part of the armamentarium of neuroscience and clinical tools for understanding brain-behavior relations, pathophysiology of brain disorders, and the effectiveness of treatment. Therefore, to realize its potential and support its large-scale application, standardizing TMS methods is important because it is more likely to increase the rigor of future TMS experiments and reproducibility across independent laboratories. This article outlines how TMS can be used to both measure and manipulate functional interactions. Here, we describe this technique in the motor system (e.g., parieto-motor pathway (Vesia et al., 2017) by measuring TMS-based output measures (e.g., MEPs), where the method is best understood. However, it is important to note that this protocol also can be adapted to target functional coupling of other subcortical (Udupa et al., 2016), cerebellar (Pinto & Chen, 2001; Ugawa et al., 1995), and cortical areas (Chiappini et al., 2018; Kohl et al., 2019; Romei, Chiappini, et al., 2016). In addition, neuroimaging techniques such as EEG (Casula, Pellicciari, Picazio, et al., 2016; Pinto & Chen, 2001; Tremblay et al., 2019; Veniero et al., 2013) and fMRI (Johnen et al., 2015; Santarnecchi et al., 2018) can be used to assess the TMS-induced changes in activity and connectivity (Bergmann et al., 2016; Cantarero & Celnik, 2015). We conclude by proposing that the study of the functional involvement of circuit-level cortical connectivity with these TMS methods in both health and disease makes it possible to develop targeted diagnoses and innovative therapies based on more sophisticated network models of brain-behavior relations.

2.3 Protocol

The following three TMS methods are described below. First, two methods are described to measure cortico-cortical connectivity using dual-site transcranial magnetic stimulation (dsTMS) while participants are either 1) at rest (resting state) or 2) performing an object-directed reach-to-grasp movement (task-dependent). Second, a cortical paired associative stimulation (cPAS) method is described to modulate the interplay between two brain areas in a controlled manner by pairing cortical stimuli (e.g., posterior parietal and primary motor cortices) to strengthen functional specific neural pathways with TMS and induce changes in cortical excitability. A representative data set is provided for each method. All the methods described in this protocol were approved by the University of Michigan Institutional Review Board in accordance with the Declaration of Helsinki.

2.3.1 Participant recruitment

1. Screen all participants for any contraindications to TMS (Keel et al., 2001; Rossi et al., 2009, 2011; Rossini et al., 1994, 2015; Wassermann, 1998) and magnetic resonance imaging (MRI) prior to recruitment. Recruit right-handed participants (Oldfield, 1971) for experiments investigating functional connectivity in the motor system.
2. Inform each participant about the study objectives, procedures, and risks approved by the local institutional review board. Obtain written consent before allowing the individual to participate in the study.

2.3.2 Electromyography (EMG) electrode placement

1. Instruct the participant to sit comfortably in the experimental chair with both arms supported in a relaxed position. Provide a chin rest for participants during TMS to keep head movement to a minimum during stimulation.
2. Clean the skin over the muscle of interest with a mild abrasive. Using a belly-tendon electrode arrangement, place one disposable Ag-AgCl electrode on the belly muscle and another on a bony landmark nearby for a reference site on both hands of the participant. Repeat this step for each muscle of interest.
3. Connect a ground electrode to the ulnar styloid process. It is important to inspect the level of surface contact of the electrodes with the skin throughout the duration of the experiment because this precludes the impedance quality of the EMG signal. Placing tape over the surface electrode can improve the degree of contact with the skin surface.
4. NOTE: For reach-to-grasp actions common muscles studied are 1) the first dorsal interosseous (FDI), 2) abductor pollicis brevis (APB), and 3) abductor digiti minimi (ADM) muscles of the hand.
5. Connect surface electrodes with an EMG amplifier and a data acquisition system. Record and store the EMG signals from the amplifier to the data collection computer with EMG software for online monitoring and offline analysis of the EMG signal. Optionally, amplify the EMG signal 1,000x, and use a band-pass filter between 2 Hz and 2.5 kHz, digitized at 5 kHz by an analog-to-digital interface.

2.3.3 Localizing brain areas for targeted TMS

2.3.3.1 Method 1: Localizing without an MRI scan

1. Using the 10–20 EEG system mark C3, located approximately over the left primary motor cortex (M1), and P3, located approximately over a part of the angular gyrus in the left

posterior parietal cortex (PPC), on the participant's scalp. Refer to methods previously described (Villamar et al., 2013) for specific steps to localize brain areas with the 10–20 EEG system (see Figures 3 and 4 from Villamar et al., 2013).

2. Alternatively, an electroencephalography (EEG) head cap can be used to approximate the brain areas on the scalp. Place an appropriately sized EEG cap on the participant's head and align the Cz position on the cap with the marked Cz position on the participant's scalp. Mark C3 and P3 using the cap.

NOTE: Localization without an individual's MRI scan has the potential to be inaccurate (Sack et al., 2009). Therefore, MRI-based neuronavigation is strongly recommended to increase the accuracy and reliability of targeting the TMS. This can potentially lead to less variability in the TMS-induced aftereffects.

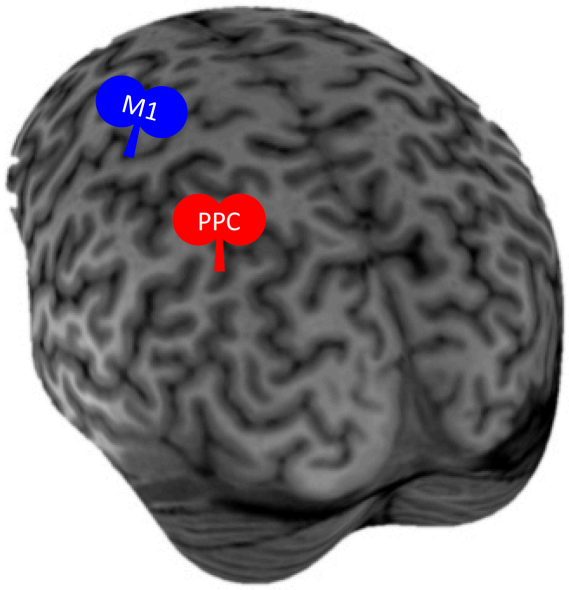

Figure 2-1 Three-dimensional reconstruction of a typical participant's anatomical MRI with marked cortical sites over the primary motor cortex (M1, blue symbol) and posterior parietal cortex (PPC, red symbol) in the left hemisphere. Neuronavigation software for TMS was employed to target individually determined cortical areas with each figure-8 TMS coil

2.3.3.2 Method 2: Using an MRI scan

1. Before the TMS session, obtain the participant's structural MRI (T1). Upload the scan to a neuronavigation system.
2. Create a three-dimensional reconstruction of the brain and skin overlay using the neuronavigation software. Place markers on the anatomical landmarks at the tip of the nose, nasion, inion, and the preauricular notches of both ears. Do not use the tragus as it can shift when ear plugs are inserted.
3. Locate the hand knob, the anatomical landmark that corresponds to M1 (Yousry et al., 1997), in the left precentral gyrus. Place a trajectory marker at this point with the neuronavigation system. This point should be aligned 45° from the midsagittal line and approximately perpendicular to the central sulcus. Record and name the anatomical landmark with the neuronavigation system (**Figure 2-1**).
4. Locate the nonmotor area of interest (e.g., over the anterior intraparietal sulcus area in PPC). Place a second trajectory marker over this anatomical landmark. Record and name the location with the neuronavigation system (**Figure 2-1**).

2.3.3.3 Perform coil and head registration with the tracking system

1. Calibrate both TMS coils with the calibration block separately using the neuronavigation system.
2. Place the head tracker securely on the participant's head so that the tracker is in view throughout the duration of the experiment.
3. Coregister the anatomical landmarks on the participant's head to the neuronavigation system. If an MRI was not obtained from the participant, use a template MRI from the Montreal Neurological Institute.

NOTE: It is important to not apply too much force with the pointer on the participant's skin to avoid discomfort and inaccuracies when performing registration. It may be valuable to check regularly throughout the course of the experiment that the head tracker has not shifted. These procedures ensure precision when applying the TMS coil to a target area for stimulation during the experiment.

2.3.4 Localizing optimal TMS coil position and determining thresholds

NOTE: In this experiment, $Coil_{M1}$ refers to the coil used to deliver stimulation to M1, while $Coil_{Two}$ refers to the coil used to deliver stimulation to the other cortical area of interest (e.g., posterior parietal cortex). Thresholding over M1 must be determined for $Coil_{Two}$ to calculate the maximum stimulator output (MSO) used over nonmotor areas. Motor threshold values should be reported to allow for comparisons and reproducibility across experiments.

2.3.4.1 Localizing and thresholding with $Coil_{Two}$

1. Position the center of $Coil_{Two}$ over the target M1 location identified in the previous section to induce a posterior-anterior current direction in the brain.
2. To find the optimal location for activation of the target muscle, deliver pulses to M1 at 30% of the machine's MSO. Observe whether the delivered stimulation produces a muscle twitch and determine the amplitude of the motor evoked potential (MEP) recorded with the EMG electrodes from the muscle activity displayed by the data acquisition system.
3. If an MEP or a visible muscle twitch is not observed, continue to increase the stimulator output by 5% increments. The position, rotation, pitch, and yaw of the TMS coil may

need to be adjusted to optimize the amplitude of the MEP. Repeat this until a response is observed.

4. Lower the intensity in a stepwise manner to the lowest intensity that produces at least 5 out of 10 MEP responses with an amplitude of ≥50 μV while the participant is at rest (Groppa, Oliviero, et al., 2012; Rossini et al., 1994, 2015). This is defined as the resting motor threshold (RMT).
5. Ensure for the duration of the thresholding session that both hands are in a resting position with both arms and hands supported with pillows.
6. Provide real-time visual or auditory feedback of muscle activity from EMG (e.g., on a monitor or speaker) throughout the session, especially if there is excessive muscle activity (e.g., older adult populations).
7. Continuously ask participant about levels of comfort.

NOTE: It is important that all procedures described above are performed separately and repeated for each TMS coil to determine the specific parameters used in the experiment for the different sized coils (e.g., localizing optimal TMS coil position and determining stimulation intensities for motor thresholding). It also is important that the interval between the TMS pulses is >5 s to avoid inducing changes in cortical excitability.

2.3.4.2 Localizing and thresholding with $Coil_{M1}$

1. Repeat the steps described above to find the optimal stimulation location with the $Coil_{M1}$.
2. Determine the lowest stimulator intensity needed to generate MEPs of ≥1 mV in 5 of 10 trials in the target hand muscle when the muscle is completely relaxed. Mark and record the position of $Coil_{M1}$ using the neuronavigation system.

2.3.5 Dual-site TMS (resting-state)

1. Use two figure-8 shaped coils (e.g., $Coil_{M1}$ and $Coil_{Two}$) connected to two individual TMS stimulators (e.g., two Magstim 200[2] units). Deliver the test stimuli (TS) over M1 with $Coil_{M1}$ (e.g., D70[2] figure-8 shaped coil, outside diameter of loop is 7 cm) and the conditioning stimuli (CS) to the other area of interest with $Coil_{Two.}$ (e.g., D50 Alpha B.I., outside diameter of each loop is 5 cm).
2. Determine the percentage of the MSO intensity for the conditioning stimulus (CS) for $Coil_{Two}$.

NOTE: The percentage of the MSO intensity is often between 70–140 of RMT and will depend on the specific parameters and objectives of the experiment (see Table 3 from Lafleur et al.). For this experiment, the CS was set at 90% of RMT, similar to parameters used elsewhere (A. N. Karabanov et al., 2013; Koch et al., 2008; Vesia et al., 2017).

3. For the test stimulus (TS), use the previously determined intensity that elicits MEP amplitudes of ~1 mV in the targeted quiescent hand muscle.
4. Set the precise interstimulus interval (ISI) between the CS and TS.
5. Use the supplied control software or external control via TTL pulses to control the ISI for the two pulses. The ISI often ranges from 4–20 ms (see Table 1 from Lafleur et al., 2016). For this experiment, the CS to PPC preceded the TS to M1 by an ISI of 5 ms.
6. Using a custom-made coding script, generate in random order the single-pulse TMS trials (TS alone) and paired-pulse TMS trials (CS-TS) at the specified ISI.
7. Position $Coil_{M1}$ over the left M1 and position $Coil_{Two}$ over the other area of interest.
8. Deliver the TS alone trials with $Coil_{M1}$. For the paired-pulse (CS-TS) trials, deliver the CS with $Coil_{Two}$ followed by the TS to $Coil_{M1}$ at the predetermined ISIs. This is illustrated in **Figure 2-2**. Repeat a minimum of 12 trials for each condition. Deliver the TS at least 1

s after the start of the trial to collect prestimulus EMG activity. Use a 4 s data acquisition sweep for each trial followed by a 1 s intertrial interval.

9. If necessary, adjust the TMS coil positions slightly to accommodate the placement of both coils over the selected targeted locations on the participant's head. Adjust and record the new location of $Coil_{M1}$ and $Coil_{Two}$ using the neuronavigation system accordingly.

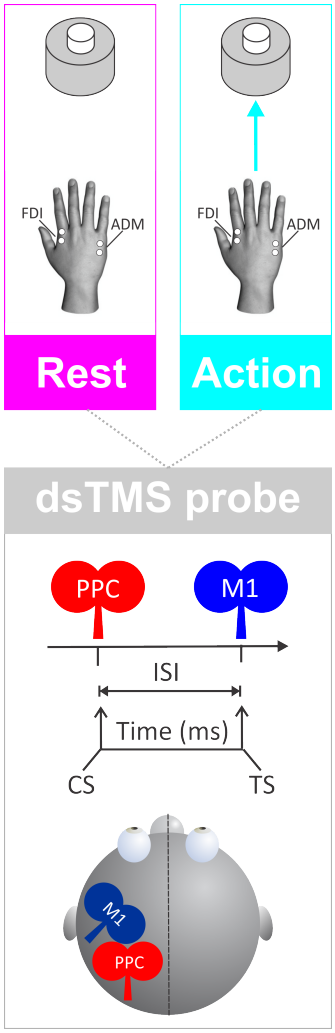

Figure 2-2 Schematic representation of the dual-site, paired-pulse transcranial magnetic stimulation with two coils (dsTMS) used to probe functional interactions between the posterior parietal cortex (PPC) and primary motor cortex (M1) at rest (resting state). A CS was applied to the PPC to examine its effect on a subsequent suprathreshold TS to M1. Any change in the amplitude of the right-hand muscle response to TMS is measured with EMG. For this experiment, the CS intensity was 90% of RMT. The intensity of TS was adjusted to elicit a MEP of ~1 mV peak-to-peak in the relaxed FDI and ADM. The ISI between pulses was 5 ms.

10. Use the trigger button on the TMS machine for the supplied control software or the custom-made coding script from the external controller to deliver the programmed TMS pulses.

NOTE: For this experiment, a data acquisition system (e.g., CED Micro 1401) and software package (e.g., Signal version 7) were used to generate stimuli, capture data, control the external equipment, and run the analysis. The custom-made coding scripts used to run and analyze data from the experiments are available from the corresponding author.

2.3.6 Dual-site TMS (task context)

NOTE: Dual-site TMS also can be used to test whether functional connectivity at rest can be modulated by different task contexts.

1. Follow the same method described in the section above to examine functional interactions between different cortical areas interconnected to M1, but during the preparatory phase of a task that engages the network (e.g., during the action plan for a grasp).
2. Determine the time course and a cortical area of interest (e.g., PPC) to study functional interactions with M1 during the preparation of a complex movement plan (e.g., object-driven precision grip or whole-hand grasp; Davare et al., 2008, 2009, 2010, 2011; Vesia et al., 2013, 2017, 2018) for selective hand muscles.
3. Using a custom-made coding script, generate in random order the timing of TS alone trials and paired-pulse trials (CS-TS) at a given ISI after the 'GO' cue during the reaction time period (plan phase) such that the MEP recordings are collected before the movement initiation (premovement period) for the task.

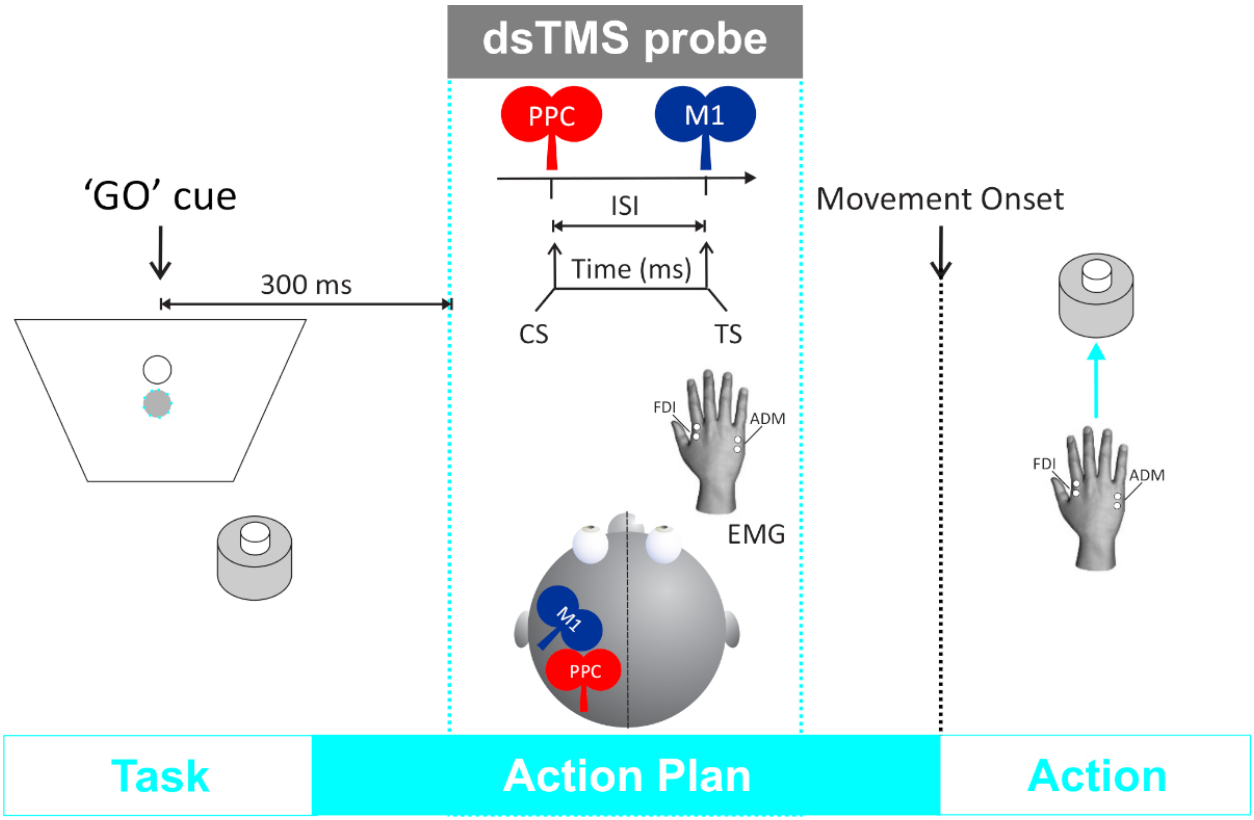

Figure 2-3 The dsTMS approach used to probe functional interactions between PPC and M1 during a reach-to-grasp movement (task context). The illumination of an LED instructed the participant to plan one of two possible rightward hand actions on the target object: 1) grasp the smaller top cylinder or 2) grasp the larger bottom cylinder. TS alone or CS–TS at the specified ISI (e.g., 5 ms) was delivered 300 ms after the 'GO' cue (e.g., LED onset) during the reaction time period (plan phase) such that MEP recordings were collected before actual movement initiation (dotted black line).

4. Deliver single-pulse TMS (TS alone) or paired-pulse TMS (CS-TS) probes between 50 and 800 ms after the 'GO' cue (Davare et al., 2009, 2010) during the action plan of complex hand movements. See **Figure 2-3** for timing of an event-related trial for this experiment. The custom-made coding scripts used to run the timing of event-related trials are available from the corresponding author.

    a. Before the testing session with TMS, have the participant perform the task for a minimum of 50 practice trials to establish a consistent reaction time. Encourage the participant to ask questions about the task to ensure reliable performance during the testing session with TMS.

b. Use the custom-made coding script to deliver all combinations of single-pulse TMS (TS alone) or paired-pulse TMS (CS-TS) and task (e.g., grasp a smaller top or grasp a larger bottom object) during the reaction time period (plan phase) such that the MEP recordings are collected before actual movement initiation.

2.3.7 Cortical paired associative stimulation (cPAS)

NOTE: This protocol involves delivering pairs of monophasic pulses to two different cortical areas over short periods to induce pathway-specific changes in synaptic strength between connections within the human brain. This approach is based on Hebbian principles of spike timing dependent plasticity (Caporale & Dan, 2008; Hebb, 1949; Jackson et al., 2006; Markram et al., 1997). Similar to dual-site TMS methods, cPAS is delivered with two TMS machines connected to two individual TMS coils over two different cortical areas (e.g., PPC and M1).

1. Using a custom-made coding script, generate 100 pairs of stimuli at 0.2 Hz (8.3 min duration each). For the experimental $cPAS_{Two \rightarrow M1}$ condition, deliver the first stimuli over the nonmotor area (e.g., PPC) with $Coil_{Two}$ with a specified pulse intensity (e.g., 90% RMT) for 5 ms before the second stimuli over M1 with $Coil_{M1}$ with a pulse intensity that elicits a MEP amplitude of ~1 mV in the targeted hand muscle.
2. It is important to control for: 1) directionality of the connectivity ($CTRL_{M1 \rightarrow Two}$); 2) timing ($CTRL_{ISI=500ms}$); and 3) stimulation site ($CTRL_{\text{Control site} \rightarrow M1}$) in separate sessions. For examples see (Fiori et al., 2018; Koch et al., 2013; Romei, Chiappini, et al., 2016; Romei, Thut, et al., 2016). The custom-made coding scripts for each cPAS condition are available from the corresponding author. The stimulation parameters (e.g., intensities and ISI) can be adjusted for different cortical areas. Refer to Table 2 from Lafleur et al. (2016) for a summary of plasticity protocols.

3. Use the procedures described in previous sections to guide the precise location of the TMS coils.
4. Obtain baseline corticospinal measurements with $Coil_{M1}$ (e.g., ~24 MEPs).
5. Randomize the participants to one of four intervention groups: 1) cPAS $_{Two \rightarrow M1}$; 2) $CTRL_{M1 \rightarrow Two}$; 3) $CTRL_{ISI=500ms}$; 4) CTRL $_{Control\ site \rightarrow M1}$.
6. For this experiment only the experimental cPAS $_{Two \rightarrow M1}$ condition was tested and the PPC was used as the area of interest. When performing multiple sessions on the same participant, it is important that each experimental session is separated by at least 48 h in a randomized order to prevent crossover effects. It also is important to repeat sessions within each participant at the same time of day to control for alertness.
7. Use the custom-made coding script to deliver the specified cPAS condition.
8. Monitor the muscle activity of the other (left) hand during the experiment with EMG to ensure the hand is fully relaxed during the protocol.

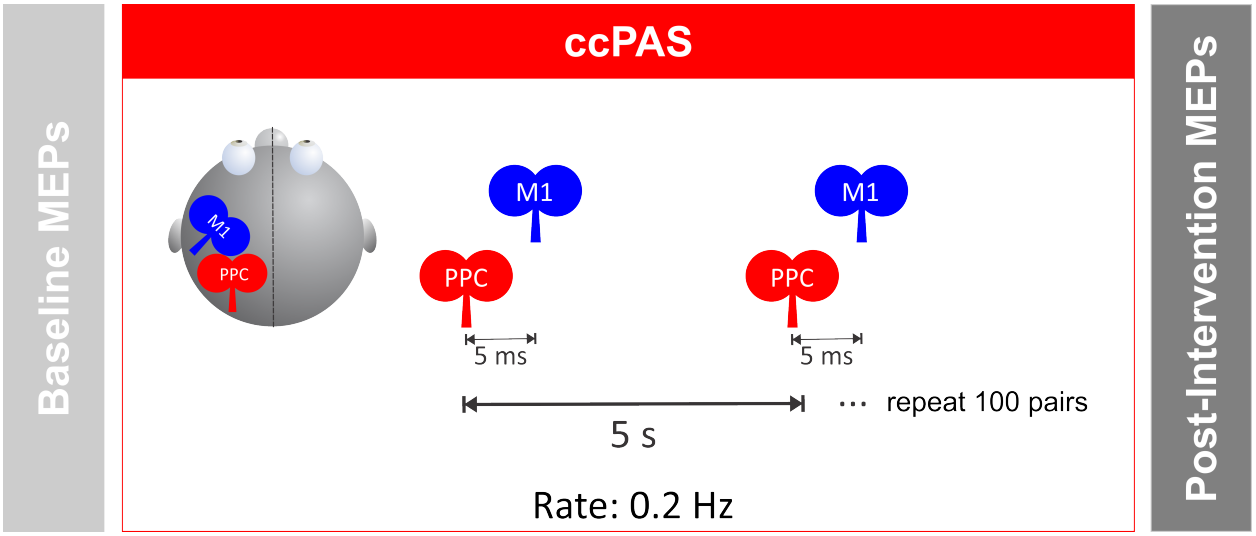

Figure 2-4 Schematic of cortical paired associative stimulation protocol (cPAS) used to strengthen functionally specific neural pathways. The first stimulus was applied to the area of interest with $Coil_{Two}$ (e.g., PPC, red coil) 5 ms before the second stimulus was delivered to M1 (blue coil) with $Coil_{M1}$. The pairs of cortical stimuli were delivered at a frequency of 0.2 Hz (once every 5 s) and repeated for 100 trials (~8.3 min).

9. Obtain corticospinal measurements with $Coil_{M1}$ (e.g., about 24 MEPs) at different times after cPAS (e.g., 0, 10, 20, 30, 40, 50, 60 min) to examine the time course of the TMS-induced effect on brain excitability.

NOTE: The experimental protocol used here is shown in **Figure 2-4**. Most studies to date have focused on the motor system because the MEP is a reliable outcome measure. However, behavioral measures (Chiappini et al., 2018; Fiori et al., 2018; Romei, Chiappini, et al., 2016) and functional connectivity strength with fMRI (Johnen et al., 2015; Santarnecchi et al., 2018) and EEG (Casula, Pellicciari, Picazio, et al., 2016; Veniero et al., 2013) following TMS manipulation of associative plasticity can also be investigated. These methods can also be adopted for different cortical areas that do not include M1 as a cortical target.

2.3.8 Data processing and analysis

1. Visually inspect EMG data offline and discard any traces showing muscle activity in which the root mean square EMG activity in the muscles exceeded a background level of 10 μV during the 100 ms immediately before the TMS pulse to ensure the muscles were at rest (Carson et al., 2004; Fujiyama et al., 2016).
2. Similarly, discard any trials with EMG activity that coincide with the TMS pulse during the movement preparation period (e.g., 800 ms window; Davare et al., 2009, 2010) in dual-site TMS task context trials to exclude anticipatory responses.
3. For each MEP trial, measure the peak-to-peak amplitude between the minimum and maximum values in mV in the time window between 50 ms before and 100 ms after the TS (Groppa, Oliviero, et al., 2012).

4. Calculate the mean of the MEP amplitudes in millivolts from the TS alone trials and the paired-pulse (CS-TS) trials for each participant. Calculate the mean across all participants. Report these values.
5. Next, normalize the mean MEP amplitude from paired-pulse stimulation (CS-TS) trials from the unconditioned single-pulse (TS alone) trials for each participant and condition. Express the MEP amplitudes as a ratio to the baseline TS condition.

$$Normalized\ MEP\ amplitude\ (Ratio) = \frac{MEP\ amplitude\ (CS \rightarrow TS)}{MEP\ amplitude\ (TS\ alone)}$$

6. Calculate the mean across all participants. Report these values.

2.4 Representative results

Figure 2-5 shows the size of an exemplar MEP response elicited in the FDI muscle by TMS for an unconditioned test stimuli (TS alone to M1, blue trace) or conditioned stimuli from PPC (CS-TS, red trace) while the participant was at rest (top panel) or planning a goal-directed grasping action to an object (bottom panel). At rest, the PPC exerts an inhibitory influence on ipsilateral M1, as shown by the decrease in MEP amplitudes potentiated by a subthreshold CS delivered over PPC 5 ms before a suprathreshold TS over M1 (top panel). During the preparation of a grasp action, this net inhibitory drive at rest from PPC switched to facilitation (a release of inhibition). To directly compare PPC-M1 interactions during rest versus task demands, the MEP amplitudes were normalized to TS alone trials for each condition and plotted as a ratio for MEP amplitude. The PPC-M1 interaction was facilitated from rest when planning an object-directed grasp (purple bars).

The top panel in **Figure 2-6** shows changes in MEP amplitudes during the administration of the cPAS protocol. MEP amplitudes induced by paired stimulation of PPC and M1 gradually increased over time during the stimulation protocol, suggesting plastic effects at the level of the parieto-motor connection, M1 corticospinal neurons, or both. The bottom panel of **Figure 2-6** shows changes in MEP amplitudes elicited in the resting FDI muscle by single-pulse TMS over M1 before and after the cPAS protocol. The size of the MEP amplitudes increased 10 min after

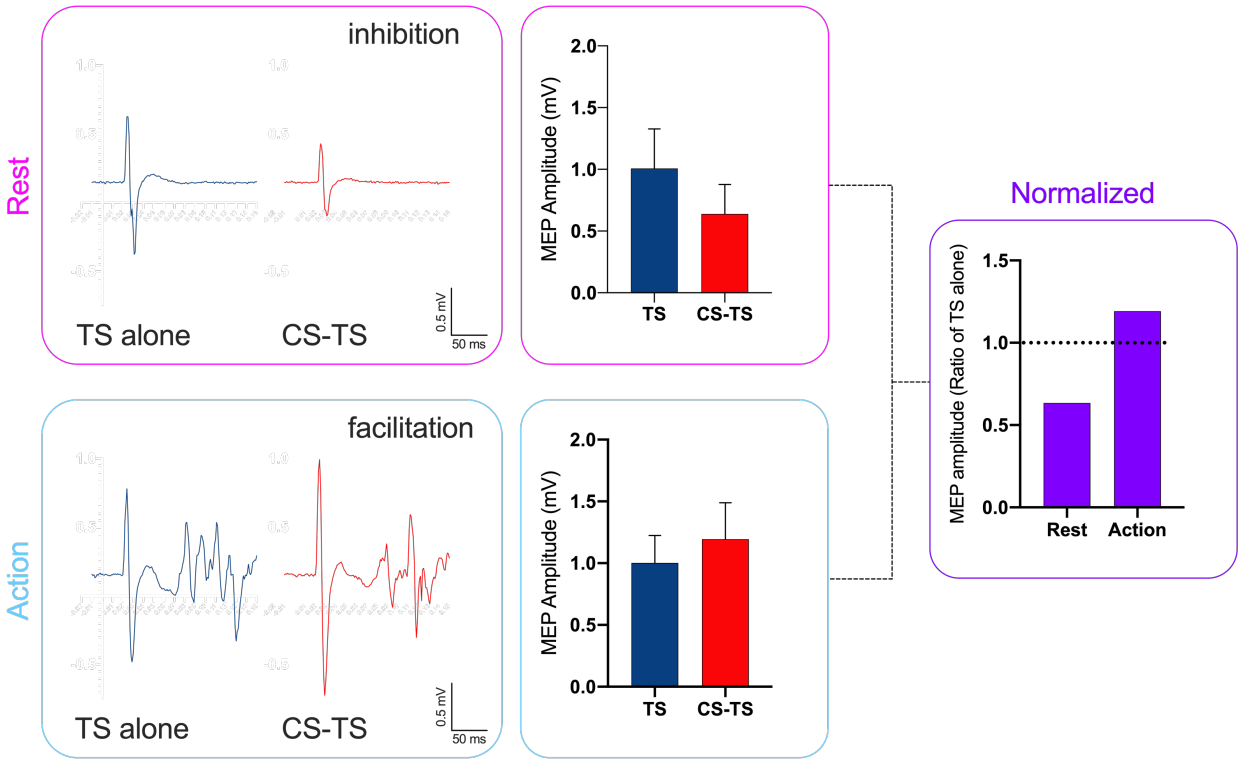

Figure 2-5 Exemplar MEP traces for an unconditioned test stimulus (TS alone, blue trace) or conditioned stimulus (CS-TS, red trace) for the resting state (top panel) and context-dependent (bottom panel) condition. Bar graphs show the MEP amplitudes from the dsTMS protocol while the participant is at rest or performing a grasping task (action). When the participant was at rest (top panel), CS-TS (red bar) decreased the mean amplitude of MEPs (inhibition) compared to the unconditioned TS alone (blue bar). In contrast, when the participant planned the reach-to-grasp task (bottom panel), the mean MEP amplitude increased (facilitation) for CS-TS (red bar) trials compared to the TS alone (blue bar) trials. To directly compare the PPC-M1 interaction for rest versus action condition, the mean MEP amplitude elicited by paired-pulse stimulation (CS–TS) was normalized by calculating the ratio of the amplitude relative to the mean unconditioned MEP amplitude (TS alone). Purple bars represent the normalized MEP amplitude for each condition. Y = 1 indicates no effect of CS on M1 excitability (dotted black line), whereas ratios higher than 1 indicate increased M1 excitability and ratios lower than 1 indicate decreased M1 excitability because of conditioned stimuli (CS-TS). Error bars represent SEM.

the cPAS protocol, suggesting motor excitability aftereffects were induced after the administration of the repeated pairs of cortical stimuli over PPC and M1.

2.5 Discussion

The dual-site TMS method described here can be employed to investigate functional interactions between different cortical areas interconnected with the primary motor cortex while a participant is at rest or planning a goal-directed action. While brain imaging is correlative, basic knowledge from dual-site TMS methods can reveal causal brain-behavior relations

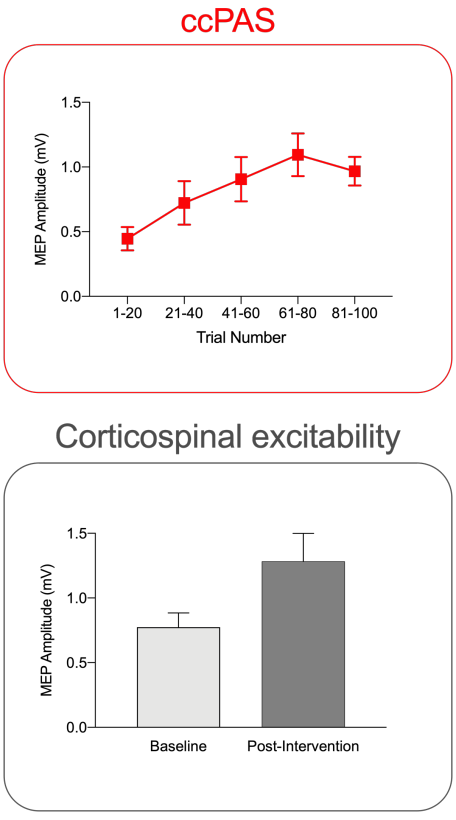

Figure 2-6 MEPs during cPAS. Top panel shows that MEP amplitudes increased during the administration of cPAS. The bottom panel shows the effect of cPAS protocol on MEP amplitude. After the cPAS intervention (red bar) corticospinal excitability increased after 10 min (dark grey bar) compared to baseline (light grey bar), as assessed by MEPs in the quiescent hand muscles. The red bar represents the paired stimulation intervention, cPAS (100 pairs at 0.2 Hz, ~8.3 min). This suggests that modulating parieto-motor interactions with cPAS can induce transient changes in motor plasticity. Error bars represent SEM.

associated with changes in cortico-cortical circuits. In addition, cortical paired associative stimulation with two TMS coils applied in areas interconnected with M1 can be employed to strengthen functionally specific connectivity for movement control and increase the efficiency of inducing plasticity. Taken together, these methods demonstrate that these TMS protocols can both measure and manipulate neural activity underlying information flow between brain areas in an anatomical-, task-, and time-dependent manner within the motor system. This affords opportunities to test different hypotheses related to the causal contribution of cortical areas to motor function.

In this light, the approach also can provide an essential foundation for understanding network connectivity at a systems-level in neurological and psychiatric patients with similar symptomology and enable its use as both a tool to diagnose and treat circuit dysfunction. Therefore, it is important for more studies to explore other cortical areas outside the motor system to test its generalizability across brain networks in both healthy and diseased brains. This is an important factor given that one cannot assume that the response to TMS in one brain region will produce the same physiological effect when applied to another region. It is also advantageous that these procedures can be extended to more complex movements, and other domains outside of movement such as cognition, perception, and mood. Indeed, several studies using dual-site TMS and cPAS have begun to examine the effects and feasibility of study in the visual and cognitive systems (Chiappini et al., 2018; Kohl et al., 2019; Romei, Chiappini, et al., 2016). Importantly, this will afford opportunities to develop a more sophisticated understanding of the neural underpinnings linking brain activity to motor, cognitive, and affective function. As a result, it is critical that a solid mechanistic knowledge about neural circuit dynamic in patient

populations is investigated before determining the usefulness of applying these protocols in future clinical settings.

Although growing evidence suggests that TMS is a novel approach capable of characterizing synaptic dysfunction and plasticity in neurological and psychiatric disorders such as Parkinson's disease, Alzheimer's disease, and stroke, the clinical utility of these assessments needs to be established on a larger scale. Moreover, to date all work in patient populations has focused only on the functional circuits while the participants are at rest. It is vital that future studies with dual-site TMS consider state- and task-dependent effects, particularly when the patient is challenged, to fill knowledge gaps in understanding how altered brain dynamics contribute to specific motor, cognitive, and affective dysfunctions. Importantly, this setting allows for unprecedented opportunities to comprehensively study functional brain circuits and plasticity noninvasively by both recording and manipulating neural activity. This can eventually be translated to novel clinical therapies for brain disorders.

Awaiting these clinical advances, a critical first step is to increase the rigor and reproducibility of TMS experiments across independent laboratories by providing well-defined methodological procedures that are easily deployable and shareable. The following guidelines for the TMS procedures described above can help standardize the design, implementation, and conclusiveness of findings. First, stimulation parameters such as the intensity, duration, ISI, timing, coil position, and anatomical locations should be carefully documented and repeated in the same task context across multiple independent laboratories to encourage large-scale testing and application. Second, brain targets should be precisely defined based on clear anatomical and functional criteria that capture brain activity within brain circuits associated with behavior. Third, neuronavigation should be used to guide the TMS coil placement when targeting said brain

circuits. It also is recommended that experiments be hypothesis-driven and use both a control task to ensure changes are related selectively to the task context and a control brain site outside the putative targeted network to rule out the nonspecific effect of stimulation. Fourth, to better inform the diagnostic accuracy and therapeutic effectiveness of these methods in future clinical settings, basic research will need to use a multimodal approach combining TMS measures and manipulations with neuroimaging and behavioral measures to better characterize the underlying pathological changes and effect of treatment. Fifth, variability of individual responses using dual-site TMS methods need to be reported because it could provide important information about how interventions can be optimized for different brain areas, leading to new treatments based on individual pathophysiological mechanisms. Finally, researchers need to be transparent when reporting findings by including negative results (Brown, et al., 2019) and make data publicly available for interpretation to increase sample sizes and promote more efficient science. This comprehensive approach will increase rigor and reproducibility in both the collection and analysis of data that can guide future basic neuroscience and clinical studies. Ultimately, this will enable improvements in experimental design and optimize targeted therapies, thereby reducing morbidity and impairments in neurological and psychiatric disorders.

Chapter 3: Reduced Facilitation of Parietal-Motor Functional Connections in Older Adults

3.1 Abstract

Age-related changes in cortico-cortical connectivity in the human motor network in older adults are associated with declines in hand dexterity. Posterior parietal cortex (PPC) is strongly interconnected with motor areas and plays a critical role in many aspects of motor planning. Functional connectivity measures derived from dual-site transcranial magnetic stimulation (dsTMS) studies have found facilitatory inputs from PPC to ipsilateral primary motor cortex (M1) in younger adults. In this study, we investigated whether facilitatory inputs from PPC to M1 are altered by age. We used dsTMS in a conditioning-test paradigm to characterize patterns of functional connectivity between the left PPC and ipsilateral M1 and a standard pegboard test to assess skilled hand motor function in 13 young and 13 older adults. We found a PPC-M1 facilitation in young adults but not older adults. Older adults also showed a decline in motor performance compared to young adults. We conclude that the reduced PPC-M1 facilitation in older adults may be an early marker of age-related decline in the neural control of movement.

3.2 Introduction

Age-related decline in cognitive and sensorimotor functions in older adults has been linked with changes in the brain's structural and functional connectivity patterns

(Damoiseaux, 2017; Seidler et al., 2010). These age-related differences in functional connectivity that mediate information flow across the brain have been attributed in part to the decline in white matter integrity in older adults (Bruijn et al., 2014; Sullivan et al., 2010; Wu & Hallett, 2005; Zahr et al., 2009). Additionally, mounting evidence from neuroimaging suggests age-related changes in cortico-cortical connectivity in the motor network of healthy older adults contribute to age-related declines in sensorimotor functions. Functional cortico-cortical connectivity measures derived from dual-site transcranial magnetic stimulation (dsTMS) in healthy older adults also have shown reduced facilitatory and inhibitory inputs from secondary motor areas, including the supplementary motor area (SMA; Green et al., 2018) and dorsal premotor cortex (PMd; Ni et al., 2014), to primary motor cortex (M1). Posterior parietal cortex (PPC), a region involved in transforming sensory information into motor commands (Andersen & Cui, 2009; Crawford et al., 2003, 2004) is strongly interconnected with motor areas through white-matter tracts of the superior longitudinal fasciculus (Makris et al., 2005). These reciprocal glutamatergic parietal-frontal circuits are likely excitatory (R. Dum & Strick, 2002; Matsumoto et al., 2007; Tokuno & Nambu, 2000) and underlie control processes for skilled voluntary movements such as dexterous finger movements required during the manipulation of objects (Davare et al., 2011; Filimon, 2010; Gallivan & Culham, 2015; Turella & Lingnau, 2014; Vesia & Crawford, 2012).

Human neuroimaging studies have implicated parieto-frontal brain regions in sensorimotor control of human hand behavior (Fabbri et al., 2014; Gallivan et al., 2011, 2013; Monaco et al., 2020; Turella et al., 2020). Anatomical findings in non-human primates have shown direct monosynaptic inputs to M1 from PPC in the control of hand movements (Bruni et

al., 2018; Rozzi et al., 2006; Strick & Kim, 1978). A similar direct functional and anatomical parieto-motor pathway has been seen in human imaging (Koch et al., 2010). A number of dsTMS findings also have shown direct facilitatory parieto-motor connectivity in both the resting and active brain for hand actions in young adults (Cattaneo & Barchiesi, 2011; A. N. Karabanov et al., 2013; Koch, Del Olmo, et al., 2007; Koch et al., 2008; Vesia et al., 2013, 2017; Ziluk et al., 2010). Similarly, recent findings from intraoperative dual cortical stimulation in humans have provided direct evidence that the inferior parietal lobule exerts short-latency excitatory effects on cortical motor output (Cattaneo et al., 2020). Importantly, a recent neuroimaging study points to reduced coupling of parietal and premotor areas as a possible mechanism for the decreased perceptual motor speed observed in older adults (Michely et al., 2018). A question that remains, however, is whether the well-established age-related decline in sensorimotor performance relates to age-related differences in parieto-motor connectivity in older adults. We used dsTMS to characterize patterns of functional PPC-M1 connectivity and a standard pegboard test to estimate skilled motor performance in young and older adults. We hypothesized that facilitatory connectivity between PPC and M1 is reduced in older adults.

3.3 Methods

3.3.1 Participants

Thirteen young adults (YA, 8 females, 19.9 ± 1.3 years) and thirteen older adults (OA, 5 females, 72.2 ± 5.5 years) provided written consent to participate in the study. All participants were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield,

1971). All participants were screened for any contraindications to TMS (Keel et al., 2001; Rossi et al., 2011) and had no history of neurological disorders. To assess weekly frequency and duration of various physical activities undertaken by older adults, we administered the Community Health Activities Model Program for Seniors self-report questionnaire (CHAMPS), which revealed that all were very physically active (total caloric expenditure per week: 3,799.5 ± 869.6; (L. M. Stewart et al., 2001). Cognitive function was assessed in the older adults using the Montreal Cognitive Assessment (MoCA score, ≥26) (Nasreddine et al., 2005) and Mini-Mental State Exam (MMSE score ≥27) (Folstein et al., 1975). Those who took CNS-active medications within 48 h of the study were excluded. All procedures were approved by the University of Michigan Institutional Review Board (HUM00155459) in accordance with the Declaration of Helsinki.

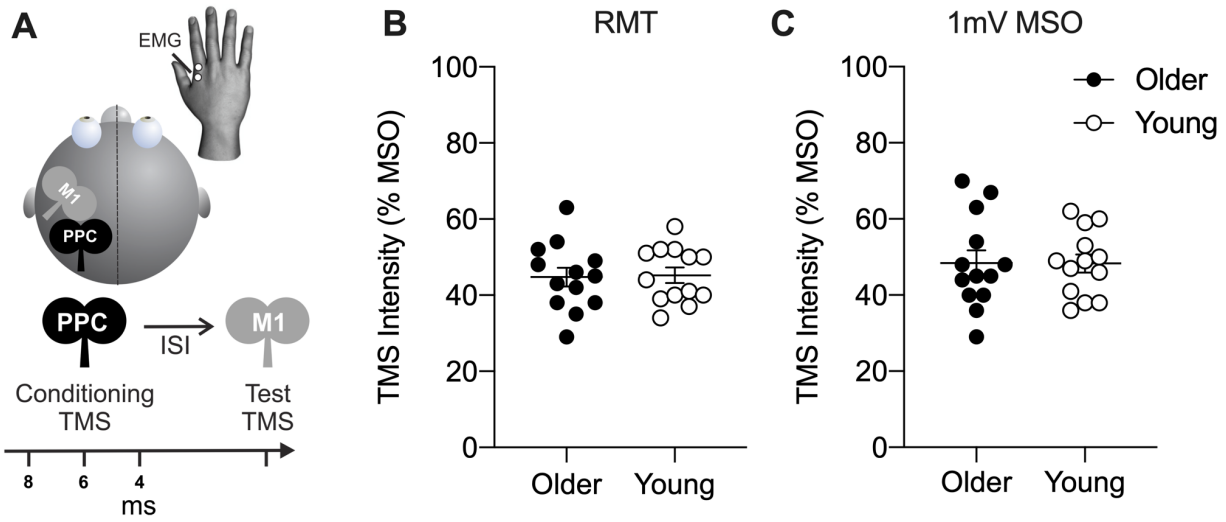

Figure 3-1 Experimental design and stimulation intensity. **(A)** Dual-site transcranial magnetic stimulation in a conditioning-test approach was used to probe connectivity between left posterior parietal cortex (PPC) and ipsilateral primary motor cortex (M1). The conditioning stimulus (CS) was delivered at an intensity of 70, 90, 110, or 130% of resting motor threshold (RMT) to the PPC. CS was delivered 4, 6, or 8 ms prior to a test stimulus (TS) delivered to primary motor cortex (M1). Resulting motor evoked potential (MEP) amplitudes were recorded using electromyography (EMG) in the right-hand target muscle at rest. **(B)** Motor excitability plots showing transcranial magnetic stimulation (TMS) intensity (expressed as a percentage of the maximum stimulator output, MSO) of resting motor threshold (RMT) and **(C)** TMS intensity to elicit a motor evoked potential (MEP) of 1 mV for older (filled circles) and young (open circles) adults. Mean and SE are presented.

3.3.2 Procedures

Transcranial magnetic stimulation in a conditioning-test approach with two coils (Goldenkoff et al., 2020; Hallett et al., 2017; Lafleur et al., 2016) was used to measure connectivity between left PPC and left M1 (**Figure 3-1A**). A test stimulus (TS) was delivered to M1 with a figure-8 coil (D70^2, 7 cm diameter) connected to a Magstim 200^2 stimulator (Magstim, Whitland, UK) with a monophasic waveform. The TS coil was held tangential to the skull at 45° from the mid-sagittal line, inducing a current in the posterior-anterior direction in the underlying cortical tissue. TS intensity was set to produce a motor evoked potential (MEP) of ~1 mV in the first dorsal interosseous muscle or the abductor pollicis brevis muscle in the right hand (Rossini et al., 2015). Left M1 was defined as the optimal scalp position for coil placement where stimulation evoked the largest MEP from the quiescent right-hand target muscle. PPC stimulation was applied to the P3 electrode position of the international 10-20 electroencephalogram (EEG) coordinate system using commercially available EEG head caps in each participant. The site is situated over angular gyrus (BA 39) of the inferior parietal lobule (Herwig et al., 2003; Okamoto et al., 2004) and corresponds with activation foci for hand actions identified by neuroimaging (Vesia & Crawford, 2012). A conditioning stimulus (CS) was delivered to PPC with another figure-8 coil (D50 Alpha B.I., 5 cm diameter) connected to a Magstim 200^2 stimulator (Magstim, Whitland, UK) with a monophasic waveform and a posterior-anterior current direction. The CS coil was held tangential to the skull at 90° from the mid-sagittal line. CS preceded TS by an inter-stimulus interval (ISI) of 4, 6, or 8 ms. PPC stimulation intensity was applied at 70, 90, 110, and 130% of resting motor threshold (RMT), similar to previous work (Koch et al., 2007). RMT was defined as the lowest intensity that evoked

MEPs of at least 50 μV in peak-to-peak amplitude in three of five consecutive trials with the PPC coil from the right-hand muscle (Rossini et al., 1994). Each stimulus-response curve was repeated for each ISI. Twelve single-pulse stimuli (TS alone) to M1 and paired-pulse stimuli (CS-TS) at each PPC stimulation intensity were delivered in random order within an experimental block (60 trials) with both hands at rest. Stimuli were applied every 5 s. The order of the ISI block for each stimulus-response curve was counterbalanced across participants. A frameless stereotactic neuronavigation system (Brainsight; Rogue Research, Montreal, Canada) was used to ensure consistency in the TMS coil position throughout the stimulation session. After the electrophysiological measurements were completed, motor skill performance was examined by a test of hand dexterity, the Grooved Pegboard Test (GPT, Lafayette Instrument # 32025) using standard procedures (Y. C. Wang et al., 2011).

3.3.3 Data analysis

Electromyography (EMG) signals were recorded from the right hand target muscle using bipolar surface electrodes (Model 2024F, Intronix Technologies Corporation), filtered (band-pass, 20 Hz to 2.5 kHz), and digitized at 5 kHz (Micro 1401 Cambridge Electronics Design). The peak-to-peak amplitude of the MEPs (mV) occurring between 15 and 100 ms after the TS were measured for each trial. Trials in which test pulses coincided with motor activity or failed to elicit reliable MEPs (i.e., value exceeded 1.5 times the interquartile range for the participant) were removed from the analysis (~2% of trials). The mean MEP amplitude for paired-pulse stimulation (CS-TS) was normalized by calculating the ratio of the amplitude relative to the mean single-pulse TS alone to M1 for each participant. Separate split-plot analyses of variance (ANOVAs) were carried out on the normalized MEP amplitudes for each PPC

stimulus-response curve at each PPC stimulation intensity using Age (two levels: young or older adults) as a between-subjects factor and ISI (three levels: 4, 6, or 8 ms) as a within-subjects factor. The Bonferroni method was used for *post-hoc t*-test comparisons. The Greenhouse-Geiser method was used to correct for sphericity. Independent sample *t* -test was used to compare motor excitability and behavioral measures between groups. Paired *t*-tests also were conducted on the absolute amplitudes of the test MEP and conditioned MEP for the PPC stimulation intensity of 90% RMT at 6 ms ISI to evaluate facilitation and inhibition within the older and young adults. Correlations between neurophysiological and behavioral data were tested with Pearson's coefficient. Statistical analysis was performed using IBM-SPSS Statistics Version 26. A significance threshold was set at $p < 0.05$. Partial η squared (η_p^2)

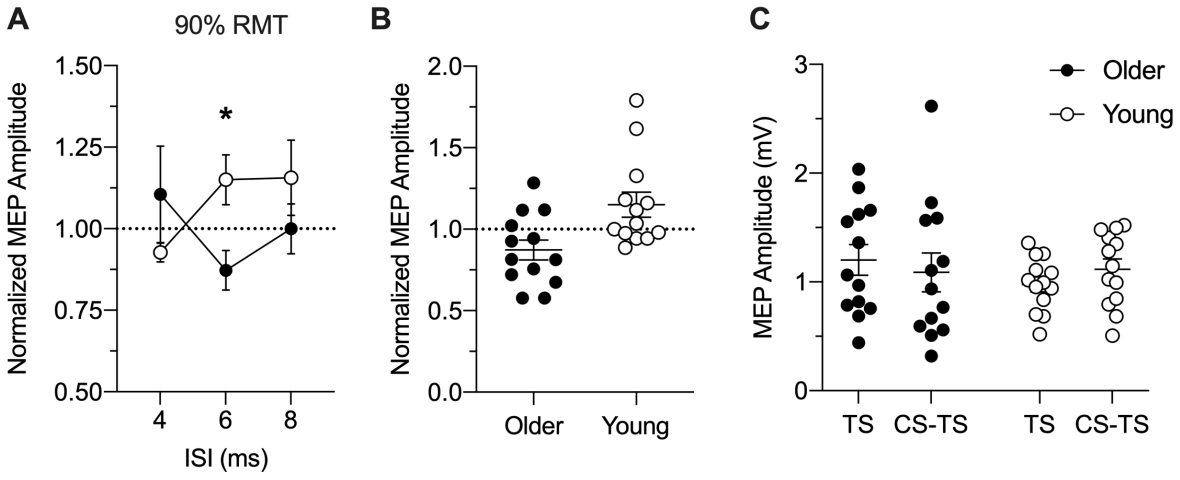

Figure 3-2 PPC-M1 connectivity in young and older adults (**A**) Group analysis of the effects of left posterior parietal cortex (PPC) stimulation at 90% resting motor threshold (RMT) intensity on motor evoked potential (MEP) amplitude induced by left M1 stimulation for older (n = 13; closed circles) and young (n = 13; open circles) adults at rest. The conditioning stimulus (CS) to PPC preceded a test stimulus (TS) to the primary motor cortex (M1) by an inter-stimulus interval (ISI) of 4, 6, or 8 ms. MEP amplitude was normalized as a ratio of the MEP amplitude evoked by paired-pulse stimulation (CS-TS) to that evoked by single-pulse stimulation (TS) to M1 alone (dashed line). Y = 1 indicates no effect of TMS to PPC on M1 excitability, whereas ratios higher than 1 indicate increased and ratios lower than 1 indicate decreased M1 excitability because of PPC stimulation. Facilitation in the ratio of MEP amplitude in young adults was reduced in older adults with PPC stimulation delivered at an intensity of 90% RMT at ISI of 6 ms. (**B**) Individual conditioned MEP amplitudes for the stimulus-response curve at 90% of RMT at the 6 ms ISI for older (n = 13, filled circles) and young (n = 13, open circles) adults normalized to TS alone (dashed line). (**C**) Individual absolute values of MEP amplitudes (mV) for the single-pulse TS to M1 and paired-pulse CS-TS to PPC at an intensity of 90% RMT at the 6 ms ISI for older (filled circles) and young (open circles) adults. Mean and SE are presented. *$p < 0.05$.

values were computed as a measure of effect size. Cutoffs for effect sizes are considered small (≥0.01), medium (≥0.06), and large (≥0.14) (Cohen, 1992). Mean and standard error values are reported.

3.4 Results

As shown in **Figure 3-1**, no significant age difference was found in measures of motor excitability (all $t_{24} < 0.71$, all $p > 0.49$). The RMT of maximum stimulator output (MSO) was 45.2 ± 2.0% MSO for young adults and 44.8 ± 2.5% MSO for older adults (**Figure 3-1B**). The intensity to elicit a MEP amplitude of 1 mV in the right-hand target muscle was 48.3 ± 2.4% MSO for young adults and 48.4 ± 3.7% MSO for older adults (**Figure 3-1C**).

Figure 3-2A shows PPC-M1 connectivity in young and older adults. Facilitation seen in the MEP amplitude ratio in young adults was reduced in older adults with PPC stimulation at 90% RMT for the ISI of 6ms (significant Age and ISI interaction: $F_{(1.96,47.0)} = 3.4$, $p = 0.043$, $\eta_p^2 = 0.12$; no main effect of Age: $F_{(1,24)} = 1.17$, $p = 0.29$, $\eta_p^2 = 0.05$; no main effect of ISI: $F_{(1.96,47.0)} = 0.34$, $p = 0.71$, $\eta_p^2 = 0.01$). Specifically, post hoc tests confirmed that the ratio of the MEP amplitude was significantly different between the age groups for the PPC stimulus-response curve at 90% RMT at the 6ms ISI (Bonferroni's t-test: $t_{22.9} = 2.84$, $p = 0.028$). The results show that the facilitation between left PPC and ipsilateral M1 connections in young adults is reduced in older adults. Closer inspection of the individual normalized data confirmed that left PPC stimulation intensity of 90% RMT at 6ms ISI caused inhibition of corticospinal excitability in ipsilateral M1 in about 69% of the older adults (**Figure 3-2B**). A similar pattern emerged at this timing and intensity when comparing the absolute amplitude of the conditioned and test MEP

(**Figure 3-2C**). Paired t-tests revealed a trend toward significance in the facilitation of the conditioned MEP compared to TS alone in young adults ($t_{12} = 2.04$, $p = 0.06$), while the analysis within older adults did not reach significance ($t_{12} = 1.38$, $p = 0.19$). It is worth noting that single-pulse TS MEPs for the older adults were more variable than young adults, possibly influencing the normalized MEP amplitude ratio.

In a series of control experiments, we also verified whether the PPC-M1 connectivity at rest would differ with different PPC stimulation intensities. In each case, no significant age difference was found in the PPC stimulus-response curve at intensities of 70, 110, or 130% RMT (**Figure 3-3**). At 70% RMT (**Figure 3-3A**), a split-plot ANOVA showed that there was no significant effect of Age [$F_{(1,24)} = 1.42$, $p = 0.25$, $\eta_p^2 = 0.06$], ISI ($F_{(1.44,34.6)} = 0.40$, $p = 0.60$, $\eta_p^2 = 0.02$), nor an interaction effect [$F_{(1.44,34.6)} = 2.52$, $p = 0.11$, $\eta_p^2 = 0.10$]. At 110% RMT (**Figure 3-**

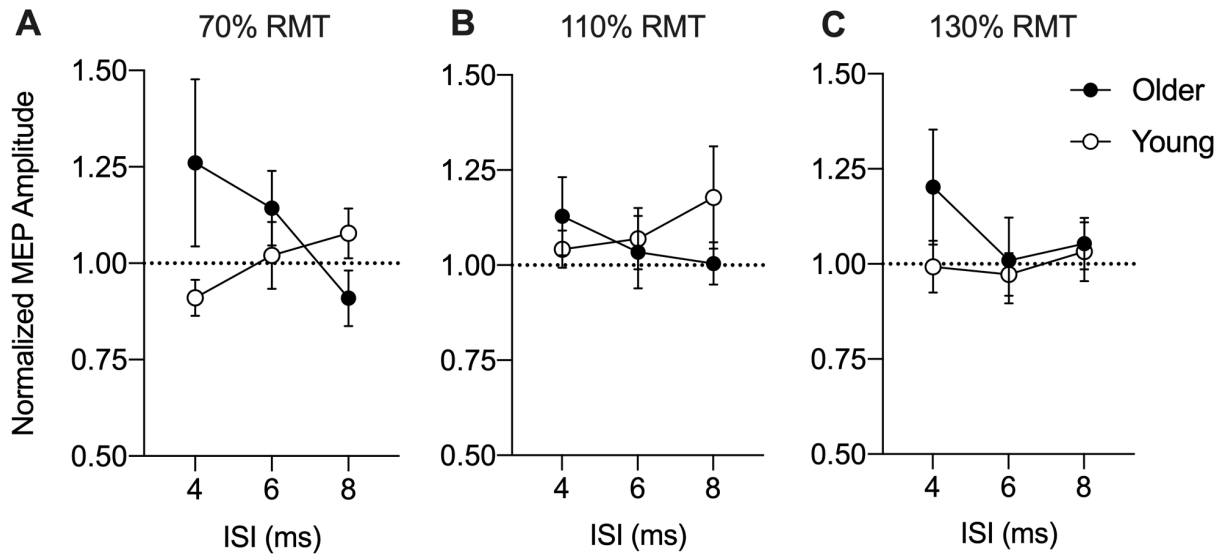

Figure 3-3 Group-averaged conditioned motor evoked potential (MEP) amplitudes for a posterior parietal cortex (PPC) stimulus-response curve at 70% (**A**), 110% (**B**), and 130% (**C**) of resting motor threshold (RMT) at an inter-stimulus interval (ISI) of 4, 6, or 8 ms normalized to a test stimulus (TS) alone (dashed line). MEP amplitudes are expressed as a ratio of the amplitude relative to the mean single-pulse TS alone to the primary motor cortex (M1) for older ($n = 13$, filled circles) and young adults ($n = 13$, open circles). Mean and SE are presented.

3B), a split-plot ANOVA showed that there was no significant effect of Age [$F_{(1,24)} = 0.28$, $p = 0.60$, $\eta_p^2 = 0.01$], ISI [$F(1.73,41.5) = 0.11$, $p = 0.90$, $\eta_p^2 = 0.005$], nor an interaction effect [$F_{(1.73,41.5)} = 1.05$, $p = 0.35$, $\eta_p^2 = 0.04$]. Similarly, at 130% RMT (**Figure 3-3C**), a split-plot ANOVA showed that there was no significant effect of Age [$F_{(1,24)} = 1.32$, $p = 0.26$, $\eta_p^2 = 0.05$], ISI [$F_{(1.93,46.29)} = 0.64$, $p = 0.53$, $\eta_p^2 = 0.03$], nor an interaction effect [$F_{(1.93,46.29)} = 0.61$, $p = 0.54$, $\eta_p^2 = 0.03$].

As shown in **Figure 3-4A**, young adults were significantly faster than older adults at completing the GPT (young adults = 68.0 ± 8.6 s vs. older adults = 90.7 ± 22.2 s, $t_{24} = 3.44$, $p = 0.003$). **Figure 3-4B** shows associations between the PPC-M1 connectivity at rest and motor skill performance in young and older adults. A correlation analysis for each age group showed that the

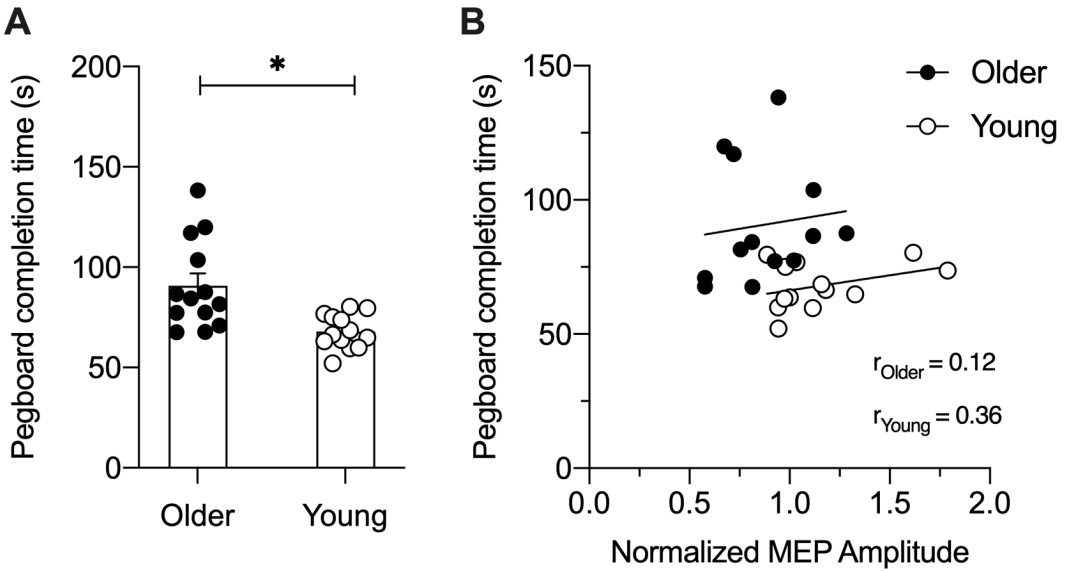

Figure 3-4 (**A**) Bar graph for group averaged completion times for the Grooved Pegboard Test in seconds (s). and (**B**) Correlation between normalized motor evoked potential (MEP)at the 6 ms inter-stimulus interval (ISI) for PPC stimulus-response curve at 90% resting motor threshold (RMT) and Grooved Pegboard Test completion time for each older (filled circles) and young adult (open circles). As expected, young adults performed the task faster compared to older adults. A simple linear regression line is superimposed over the individual data points for each group. Normalized MEP amplitude did not correlate with the Grooved Pegboard Test performance in both young and older adults (*all p's* > 0.2). Error bars represent SE. *$p < 0.05$.

normalized MEP amplitude for the PPC stimulation intensity of 90% RMT at the 6ms ISI did not correlate with GPT completion time in both young ($r = 0.130$; $p = 0.23$) and older adults ($r = 0.015$; $p = 0.69$).

3.5 Discussion

A reduction of facilitation in a parieto-motor connection responsible for skilled hand movements was demonstrated in older adults compared to young adults. Using a dsTMS approach, we found that a conditioning stimulus to PPC with a 90% RMT intensity delivered 6 ms prior to a test stimulus to M1 resulted in a facilitation of the MEP amplitude in young but not older adults. In fact, the PPC-M1 interaction in the older group changed from facilitation to inhibition. The present findings are in line with prior dsTMS work in young adults showing short-latency PPC-M1 functional interactions are selectively facilitated at rest when applying CS to PPC at an intensity of 90% RMT (Karabanov et al., 2013; Koch et al., 2007). In the current study, the reduced PPC-M1 facilitation in older adults may be related to impairments of high-level movement planning signals in PPC as demonstrated by their slowed completion time of the GPT (Andersen & Cui, 2009). However, future work will need to better characterize the relationship between functional PPC-M1 connectivity and skilled motor performance. For instance, previous dsTMS studies have shown that functional PPC-M1 connectivity is modulated early in the motor plan for different types of hand actions at a similar ISI and conditioning stimulation intensity in young adults (Koch et al., 2008; Vesia et al., 2013, 2017). Yet, no work has investigated whether there is a relationship between functional PPC-M1 interactions during grasp preparation and manual dexterity in older adults. Future investigation is needed to determine

whether similar age-related differences occur during these action-associated processes. It also should be noted that it remains unclear whether the non-significant association between reduced facilitation of parieto-motor functional connections and manual dexterity in older adults is present in a larger sample size given the moderate sample size in the current study. One possible explanation of the current results is that widespread motor plans involving multiple, parallel parieto-premotor-motor circuits could modulate corticospinal output associated with sensorimotor hand control (Davare et al., 2010, 2011; Koch & Rothwell, 2009; Turella & Lingnau, 2014; Vesia et al., 2018; Vesia & Davare, 2011). It also is possible that the relationship between cortico-cortical connections in the motor system and skilled hand behavior likely encompasses a much broader range of brain regions within frontal, parietal, and temporal cortices to support the flexibility of human hand behavior(Gallivan & Culham, 2015; Grafton, 2010; Monaco et al., 2020; Turella et al., 2020).

This interpretation is in line with prior dsTMS studies demonstrating age-related decline between M1 and frontal areas in the motor cortical network such as dorsolateral prefrontal cortex (Fujiyama et al., 2016), SMA (Green et al., 2018), and PMd (Ni et al., 2014). Together, these findings suggest an age-related reduction in functional connectivity from action-associated cortical areas to M1 in older adults. It is possible that the degraded facilitatory inputs from PPC to M1 in older adults likely represent an early marker of age-related decline for functional connectivity underlying complex motor skills. This view is in line with theoretical suggestions that older adults recruit frontal cortical areas to compensate for bottom-up sensory processing in posterior cortical areas when performing more cognitive-demanding motor tasks (Davis et al., 2008). Indeed, a large body of research provides complementary evidence linking these age-

related differences in functional activation and connectivity patterns with cognitive and motor performance (see reviews: Damoiseaux, 2017; Seidler et al., 2010). Functional neuroimaging studies have consistently demonstrated enhanced prefrontal influences on the motor system in response to increased task demands in older adults (Cabeza et al., 2018; Heuninckx et al., 2005; Wu & Hallett, 2005). One such study found that prefrontal areas compensated for decreased parietal influences on premotor areas associated with a decline in perceptual motor speed with advancing age(Michely et al., 2018). This is also consistent with evidence linking age-related decline in cognitively demanding motor tasks with structural changes in white matter tracts that connect sensorimotor, frontal, and parietal regions in older adults (Stewart et al., 2014). The reduced efficacy of this connection is also supported by findings in individuals with Parkinson's disease (Palomar et al., 2013) and stroke (Schulz et al., 2015) that show a more favorable motor outcome related to higher levels of communication between frontal and parietal areas in the motor system. Additionally, dsTMS evidence has shown that this selective age-related decrease in PPC-M1 facilitation in healthy older adults is exacerbated at early clinical stages of Alzheimer's disease (Bonnì et al., 2013). This decreased functional connectivity precedes disease-related changes in cognitive-related frontal areas and could in part represent a key driver of cognitive decline in Alzheimer's disease (Koch et al., 2019).

It is worth noting that neurobiological aging is a complex process involving interactions between local cortical and brain network plasticity (Freitas et al., 2013). In the case of aging, compensatory processes likely depend on the neural reorganization and recruitment of alternative circuits to attenuate cognitive and motor declines that occur with age (Cabeza et al., 2018). Future longitudinal studies delineating the specific contribution of PPC on motor related frontal

circuits combining TMS with neuroimaging approaches will be needed to gain insight into the mechanisms of system-level plasticity across the lifespan. We recognize that age-related neural decline such as brain atrophy, synaptic loss, and white matter degradation could account for the observed MEP amplitude differences between young and older adults (Farokhian et al., 2017; Giorgio et al., 2010). However, we believe a global effect on mechanisms underlying aging is unlikely to account for the highly specific reduction in PPC-M1 facilitation in the current study. A methodological limitation of the study is that we did not selectively localize PPC sites for hand actions at the individual level using fMRI or task-based dsTMS. Prior dsTMS work has shown anatomical and functional differences in connectivity between PPC regions and M1 (Karabanov et al., 2013). This raises the possibility that the effects at other ISIs and conditioning stimulation intensities in our study could be dependent on different neural substrates. Further studies will need to examine the effect of nearby parietal regions on motor excitability to account for the individual differences in functional connectivity among older adults. Finally, we recognize that the older adults tested in the current study were high-functioning and in relatively good health based on self-reports. Therefore, future work is needed with a more heterogenous subset of older participants to clarify the effects of physical activity and other environmental factors on age-related cognitive and motor deficits.

We conclude that the reduced PPC-M1 facilitation in older adults may be an early marker of age-related decline in the neural control of movement. Our findings could have implications for understanding functional parieto-frontal connectivity affected by advancing age in both healthy and clinical populations. Importantly, dsTMS methods could be used to develop better diagnostic tools and treatment approaches (Fox et al., 2012; Goldenkoff et al., 2020; Hallett et

al., 2017). We propose that prospective strengthening of PPC-M1 circuitry in healthy adults might be a fruitful therapeutic path to counteract the gradual age-related breakdown in functional connectivity within the motor-related network associated with motor impairments. It is possible that the preservation of these neural substrates could enhance resilience of the intact circuitry and minimize compensatory shifts in brain networks that maintain optimal cognitive and motor performance.

Chapter 4: Repeated Spaced Cortical Paired Associative Stimulation Promotes Additive Plasticity in the Human Parietal-Motor Circuit

4.1 Abstract

Repeated spaced sessions of repetitive transcranial magnetic stimulation (TMS) to the human primary motor cortex can lead to dose-dependent increases in motor cortical excitability. However, this has yet to be demonstrated in a defined cortical circuit. We aimed to examine the effects of repeated spaced cortical paired associative stimulation (cPAS) on excitability in the motor cortex. cPAS was delivered to the primary motor cortex (M1) and posterior parietal cortex (PPC) with two coils. In the multi-dose condition, three sessions of cPAS were delivered 50-min apart. The single-dose condition had one session of cPAS, followed by two sessions of a control cPAS protocol. Motor-evoked potentials were evaluated before and up to 40 min after each cPAS session as a measure of cortical excitability. Compared to a single dose of cPAS, motor cortical excitability significantly increased after multi-dose cPAS. Increasing the number of cPAS sessions resulted in a cumulative, dose-dependent effect on excitability in the motor cortex, with each successive cPAS session leading to notable increases in potentiation. Repeated spaced cPAS sessions summate to increase motor cortical excitability induced by single cPAS. Repeated spaced cPAS could potentially restore abilities lost due to disorders like stroke.

4.2 Introduction

Modulating neural plasticity through techniques such as transcranial magnetic stimulation (TMS) is promising for research and clinical applications. By administering repetitive TMS pulses to specific brain regions, it is possible to modify functional connectivity and cortical excitability, thereby influencing neural plasticity. For example, animal studies have shown that delivering repeated theta-burst stimulation sessions in a spaced manner can produce an additive plasticity response (Cao & Harris, 2014; Kramár et al., 2012). Similarly, an 'accelerated' application protocol, which consists of repeated sessions of theta-burst stimulation in a single day, has demonstrated a dose-dependent increase in excitability in the human primary motor cortex (M1; Nettekoven et al., 2014, 2015; Tse et al., 2018; Yu et al., 2020). Several studies have supported the idea that a 50-60 min interval between stimulation sessions can enhance the efficacy of plasticity-inducing accelerated TMS protocols (Thomson & Sack, 2020). This interval has been shown to induce additive responses in neural plasticity induction and motor function enhancement (Thomson & Sack, 2020), has been effective in behavioral studies investigating the benefits of spaced training (Smolen et al., 2016), and is believed to maximize stimulation-induced synaptic changes (Kramár et al., 2012). However, it remains to be demonstrated whether the additive plasticity response to stimulation focused on a single brain region can be achieved by concurrently stimulating multiple brain regions within a defined cortical circuit.

Cortical paired associative stimulation (cPAS) is a technique that involves delivering repeated pairs of TMS pulses using two coils to enhance the efficiency of neural communication between cortical regions within well-defined functional circuits in the brain (Goldenkoff et al., 2020; Guidali et al., 2021; Koch, 2020; Lafleur et al., 2016). This multifocal TMS protocol

utilizes the principles of Hebbian spike-timing-dependent plasticity (STDP; Hebb, 1949; Markram et al., 2011) and has been shown to strengthen neural circuits through a mechanism similar to long-term potentiation (LTP; Koch et al., 2013). For instance, applying cPAS to cortical regions interconnected with M1, such as the posterior parietal cortex (PPC), can lead to persistent increases in motor cortical excitability (Chao et al., 2015; Koch et al., 2013). However, the dose-dependent effects of cPAS in inducing synaptic plasticity within this parietal-motor circuit remain unknown. We hypothesized that employing a multi-dose cPAS protocol would yield additive benefits similar to those reported with other multi-dose rTMS protocols. Specifically, we expected that repeated sessions of cPAS targeting the parietal-motor circuit with 50 min intervals between sessions would increase motor cortical excitability more than a single cPAS session. Additionally, we hypothesized that the repeated sessions of cPAS would have a cumulative effect and influence each other, resulting in greater potentiation than the preceding cPAS session.

4.3 Methods and materials

4.3.1 Participants

Data were collected from fifteen right-handed adults (10 female, 5 male, 19-52 years, average age = 32.1, SD =10.8 years). All participants were right-handed based on the Edinburgh Handedness Inventory (Oldfield, 1971) and provided written informed consent. Participants underwent a TMS safety screening (Keel et al., 2001; Rossi et al., 2011) and confirmed that they were not using psychiatric drugs or experiencing any known neurological and psychiatric conditions. All procedures followed the operational guidelines and safety recommendations for

TMS use in healthy participants (Rossi et al., 2020). The Institutional Review Board approved the study at the University of Michigan (HUM00196773).

4.3.2 Electromyographic recordings

Electromyographic (EMG) signals were recorded from the relaxed first dorsal interosseous and abductor pollicis brevis muscles in the right hand using 9-mm diameter Ag-AgCl surface electrodes arranged in a tendon-belly configuration. The EMG signal was amplified (1000x), band-pass filtered (20 Hz - 2.5 kHz; Model 2024F; Intronix Technologies Corporation, Bolton, Canada), digitized at 5 kHz by an analog-to-digital interface (Micro 1401; Cambridge Electronics Design, Cambridge, UK), and recorded by a computer using Signal software (Cambridge Electronics Design, Cambridge, UK) for off-line analysis.

4.3.3 Measures of motor cortical excitability elicited by TMS

A Magstim 200^2 stimulator with a figure-8 coil (D70^2, 7 cm diameter) was used (Magstim, Whitland, UK), similar to our previous work (Goldenkoff et al., 2023). We monitored the TMS coil position using a standard MRI template with a frameless stereotactic neuronavigation system (Brainsight 2, Rogue Research Inc., Montreal, Canada). The coil was placed tangential to the scalp at a 45° angle from the midsagittal line, targeting the left primary motor cortex (M1). The coil placement was adjusted to the location where the single-pulse TMS produced the largest motor-evoked potential (MEP) from the targeted muscles of the right hand. TMS intensity was set at the minimum level required to elicit MEP amplitudes of 1 mV in at least five out of ten trials in the relaxed hand muscles for each participant (Groppa, Oliviero, et al., 2012; Rossini et al., 1994, 2015). Peak-to-peak amplitude of the MEPs (mV) occurring between 15 and 100 ms after the TMS pulse was measured for each trial to quantify motor

cortical excitability. Twenty-four MEPs were elicited for each measurement. Single-pulse TMS was applied at 5 s intervals between each trial. The same TMS intensity was used to assess changes in LTP-like plasticity in M1 (Chen & Udupa, 2009) after each cPAS session. Trials were repeated if TMS pulses coincided with motor activity or failed to elicit reliable MEPs (i.e. when the Brainsight neuronavigation system indicated a deviation of the TMS coil center from the sampled target).

4.3.4 Individual-specific parietal stimulation locations

Connectivity between left PPC and left M1 was measured using a conditioning-test approach with two coils (Goldenkoff et al., 2020; Hallett et al., 2017; Van Malderen et al., 2022; Vesia et al., 2013, 2017). This technique has been described elsewhere (Goldenkoff et al., 2023). A conditioning stimulus (CS) was delivered over each PPC target in the grid 5 ms before delivering a test stimulus (TS) to M1. The CS was applied with a branding-iron-style figure-8 coil (D50 Alpha B.I., 5 cm diameter) connected to a Magstim 200^2 stimulator. The TS was applied with a figure-8 coil ($D70^2$, 7 cm diameter) connected to a separate Magstim 200^2 stimulator. Motor cortical excitability thresholds were determined for each participant using the individual coils. The TS pulse intensity for the $D70^2$ coil was adjusted to induce MEP amplitudes of ~1mV in five out of ten trials in the relaxed targeted right-hand muscle. At baseline, the resulting MEPs were 51.1% ± 10.3% of the maximum stimulator output (MSO) for the M1 coil. The CS pulse intensity of the D50 coil was 90% of the resting motor threshold (RMT), defined as the lowest intensity that evoked MEPs of at least 50 μV in peak-to-peak amplitude in three of five consecutive trials from the right-hand target muscle (Rossini et al., 1994). The MSO of the RMT was 49.0% ± 9.1% for the PPC coil. The PPC coil was positioned tangentially to the skull, the handle pointing downward and rotated medially by 15°.

Individualized left PPC locations were determined using a function-based dual-site search-grid TMS technique. This approach uses a ‘hunting procedure’ to target personalized functional interactions in the cortical grasping network. The procedure is similar to motor mapping for hand muscles, using a 'hot spotting' technique to locate the scalp position that yields the maximum TMS response with the minimum stimulator intensity over M1 (Neva et al., 2015; Neva, Singh, et al., 2014; Neva, Vesia, et al., 2014). First, the electrode position for the P3 (left PPC) was identified on each participant using the 10-20 electroencephalogram (EEG) coordinate system based on individual head circumference measurements (for details, refer to Goldenkoff et al., 2020; Villamar et al., 2013). This point was chosen because it reliably targets the Brodmann area 7/40 in the inferior parietal lobule (Chao et al., 2015; Goldenkoff et al., 2023; Herwig et al., 2003; Okamoto et al., 2004; Schintu et al., 2016; Vesia et al., 2010). A 3x3 rectangular search grid, with positions separated by 1 cm, was then marked on the scalp using Brainsight centered on the P3 target. To activate the parietal-motor circuit, participants were instructed to grasp a cylindrical object (7 cm diameter, 6.5 cm height) positioned 30 cm in front and 10 cm to the right of the starting hand position when an LED light flashed on (Vesia et al., 2017). TS intensity was adjusted to elicit MEPs of about 1 mV from the right-hand muscle during the planning phase of the movement. We used the dual-site TMS technique to randomly deliver about ten pairs of pulses on each grid position to locate the PPC 'scalp hotspot' that produced the largest MEPs from the right-hand muscles. If we found multiple locations that produced MEPs greater than 1.2 mV, we delivered about five consecutive pulses to each location and selected the one with the highest MEP amplitude. We then confirmed that the amplitude was larger than 1.2 mV in three of five trials. If this criterion was not met, we restarted the process. **Figure 4-1A** shows the heat map for the selected parietal grid position for the participants. Four participants underwent

individual cortical stimulation site mapping using Brainsight software in Montreal Neurological Institute (MNI) space (**Figure 4-1B**). Neuronavigation was used to position both coils accurately

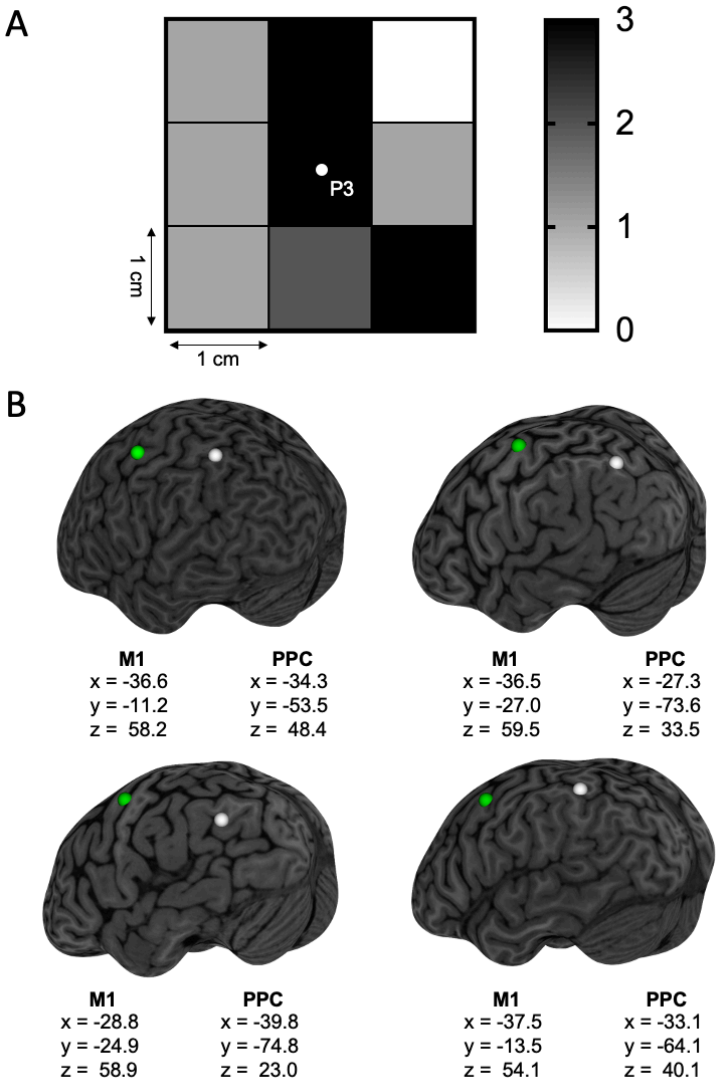

Figure 4-1 iTBS PPC and M1 target locations for participants. (**A**) Participants' parietal target search grid spot indicated on the heat map. A 3x3 grid of search positions, each separated by 1 cm, is centered on the electrode position for the left posterior parietal cortex (P3) in the 10-20 electroencephalogram (EEG) coordinate system for each participant. (**B**) Three-dimensional rendering of a participant's anatomical MRI with marked 'scalp hotspots' over the primary motor cortex (M1, green circle) and posterior parietal cortex (PPC, white circle) in the left hemisphere for four participants. M1 'scalp hotspot' was the location where single-pulse transcranial magnetic stimulation (TMS) elicited the largest motor-evoked potential (MEP) in the targeted right-hand muscle. The PPC 'scalp hotspot' was determined using a dual-site TMS grid-search targeting method for personalized functional stimulation of the grasping motor network. The scalp locations for each participant were projected onto a T1-weighted magnetic resonance image (MRI) using frameless stereotactic neuronavigation. Cortical areas where stimulation reached the brain in Montreal Neurological Institute (MNI) coordinates (mean +/- SD) were computed using Brainsight software. Neuronavigation software for TMS targeted individually determined cortical areas with each figure-8 TMS coil.

during the localization and experiment.

4.3.5 Cortical paired associative stimulation (cPAS)

Repetitive low-frequency pairs of cortical stimuli were delivered using a small figure-8 coil (D50 Alpha B.I., 5 cm diameter) to PPC and another figure-8 coil (D70^2, 7 cm diameter) to M1, both connected to a Magstim 200^2 stimulator. The pulse intensity for the PPC coil was set at 90% of the RMT. The pulse intensity that elicited the MEP of approximately 1 mV in the target muscle was used for the M1 coil. cPAS consisted of 100 pairs of monophasic waveform pulses at 0.2 Hz, totaling 8.3 min (Goldenkoff et al., 2020; Koch et al., 2013). The interpulse interval of the paired pulses differed for the cPAS conditions (**Figure 4-2A**). For the Hebbian spike-timing-dependent plasticity (STDP) protocol, PPC stimulation preceded M1 stimulation by 5 ms (Goldenkoff et al., 2020; Koch et al., 2013). For the control cPAS protocol, PPC stimulation preceded M1 stimulation by 500 ms to control for timing contiguity for paired associative plasticity in the parietal-motor circuit (Johnen et al., 2015; Koch et al., 2013).

4.3.6 Experimental design

This study employed a within-subjects, counterbalanced design. Participants underwent a multi-dose and a single-dose condition on different days, with an average interval of 6.8 days between the experimental conditions (range = 2-15 days; **Figure 4-2B**). There was no relationship between the duration of the washout period and cPAS-induced changes in motor cortical excitability between the two sessions ($R^2 = 0.085$ and $p = 0.293$). To induce associative motor plasticity, we applied 100 paired TMS pulses using two coils, with stimulation to PPC preceding stimulation to M1 by 5ms. This timing follows the principles of Hebbian STDP and has been shown to strengthen the parietal-motor circuit through an LTP-like mechanism (Koch et

al., 2013). As a control condition, we repeated the application of paired TMS pulses to PPC and M1, but with a timing alteration whereby PPC stimulation preceded M1 by 500 ms. This control cPAS protocol delivered the same number of pulses at the same frequency but does not induce STDP or subsequent LTP-like plasticity effects mechanism (Koch et al., 2013). In the multi-dose condition, three consecutive sessions of cPAS were administered to produce the LTP-like effects. The single-dose condition consisted of one session of cPAS, followed by two sessions of the control cPAS. Each cPAS session was administered 50 min apart, following a spaced administration protocol (Smolen et al., 2016). We assessed the plasticity response to cPAS in

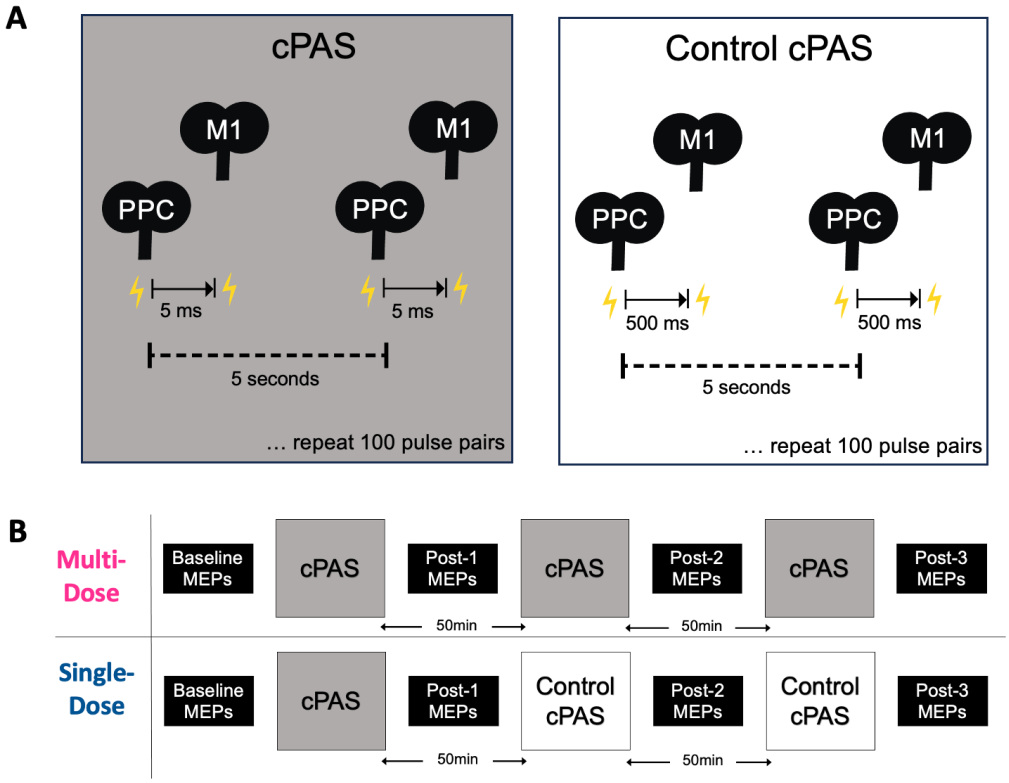

Figure 4-2 Schematic of the intervention and experimental design. (**A**) Schematic of cortical paired associative stimulation protocol (cPAS) in the parietal-motor circuit. In the cPAS condition (Hebbian stimulation), posterior parietal cortex (PPC) stimulation preceded primary motor cortex (M1) stimulation by 5 ms. In contrast, in the control cPAS condition (non-Hebbian stimulation), the interpulse interval was 500 ms to control for timing contiguity for paired associative plasticity in the parietal-motor circuit. The pairs of cortical stimuli were delivered at a frequency of 0.2 Hz (once every 5 s) and repeated for 100 trials (~8.3 min). (**B**) Experimental design. Motor-evoked potentials (MEPs) were collected before (baseline), and after three consecutive cPAS sessions spaced 50 min apart. Multi-dose stimulation and single-dose control conditions were administered on separate days and counterbalanced.

both conditions by quantifying the MEP amplitude in the right-hand muscles. Measures were taken before (baseline) and immediately after each cPAS session (Post-1, Post-2, Post-3). Measurements were repeated twice after each cPAS session (at 20 min and 40 min post-stimulation) to obtain a broader sample over time. We collated the MEP values as a previous experiment from our laboratory demonstrated consistent MEP sizes after cPAS at these time points. The same stimulation locations and intensities for M1 and PPC were used for each participant for both the multi-dose and single-dose conditions across both days.

4.3.7 Statistical analysis

The data were analyzed using R Statistical Software (v4.2.3; R Core Team 2023). To model the effect of dose condition and time on MEP amplitude, we fit a Bayesian hierarchical generalized linear model (GLM). As MEP amplitudes are strictly positive with positive skew, we specified a Gamma likelihood function and a log-link function. The model included fixed effects of condition (single-dose or multi-dose), time (Baseline, Post-1, Post-2, Post-3), and their interaction. We included all individual MEP amplitudes from each trial for every participant in the model. The model additionally allowed intercepts and slopes to vary by subject. A posterior distribution over possible parameter values was sampled using Markov chain Monte Carlo (MCMC) sampling implemented in rstan (Stan Development Team, 2023; Version 2.32.3) via the brms package (Bürkner, 2017, 2018); Version 2.20.4).

$$MEP_i \sim Gamma(\mu_i, shape)$$

$$\log(\mu_i) = \alpha_s + \beta_{Condition} Condition_i + \beta_s Time_i + \beta_{Condition \times Time} Condition_i Time_i$$

$$\alpha_s \sim \alpha + \sigma_\alpha z_{s\alpha}$$

$$\beta_s \sim \beta_{Time} + \sigma_\beta z_{s\beta}$$

$$\alpha \sim Student\_t(3, -0.1, 2.5)$$

$$\sigma_\alpha \sim Student\_t(3, 0, 2.5)$$

$$\sigma_\beta \sim Student\_t(3, 0, 2.5)$$

$$z_{s\alpha} \sim Normal(0,1)$$

$$z_{s\beta} \sim Normal(0,1)$$

$$\beta \sim Normal(0,1)$$

$$shape \sim Gamma(1, 0.01)$$

where α_s denotes a subject-specific intercept and $\beta_{Condition}$, β_{Time}, and $\beta_{Condition \times Time}$ denote parameter estimates for the effect of dose condition, time, and their interaction. We specified a weakly informative prior distribution for the fixed effects (β) with a mean of 0 and a standard deviation of 1 (i.e., N(0,1)). As regression coefficients for a Gamma likelihood GLM with a log link function are interpreted as multiplicative factors rather than slopes, an N(0,1) prior indicates that *a priori,* we believe that a change in factor level (e.g., Baseline to Post-3) is associated with an increase or decrease in MEP amplitude by a factor between 1 and 7.1 (i.e., [exp(0), exp(1.96)]). The brms package implements a non-centered parameterization for random effects and random slopes (Betancourt & Girolami, 2015) which for our model parameterizes subject-specific intercepts (α_s, β_s) using an overall intercept (random intercept: α, random slope: β_{Time}), subject-specific offsets ($z_{s\alpha}, z_{s\beta}$), and scaling parameters ($\sigma_\alpha, \sigma_\beta$). This parameterization decorrelates the sampling of random effects from high-order hyperparameters allowing for improved sampling efficiency (Betancourt & Girolami, 2015). Default prior specifications from the brms package were used for parameters associated with subject-specific intercepts ($\alpha, z_{s\alpha}, z_{s\beta}, \sigma_\alpha,$ and σ_β) , as well as the residual shape parameter ($shape$). By default, the location parameter for α was set to $median(log(MEP))$ and the scale parameter for α and σ was set to $max(mad(MEP), 2.5)$ where mad represents the median absolute difference. We

selected our model after the fitted model with both random intercepts and slopes had a lower Watanabe–Akaike information criterion than a model fit separately with only random intercepts. We ran four separate chains with 7000 iterations each. The first 2000 iterations were discarded as warm-ups. R-hat values were all very close to 1 (R-hat $\leq$ 1.001), and the effective sample size exceeded 5000 for all parameters indicating that MCMC chains had converged, and minimal autocorrelation was in the sampling. Posterior predictive checks confirmed that distributional assumptions were met and that the specified model could generate data that resembled the actual data. For each parameter in the model, we report the median, 95% highest density interval (HDI), and the probability of direction (pd). The HDI represents the interval for which all values within that interval have a higher probability density than points outside. Due to the log-link function, we exponentiate the median and 95% HDI values for reporting so that values represent multiplicative factors on the original response scale (e.g., a one-unit change in *x* is associated with an increase in MEP amplitude by a factor of exp(0.1) = 1.11). pd is an index of effect existence (ranging from 50% to 100%), representing the probability that an effect goes in a particular direction (e.g., effect *x* has a 99% probability of being negative). Note that pd represents the probability that the effect is negative or positive before exponentiation and the likelihood that the effect is less than or greater than one after exponentiation. We consider a pd greater than 95% to be strong evidence for an effect, a pd between 80% and 95% to provide some proof of an effect, and a pd less than 80% to indicate limited evidence for an effect.

To examine the effect of dose condition for each time point individually, we took draws from the expectation of the posterior predictive distribution (μ_i in the above model formula) for each stimulation condition and time point. Then, we subtracted the extracted values for the earlier

time point for each condition from those of a later time point (e.g., Post-3 – Post-1), generating a difference distribution. We report each comparison's median, 95% HDI, and pd.

4.4 Results

Participants reported no undesirable side effects after stimulation. We examined the impact of repeated spaced cPAS on MEP amplitudes across four time points (**Figure 4-3**). To do so, we fit a Bayesian hierarchical gamma GLM with fixed effects for dose condition (single- and multi-dose), time (Baseline, Post-1, Post-2, Post-3), and their interaction (**Table 4-1**). We found strong evidence that MEP amplitudes increased the MEP amplitude in the multi-dose and single-dose conditions following the first bout of Hebbian cPAS. Post-1 cPAS MEP amplitudes

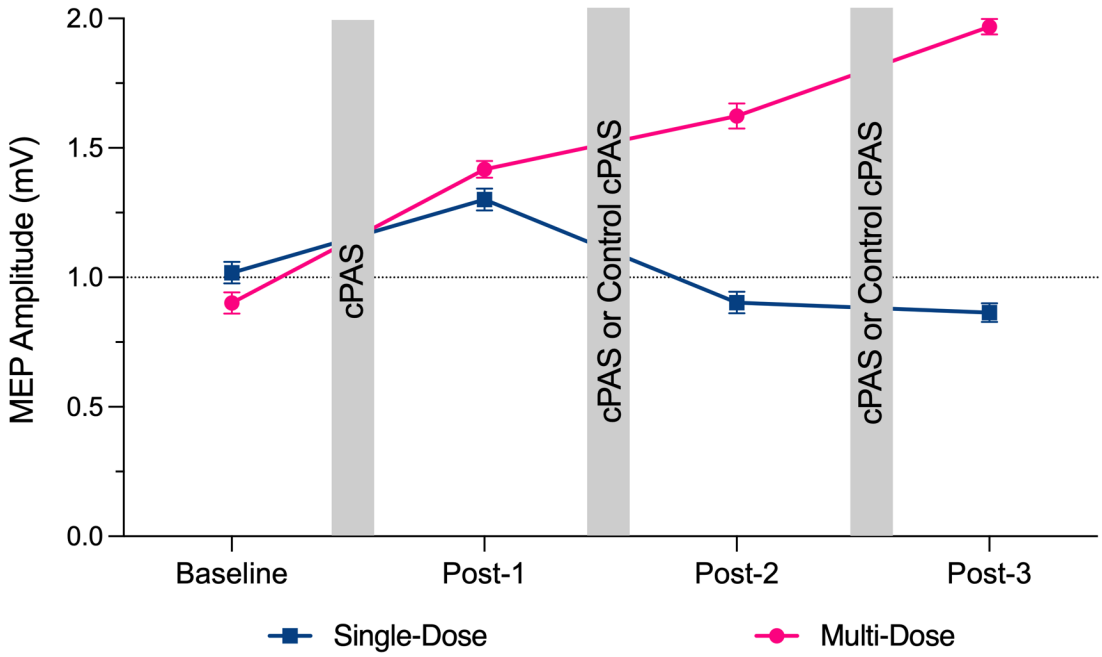

Figure 4-3 Mean motor-evoked potential (MEP) amplitude across participants for the multi-dose (pink circles) and single-dose (blue squares) experimental conditions. Post-1 to Post-2 and Post-2 to Post-3 time points indicate an increased cumulative dose effect on cortical paired associative stimulation (cPAS) induced motor potentiation. Error bars represent the within-subject standard error of the mean (SEM); Morey, 2008).

increased by 52.9% relative to MEPs at baseline in the multi-dose condition (median: 0.48, 95% HDI [0.36, 0.60], pd = 100%). Similarly, there was a 29.5% increase in MEP amplitudes following cPAS in the single-dose condition relative to the MEPs at baseline (median: 0.3, 95% HDI [0.18,0.42], pd = 100%). While there was strong evidence of differences in baseline MEP amplitude between the two experimental conditions (multi-dose – single-dose, median: -0.1, 95% HDI [-0.21, 0.00], pd = 98%), there was only some evidence for MEP differences following a single session of cPAS (multi-dose – single-dose, median: 0.08, 95% HDI [-0.03, 0.18], pd = 92%), indicating that the differences in MEPs were larger at baseline than the differences at the Post-1 time point. These results suggest that any effect on motor cortical excitability induced by cPAS after the Post-1 time point is unlikely to be represented by the difference in MEPs between experimental conditions at baseline. The direction of these effects signifies that a Hebbian cPAS protocol between the PPC and M1, without prior neuromodulating stimulation, leads to the

Stimulation Dose Condition	Time-Point	Median	95% HDI	pd (%)
Single-dose	Post-3 – Baseline	**-0.16 mV**	**-0.25 – -0.06**	**100%**
	Post-2 – Baseline	**-0.13 mV**	**-0.22 – -0.03**	**100%**
	Post-1 – Baseline	**0.30 mV**	**0.19 – 0.41**	**100%**
	Post-3 – Post-2	-0.03 mV	-0.10 – 0.04	82%
	Post-2 – Post-1	**-0.42 mV**	**-0.52 – -0.33**	**100%**
Multi-dose	Post-3 – Baseline	**1.03 mV**	**0.87 – 1.19**	**100%**
	Post-2 – Baseline	**0.67 mV**	**0.54 – 0.80**	**100%**
	Post-1 – Baseline	**0.48 mV**	**0.37 – 0.60**	**100%**
	Post-3 – Post-2	**0.36 mV**	**0.23 – 0.51**	**100%**
	Post-2 – Post-1	**0.19 mV**	**0.07 – 0.30**	**100%**
Multi-dose – Single-dose	Baseline	**-0.10 mV**	**-0.21 – 0.00**	**97%**
	Post-1	0.08 mV	-0.03 – 0.19	94%
	Post-2	**0.69 mV**	**0.57 – 0.81**	**100%**
	Post-3	**1.08 mV**	**0.93 – 1.24**	**100%**

Table 4-1 Posterior predictive summary for the effect of stimulation dose on MEP amplitude across time points. Bolded values indicate pd > 95%. Abbreviations: HDI, highest density interval; pd, probability of direction

facilitation of motor potentiation, as indicated by the increased MEP amplitude in both experimental conditions on different days.

Next, we examined whether the effects of repeated sessions of cPAS on motor cortical excitability depend on dose. For the multi-dose condition, there was strong evidence that Post-2 MEP amplitudes increased by 13.4% relative to MEPs Post-1 (median: 0.19, 95% HDI [0.00, 0.38], pd = 0.98%). Similarly, we found strong evidence that Post-3 MEP amplitudes increased by 21.8% relative to MEPs Post-2 (median: 0.34, 95% HDI [0.14, 0.54], pd = 100%). This effect is specific to the multi-dose condition. In contrast, we found strong evidence for a 32.9% decrease in MEP amplitudes following the Post-2 time point in the single-dose condition relative to the Post-1 MEP amplitudes (median: -0.43, 95% HDI [-0.54, -0.31], pd = 100%). There was limited evidence for an effect of the control-cPAS on motor cortical excitability between Post-2

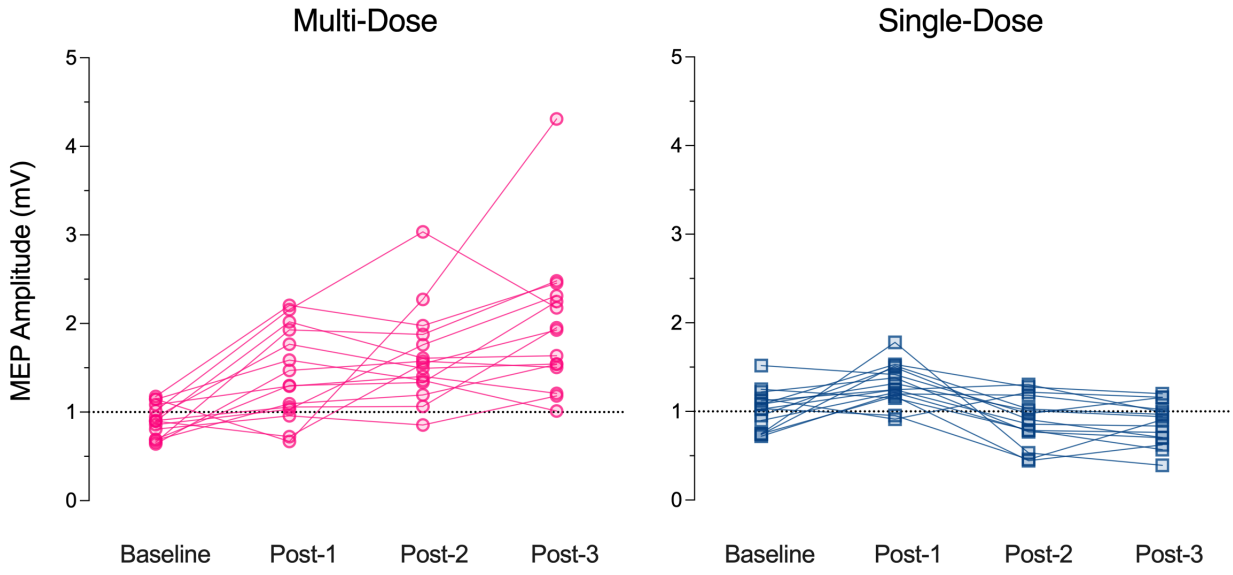

Figure 4-4 Individual plots of change in potentiation at each timepoint. Mean motor-evoked potential (MEP) amplitudes for the multi-dose (left panel) and single-dose (right panel) conditions are represented by open symbols and interconnecting lines. Results demonstrate consistent increases in MEPs with the cPAS protocol using a 5 ms interval between paired pulses.

and Post-3 time points (median: -0.02, 95% HDI [-0.12, 0.09], pd = 63%). We also found strong evidence that MEP amplitudes were notably larger in the multi-dose condition compared to the single-dose condition at Post-2 (median: 0.69, 95% HDI [0.56, 0.84], pd = 100%) and Post-3 time points (median: 1.08, 95% HDI [0.89, 1.21], pd = 100%). The same patterns of effects were identified when inspecting the mean MEP amplitudes at the individual level (**Figure 4-4**). These results demonstrate a cumulative, dose-dependent effect on excitability in the motor cortex, with each successive cPAS session leading to notable increases in potentiation.

4.5 Discussion

The present study provides evidence supporting a dose-dependent, cumulative effect of repeated spaced multifocal stimulation on motor cortical excitability. This study employed a multi-dose TMS approach with two coils to induce associative plasticity between interconnected cortical areas within the motor network. Our findings demonstrate a significant increase in MEP size after the cPAS session, indicating successful induction of STDP (Koch et al., 2013). Notably, MEP magnitude was significantly larger in the multi-dose condition relative to the single-dose condition only after the second and third sessions of cPAS. Furthermore, the size of MEPs increased after each successive cPAS application in the multi-dose condition.

The observed increase in MEP size after each application of cPAS aligns with animal studies that have shown a similar pattern of added potentiation. Studies in rodents have shown that spaced, repeated applications of theta burst stimulation can produce a cumulative effect on LTP (Cao & Harris, 2014; Kramár et al., 2012). This animal work demonstrated that after three spaced LTP-inducing stimulations, the potentiation increased nearly threefold compared to the response following the first stimulation (Kramár et al., 2012), which aligns with the dose-dependent outcomes observed in the present study. The increased potency of repeated

stimulation is believed to be due to a priming effect on synapses that initially had very high plasticity thresholds and did not respond to the first stimulation (G. Lynch et al., 2013). It is also possible that smaller synapses with fewer AMPA receptors require multiple activations to undergo an LTP response (Cao & Harris, 2014; Malenka & Bear, 2004; Malenka & Nicoll, 1999).

The present findings align with human studies that have shown dose-dependent effects of repeated bouts of theta burst stimulation to the motor cortex on local excitability and interconnected parietal-frontal regions within the motor network (Nettekoven et al., 2014, 2015; Tse et al., 2018; Yu et al., 2020). For instance, previous studies have demonstrated that applying three sessions of theta burst stimulation to the motor cortex causes dose-dependent increases in motor cortical excitability (Nettekoven et al., 2014; Yu et al., 2020). These TMS-induced changes in motor activity are not exclusively local but also extend to remote interconnected brain regions, leading to enhanced functional connectivity between M1 and the premotor cortex (Nettekoven et al., 2014). Our results extend these findings on multi-dose TMS protocols to a single brain region and their capacity to induce additive plasticity effects in a cortical network. It is likely that the network-level interactions influencing the plasticity response to stimulation can be enhanced by simultaneously stimulating multiple brain regions connected to the motor cortex to selectively target circuits involved in motor control and maximize stimulation specificity (Cárdenas-Morales et al., 2014; Fischer et al., 2017; Goldenkoff et al., 2020; Hordacre et al., 2021; Johnen et al., 2015; Koch, 2020; Nettekoven et al., 2014, 2015; Ruffini et al., 2018).

In the present study, we targeted a parietal-motor circuit involved in motor control (Breveglieri et al., 2023; Davare et al., 2010, 2011; Koch, Del Olmo, et al., 2008; Koch & Rothwell, 2009; Rothwell, 2011; Turella & Lingnau, 2014; Van Malderen et al., 2022; Vesia et

al., 2010, 2013, 2017; Vesia & Crawford, 2012; Vesia & Davare, 2011) to modulate connectivity in a controlled manner (Hernandez-Pavon et al., 2023; Jackson et al., 2006) while potentially minimizing unintended activation from the stimulation (Beynel et al., 2020; Fox et al., 2012; Liew et al., 2014; C. J. Lynch et al., 2022; Sale et al., 2015; Siebner et al., 2009). This cPAS protocol provides precise temporal and spatial stimulation to the two cortical regions with long-lasting effects (Casula, Pellicciari, Picazio, et al., 2016; Chao et al., 2015; Fiori et al., 2018; Johnen et al., 2015; Santarnecchi et al., 2018; Veniero et al., 2013). The mechanisms of action for cPAS are believed to follow Hebbian STDP rules (Caporale & Dan, 2008; Hebb, 1949; Jackson et al., 2006; Markram et al., 1997, 2011), leading to an LTP-like response at the targeted motor site (Chao et al., 2015; Koch et al., 2013). Our findings further advance these cPAS findings by demonstrating an additive effect on motor cortical excitability following repeated spaced sessions. However, it still needs to be determined whether the magnitude of the LTP-like effects on the motor system observed in the present study affects motor behavior and learning (Jung & Ziemann, 2009; A. Karabanov et al., 2015; F. Müller-Dahlhaus & Ziemann, 2015; Ziemann et al., 2004).

The present study has some limitations worth noting. First, our study employed a 50-min interval between cPAS sessions (Cao & Harris, 2014; Kramár et al., 2012; Smolen et al., 2016) to promote additive potentiation in response to repeated sessions (Thomson & Sack, 2020). It remains to be seen whether the time interval between cPAS sessions affects neural excitability in a dose-dependent manner. Second, we evaluated motor cortical excitability immediately after stimulation. Future study is required to determine whether the changes persist beyond the 40-min period we tested. Additionally, the mechanisms underlying the enduring effects of repeated spaced cPAS on motor function over multiple days require further investigation through

neurophysiology and neuroimaging (Freedberg et al., 2019; J. X. Wang & Voss, 2015). The interplay could be significant from a clinical perspective, potentially guiding the development of more effective stimulation protocols aimed at modifying specific cortical circuits in patients with motor disorders (Grefkes et al., 2010; Grefkes & Fink, 2011, 2014, 2016; Guggisberg et al., 2019; Hensel et al., 2023; Liew et al., 2014; Raffin & Hummel, 2018; Volz et al., 2015; Hummel, 2018; Volz et al., 2015). Such approaches could enhance plasticity in motor networks and facilitate their rehabilitation (Buch et al., 2017; Dayan & Cohen, 2011). As the current study aimed to investigate the dose-dependent effects of cPAS on motor cortical excitability, a sham cPAS condition where the current did not reach the cortex was not included. A comparison with the sham cPAS condition would have allowed for a full examination of stimulation-induced placebo effects. Future studies could incorporate sham stimulation to differentiate better the effects of time on motor cortical excitability (Boucher et al., 2021). Finally, the participants in the study were young, healthy adults. Because aging can show different responses to exogenous induction of plasticity (Opie et al., 2019; Turrini et al., 2023) and reduce parietal-motor connectivity essential to motor control (Goldenkoff et al., 2021), future work is warranted to determine whether repeated cPAS could be used to increase the plasticity response in old adults. Furthermore, it remains to be determined whether multi-dose cPAS targeted at this parietal-motor circuit can effectively foster plasticity to recover residual motor function after stroke (Goldenkoff et al., 2021; Schulz et al., 2015).

4.6 Conclusion

This study is the first to demonstrate an additive effect of repeated cPAS on the parietal-motor circuit. These findings have implications for understanding how increasing the number of

cPAS applications can amplify effects on cortical excitability, thereby guiding the effective use of cPAS in both experimental and clinical settings. Given the substantial effects of multi-dose cPAS reported here, it would be beneficial to examine its impact on plasticity across the lifespan (Goldenkoff et al., 2021), motor performance (Fiori et al., 2018), motor learning (Reis et al., 2008), and motor recovery after neurological disorders such as stroke (Grefkes et al., 2020; Grefkes & Fink, 2014; Liew et al., 2014; Raffin & Hummel, 2018).

Chapter 5: Altered Motor Excitability Responses After Repeated Paired Associative Stimulation to the Parietal-Motor Pathway in Older Adults

5.1 Abstract

Neuroplasticity associated with motor function can decline across the adult lifespan. The underlying mechanisms are multifactorial and can partly be attributed to decreased cortico-cortical connectivity. We previously showed that repeated spaced cortical paired associative stimulation (cPAS) to the primary motor cortex (M1) and the posterior parietal cortex (PPC) has a dose-dependent effect on motor excitability in young adults. The present study investigated whether aging affects this additive plasticity in older adults. In the multi-dose cPAS condition, three sessions of cPAS were administered with a 50-min interval between each session. In the single-dose cPAS condition, one session of cPAS was followed by two sessions of a control cPAS protocol. We measured motor-evoked potentials (MEPs) before and after each cPAS session. Multi-dose cPAS prevented the suppressive effect on MEPs observed after a single cPAS session. We found no increases in potentiation after repeated spaced cPAS, indicating a reduced additive metaplastic response in older adults. These findings suggest that repeated spaced cPAS may have limited utility in augmenting plasticity induction in older adults.

5.2 Introduction

Neuroplasticity refers to the brain's ability to change the strength of synaptic connections and modify neuronal activity. It contributes to various forms of human behavior, such as learning

new skills, controlling movements, and recovering from brain damage (Cooke & Bliss, 2006; Dayan & Cohen, 2011; Nudo et al., 2001; Sanes & Donoghue, 2000). Over the lifespan, the aging process typically results in a decline in the control of voluntary movement due to changes in cortical excitability, functional connectivity patterns, sensorimotor function, and neuroplasticity regulation (Bhandari et al., 2016; Damoiseaux, 2017; Seidler et al., 2010). These changes can impair skilled movements such as speed, manual dexterity, and skilled motor learning (Carment et al., 2018; Darling et al., 1989; Gorniak et al., 2011; Olafsdottir et al., 2007; Ranganathan et al., 2001; Trewartha et al., 2014). While the mechanisms underlying age-related motor decline are complex and multifactorial (*see* Seidler et al., 2010; Ward, 2006), a pivotal influence is the reduced neuroplastic capacity in older adults (S. Burke & Barnes, 2006; Mahncke et al., 2006). As a result, increasing the neuroplasticity response in older adults could be an effective avenue to enhance motor function in this population.

Non-invasive brain stimulation techniques, like transcranial magnetic stimulation (TMS), can induce, measure, and modify neuroplasticity (Goldenkoff et al., 2020; Hallett, 2007; Hallett et al., 2020). Administering repeated trains of TMS can produce neuroplastic change (Sanes & Donoghue, 2000) by altering synaptic efficacy and inducing long-term potentiation (LTP) in the human motor system (Ziemann et al., 2008). However, the persisting effects of TMS on enduring motor activity change markedly with age. Previous studies assessing the mechanisms of neuroplasticity by TMS show attenuated potentiation-like responses with aging (Freitas et al., 2011; J. F. M. Müller-Dahlhaus et al., 2008; Opie, Vosnakis, et al., 2017; Todd et al., 2010; Turrini et al., 2023). Several factors influence the physiological effects of TMS (Freitas et al., 2013; Jannati et al., 2023; A. Karabanov et al., 2015; Pascual-Leone et al., 2011; Ridding & Ziemann, 2010). A critical factor that affects neuroplasticity modification is metaplasticity, a

phenomenon by which the history of synaptic activity alters a neuron's subsequent response to stimuli (Müller-Dahlhaus and Ziemann, 2015;Abraham and Bear, 1996). Conceptually, this mechanism provides a strategic approach to manipulate neuroplasticity by priming synapses in the target area, with the aim of optimizing synaptic changes induced by stimulation (Kramár et al., 2012). It has been suggested that delivering repeated stimulation at optimal spaced intervals (Kramár et al., 2012; G. Lynch et al., 2013; Smolen et al., 2016) can promote the additive metaplastic mechanisms that cause LTP by increasing repeated excitatory stimulation (Thomson & Sack, 2020).

In agreement with this notion, past studies suggest that repeated spaced stimulation sessions applied to the primary motor cortex (M1) can promote neuroplasticity in young adults (Nettekoven et al., 2014, 2015; Tse et al., 2018; Yu et al., 2020). In further support of this, we recently demonstrated in young adults that multiple sessions of cortical paired associative stimulation (cPAS) to a parietal-motor circuit at optimally spaced intervals can improve synaptic efficiency, leading to a cumulative, dose-dependent increase in potentiation (Goldenkoff et al., under review). Specifically, we found that applying repeated pairs of TMS pulses to the posterior parietal cortex (PPC) and M1 with two coils in three-spaced sessions increased motor cortical excitability after each successive application of cPAS. To date, however, the existence of an additive effect of repeated cPAS on the parietal-motor circuit in older adults has not been tested directly.

In the present study, we used three repeated sessions of cPAS spaced 50 min apart in a parietal-motor circuit involved in skilled motor control to induce LTP-like neuroplasticity in M1. We investigated the dose-response effect on motor cortical excitability after each cPAS session in older adults. Because the parietal-motor connections (Bernard et al., 2013; Goldenkoff et al.,

2021) and neuroplastic capacity (Bhandari et al., 2016; Freitas et al., 2011; J. F. M. Müller-Dahlhaus et al., 2008; Tang et al., 2019; Turrini et al., 2022) are reduced in older adults compared to young adults, we predicted that repeated bouts of stimulation would be needed to induce neuroplasticity changes in older adult brains. We also predicted that repeated sessions of cPAS would have a cumulative effect and influence each other, resulting in greater potentiation than the preceding cPAS session. Based on previous observations of age-related decline in response to TMS (Fathi et al., 2010; Freitas et al., 2011; J. F. M. Müller-Dahlhaus et al., 2008; Opie, Vosnakis, et al., 2017; Todd et al., 2010; Turrini et al., 2023), we predicted the effect would be less pronounced in older adults compared to young adults (Goldenkoff et al., under review).

5.3 Methods

5.3.1 Participants

Fifteen right-handed, healthy older adults (7 females, age: 73.5 ± 2.9 years, range: 69-79 years) participated in the study after completing a health and safety questionnaire to screen for contraindications to TMS and neurological impairments (Keel et al., 2001; Oldfield, 1971; Rossi et al., 2020). We determined the sample size for our study based on our prior research (Goldenkoff et al., under review). Using a previous effect size ($\eta_p^2 = 0.04$) and an estimated dropout rate of 10%, we calculated the minimum required sample size to detect a significant effect at $\alpha < 0.05$ with a power of 0.8 using G*Power 3.1.9.7. All participants provided informed written consent, and the Institutional Review Board at the University of Michigan (IRB#:

HUM00196773) approved experimental procedures in accordance with the Declaration of Helsinki.

5.3.2 Electromyographic (EMG) recordings

EMG was recorded from the relaxed first dorsal interosseous and abductor pollicis brevis muscles in the right hand with 9-mm diameter Ag-AgCl surface electrodes in a tendon-belly arrangement. The EMG signal was amplified (1000x), band-pass filtered (20 Hz - 2.5 kHz; Model 2024F; Intronix Technologies Corporation, Bolton, Canada), digitized at 5 kHz by an analog-to-digital interface (Micro 1401; Cambridge Electronics Design, Cambridge, UK), and recorded by a computer using Signal software (Cambridge Electronics Design, Cambridge, UK) for off-line analysis.

5.3.3 Transcranial magnetic stimulation (TMS)

A Magstim 200^2 stimulator with a figure-8 coil (D70^2, 7 cm diameter) was used to assess motor cortical excitability by eliciting motor evoked potentials (MEPs) in the targeted muscles from M1(Magstim, Whitland, UK). The coil was placed tangential to the scalp and at a 45° angle from the midsagittal line to target the left M1. The placement of the coil was adjusted to the location where the single-pulse TMS produced the largest MEP from the targeted muscles of the right hand. TMS intensity was set at the lowest intensity needed to elicit MEP amplitudes of ~1 mV in at least five out of ten trials in the relaxed hand muscles for each subject (mean and SD: 49.5 ± 11.9% MSO). The peak-to-peak amplitude of the MEPs (mV) occurring between 10 and

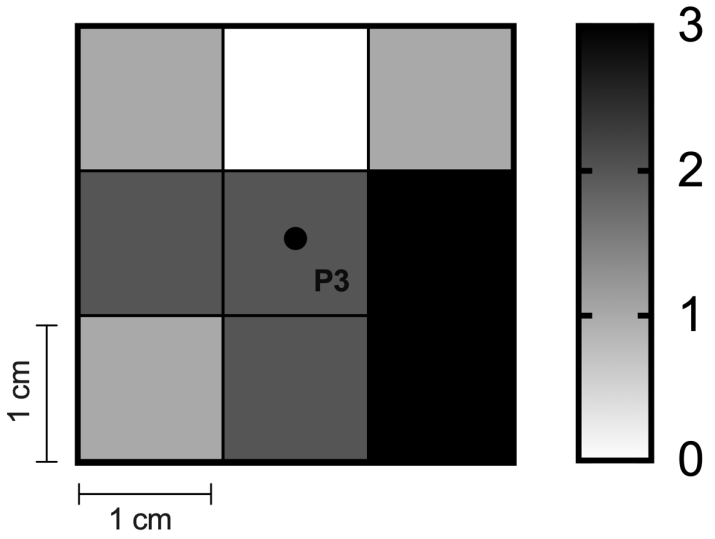

Figure 5-1 Heat map indicating the area relative to P3 that we targeted as the PPC 'scalp hotspot' for each participant. The target was determined using a dual-site TMS grid search targeting method for personalized functional stimulation of the grasping motor network described previously (Goldenkoff et al., 2023; Goldenkoff et al., *under review*). Briefly, we created a 3x3 rectangular search grid centered on P3 using Brainsight stereotactic software. While participants were performing a simple reach-and-grasp task, we delivered paired conditioning-test pulses to each grid location and M1 during the planning phase of the movement. The test stimulus pulse to M1 was adjusted to elicit an MEP of 1mV from the right hand. Ten conditioning stimuli were applied randomly at each grid position with a 5ms interstimulus interval. The PPC stimulation target was selected as the point on the grid where CS consistently elicited the largest MEP from the contralateral muscles of the right (response) hand in three of five consecutive trials compared to other grid positions (MEPs >1.2 mV).

50 ms after the TMS pulse was measured for each trial to quantify motor cortical excitability. Forty-eight MEPs were recorded for each measurement. The same TMS intensity was used to determine changes in LTP-like neuroplasticity in M1 after each cPAS cortical paired associative stimulation session.

5.3.4 Cortical paired associative stimulation

Repetitive pairs of cortical stimuli were delivered with a figure-8 coil (D50 Alpha B.I., 5 cm diameter) to PPC and a figure-8 coil (D70^2, 7 cm diameter) to M1, each connected to a Magstim 200^2 stimulator. Individualized left PPC locations were determined using a function-based dual-coil TMS technique described previously (see Goldenkoff et al., 2020; Goldenkoff et

al., *under review* for details). **Figure 5-1** displays a heat map of participants at the selected parietal grid position. The pulse intensity for the PPC coil was set at 90% of the RMT (42.8 ± 10.4 % MSO). The M1 coil was set to a pulse intensity that elicited an MEP of approximately 1 mV in the target muscle (49.5 ± 11.9% MSO). cPAS protocol consists of 100 pairs of monophasic waveform pulses at 0.2 Hz for a total of ~8.3 min (Goldenkoff et al., under review; Goldenkoff et al., 2020; Koch et al., 2013). The interpulse interval (IPI) of the paired pulses differs for the cPAS conditions. For the Hebbian spike-timing-dependent plasticity (STDP) protocol, PPC stimulation preceded M1 stimulation by 5 ms (Goldenkoff et al., under review; Goldenkoff et al., 2020; Koch et al., 2013). For the control cPAS protocol, PPC stimulation preceded M1 stimulation by 500 ms to control for timing contiguity for paired associative plasticity in the parietal-motor circuit (Johnen et al., 2015; Koch et al., 2013; Goldenkoff et al., under review). A frameless stereotactic system (Brainsight, Rogue Research Inc., Montreal, Canada) was used to accurately place both coils throughout the experiment.

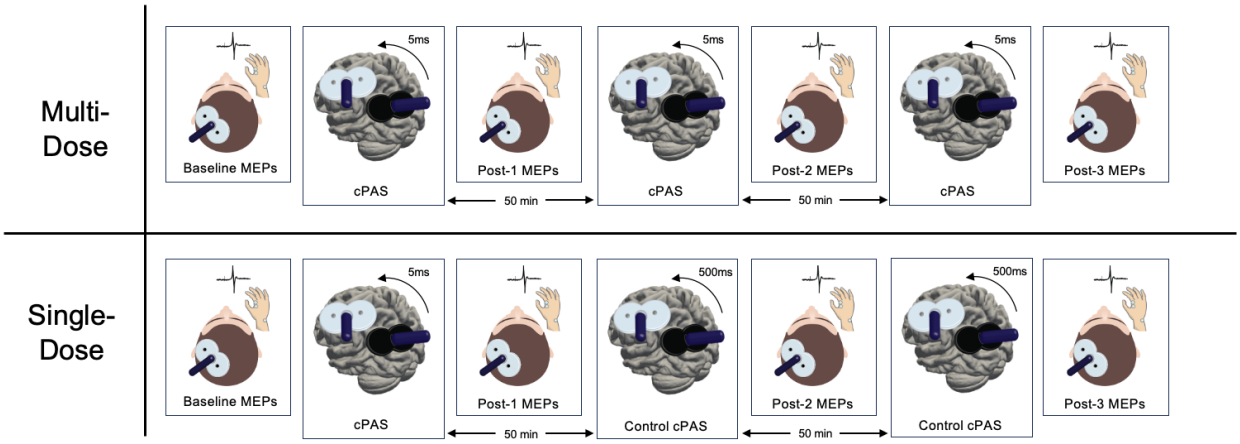

Figure 5-2 Experimental design. 48 motor-evoked potentials (MEPs) were collected before (baseline) and after three consecutive cPAS sessions spaced 50 min apart (Post-1, Post-2, and Post-3). Multi-dose stimulation (three bouts of Hebbian-like cPAS with 5ms interstimulus interval between PPC and M1 stimulation) and single-dose control (one Hebbian-like cPAS followed by two control cPAS sessions where PPC was stimulated 500 ms prior to M1) conditions were administered on separate days and counterbalanced. During both cPAS and control cPAS, the pairs of cortical stimuli were delivered at a frequency of 0.2 Hz (once every 5 s) and repeated for 100 trials (~8.3 min).

5.3.5 Experimental Design

We used similar methods from our previous study in young adults (Goldenkoff et al., under review*)*. **Figure 5-2** depicts the experimental design. The experiment compared two interventional protocols using a within-subjects, counter-balanced protocol over two visits that were conducted an average of 8.5 ± 8.6days apart. The multi-dose cPAS condition tested the effects of three serial sessions of a Hebbian-like cPAS protocol where PPC stimulation preceded M1 stimulation by 5ms. The timing of this protocol was designed to strengthen the connections between PPC and M1 via LTP-like mechanisms and the principles of spike-timing-dependent plasticity (Koch et al., 2013). In the single-cPAS condition, participants underwent one session of cPAS with a 5ms interstimulus interval and two sessions of a non-Hebbian (control) cPAS protocol where PPC was stimulated 500 ms prior to M1. The cPAS control condition delivered the same number of pulses at the same frequency but prevented subsequent LTP-like plasticity effects resulting from STDP. For each stimulation protocol, one hundred pulse pairs were delivered at 0.2 Hz for a total of 8.3 min. Each cPAS delivery was followed by a 50 min intersession interval to maximize the additive effect of stimulation on neuroplasticity, as per the principles of spaced learning theory (Smolen et al., 2016). We investigated the responses to cPAS by measuring the amplitude of MEPs elicited by single-pulse TMS over M1 at baseline and after each cPAS session (Post-1, Post-2, Post-3 time points). The same stimulation locations and intensities for M1 and PPC were used for each participant for both the multi-dose and single-dose conditions across both days.

5.3.6 Statistical Analysis

The data were analyzed using R Statistical Software (v4.2.3; R Core Team 2023) To model the effect of dose condition and time on MEP amplitude, we fit a Bayesian hierarchical

generalized linear model (GLM). As MEP amplitudes are strictly positive with positive skew, we specified a Gamma likelihood function and a log-link function. The model included fixed effects of condition (single- or multi-dose), time point (Baseline, Post-1, Post-2, Post-3), and their interaction. We included all individual MEP amplitudes from each trial for every participant in the model. The model additionally allowed intercepts and slopes to vary by subject. A posterior distribution over possible parameter values was sampled using Markov chain Monte Carlo (MCMC) sampling implemented in rstan (Stan Development Team, 2023; Version 2.32.3) via the brms package (Bürkner, 2017, 2018; Version 2.20.4).

$$MEP_i \sim Gamma(\mu_i, shape)$$

$$\log(\mu_i) = \alpha_s + \beta_{Condition} Condition_i + \beta_s Time_i + \beta_{Condition \times Time} Condition_i Time_i$$

$$\alpha_s \sim \alpha + \sigma_\alpha z_{s\alpha}$$

$$\beta_s \sim \beta_{Time} + \sigma_\beta z_{s\beta}$$

$$\alpha \sim Student\_t(3, -0.1, 2.5)$$

$$\sigma_\alpha \sim Student\_t(3, 0, 2.5)$$

$$\sigma_\beta \sim Student\_t(3, 0, 2.5)$$

$$z_{s\alpha} \sim Normal(0,1)$$

$$z_{s\beta} \sim Normal(0,1)$$

$$\beta \sim Normal(0,1)$$

$$shape \sim Gamma(1, 0.01)$$

where α_s denotes a subject-specific intercept and $\beta_{Condition}$, β_{Time}, and $\beta_{Condition \times Time}$ denote parameter estimates for the effect of dose condition, time, and their interaction. We specified a weakly informative prior distribution for the fixed effects (β) with a mean of 0 and a standard deviation of 1 (i.e., N(0,1)). As regression coefficients for a Gamma likelihood GLM with a log

link function are interpreted as multiplicative factors rather than slopes, an N(0,1) prior indicates that *a priori,* we believe that a change in factor level (e.g. Baseline to Post-3) is associated with an increase or decrease in MEP amplitude by a factor between 1 and 7.1 (i.e., [exp(0), exp(1.96)]). The brms package implements a non-centered parameterization for random effects and random slopes (Betancourt & Girolami, 2015) which for our model parameterizes subject-specific intercepts (α_s, β_s) using an overall intercept (random intercept: α, random slope: β_{Time}), subject-specific offsets $(z_{s\alpha}, z_{s\beta})$, and scaling parameters $(\sigma_\alpha, \sigma_\beta)$. This parameterization decorrelates the sampling of random effects from high-order hyperparameters allowing for improved sampling efficiency (Betancourt & Girolami, 2015). Default prior specifications from the brms package were used for parameters associated with subject-specific intercepts $(\alpha, z_{s\alpha}, z_{s\beta}, \sigma_\alpha,$ and $\sigma_\beta)$, as well as the residual shape parameter $(shape)$. By default, the location parameter for α was set to $median(log(MEP))$ and the scale parameter for α and σ was set to $max(mad(MEP), 2.5)$ where mad represents the median absolute difference. We selected our model after the fitted model with both random intercepts and slopes had a lower Watanabe–Akaike information criterion than a model fit separately with only random intercepts.

We ran four separate chains with 7000 iterations each. The first 2000 iterations were discarded as warm-ups. R-hat values were all very close to 1 (R-hat ≤ 1.001), and the effective sample size exceeded 5000 for all parameters indicating that MCMC chains had converged, and minimal autocorrelation was in the sampling. Posterior predictive checks confirmed that distributional assumptions were met and that the specified model could generate data that resembled the actual data. For each parameter in the model, we report the median, 95% highest density interval (HDI), and the probability of direction (pd). The HDI represents the interval for which all values within that interval have a higher probability density than points outside. Due to

the log-link function, we exponentiate the median and 95% HDI values for reporting so that values represent multiplicative factors on the original response scale (e.g., a one-unit change in x is associated with an increase in MEP amplitude by a factor of exp(0.1) = 1.11). pd is an index of effect existence (ranging from 50% to 100%), representing the probability that an effect goes in a particular direction (e.g., effect x has a 99% probability of being negative). Note that pd represents the probability that the effect is negative or positive before exponentiation and the likelihood that the effect is less than or greater than one after exponentiation. We consider a pd greater than 95% to be strong evidence for an effect, a pd between 80% and 95% to provide some proof of an effect, and a pd less than 80% to indicate limited evidence for an effect.

To examine the effect of dose condition for each time point individually, we took draws from the expectation of the posterior predictive distribution (μ_i in the above model formula) for each stimulation condition and time point. Then, we subtracted the extracted values for the earlier time point for each condition from those of a later time point (e.g. Post-3 – Post-1), generating a difference distribution. We report each comparison's median, 95% HDI, and pd.

5.4 Results

To investigate the effect of number of cPAS doses delivered on MEP amplitude, we fit a Bayesian hierarchical gamma GLM to MEP amplitudes with fixed effects of dose condition (single- and multi-dose), time point (Baseline, Post-1, Post-2, Post-3), and their interaction. Across both conditions, there was strong evidence for MEP amplitude differences at Baseline (multi-dose – single-dose, Median: -0.07, 95% HDI [-0.14, -0.01], pd = 0.95). However, this group difference decreases and is reduced to merely some evidence of a difference after each group receives its initial dose of cPAS, as assessed at the Post-1 time point (Median: -0.03, 95%

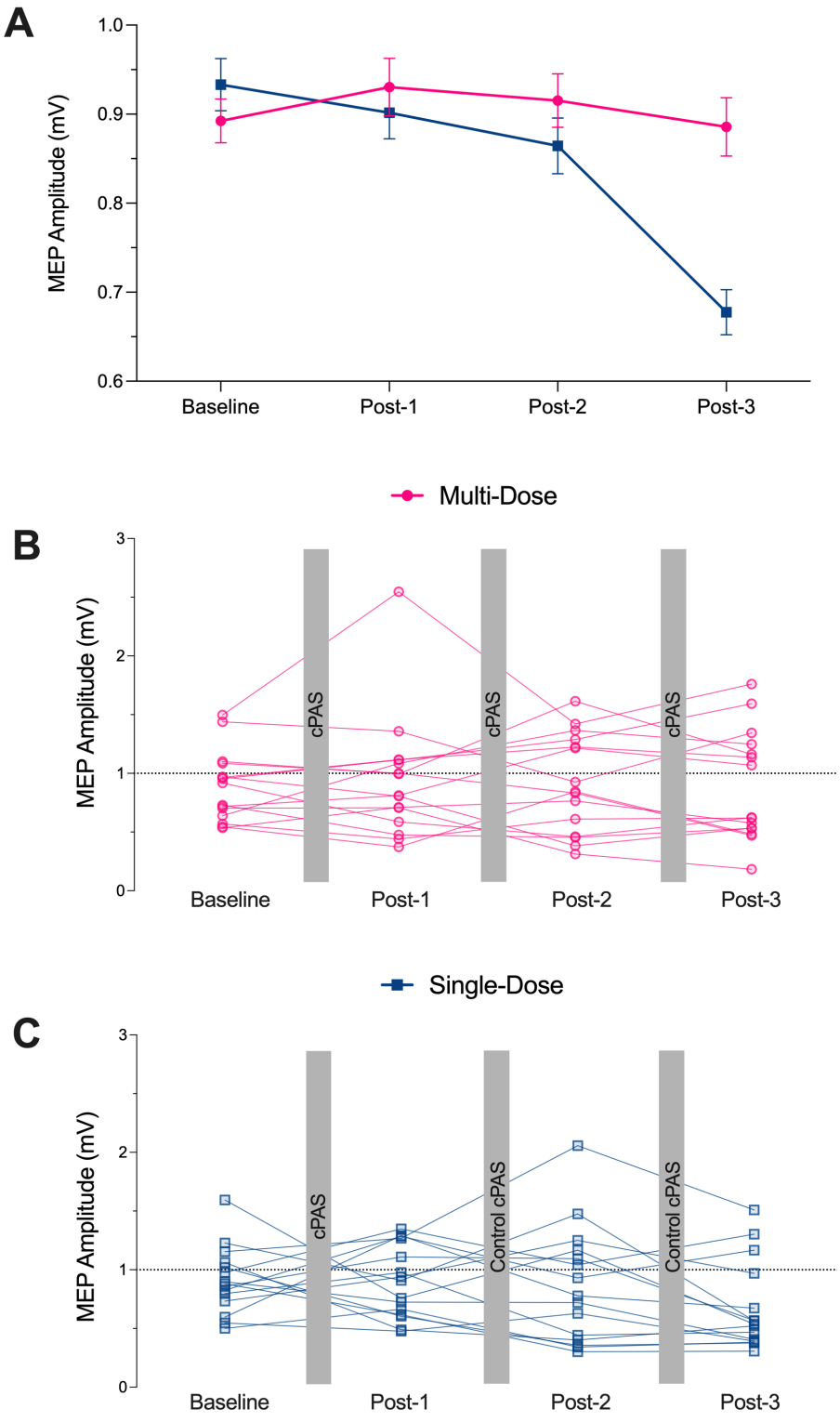

Figure 5-3 Group and individual motor excitability measures at each timepoint. (**A**) motor-evoked potential (MEP) amplitude across participants for the multi-dose (pink circles) and single-dose (blue squares) experimental conditions. Post-1 to Post-2 and Post-2 to Post-3 time points indicate an increased cumulative dose effect on cortical paired associative stimulation (cPAS) induced motor potentiation. Error bars represent the within-subject standard error of the mean (SEM) (Morey and Rouder, 2022). Open symbols and interconnecting lines represent individual mean MEP amplitudes for the (**B**) multi-dose and (C) single-dose conditions.

HDI [-0.11, 0.04], pd = 0.80). Once the groups differed in their cPAS dosages represented in two additional active or control cPAS doses, we found strong evidence that MEP amplitudes were greater for the multi-dose condition than the single-dose condition during both the Post-2 (Median: 0.09, 95% HDI [0.01, 0.17], pd = 0.99) and Post-3 (Median: 0.19, 95% HDI [0.11, 0.27], pd = 1.00) time points (**Figure 5-3A**). The enhanced effect which the multi-dose condition has on MEPs relative to the control single-dose condition increases over time. Relative to the single-dose condition, MEP amplitudes in the multi-dose condition were 21.7% and 46.2% larger at Post-2 and Post-3 time points, respectively.

Within the multi-dose condition, we found no evidence of MEP amplitude changes from baseline to Post-3. Between Baseline and Post-1 time points, MEP amplitudes increased by 2.4% (Median: 0.00, 95% HDI [-0.14, 0.16], pd = 0.51, for all comparisons, see **Table 5-1)**. From

Stimulation Condition	Time-Point	Median	95% HDI	pd (%)
Single-dose	**Post-3 – Baseline**	**-0.33 mV**	**-0.52 – -0.14**	**100%**
	Post-2 – Baseline	-0.18 mV	-0.40 – 0.06	93%
	Post-1 – Baseline	-0.03 mV	-0.13 – 0.12	66%
	Post-3 – Post-2	**-0.16 mV**	**-0.31 – -0.01**	**99%**
	Post-3 – Post-1	**-0.30 mV**	**-0.43 – -0.17**	**100%**
	Post-2 – Post-1	-0.14 mV	-0.36 – 0.08	91%
Multi-dose	Post-3 – Baseline	-0.09 mV	-0.29 – 0.14	78%
	Post-2 – Baseline	-0.02 mV	-0.26 – 0.22	59%
	Post-1 – Baseline	0.00 mV	-0.14 – 0.16	51%
	Post-3 – Post-2	-0.06 mV	-0.23 – 0.10	77%
	Post-3 – Post-1	-0.09 mV	-0.23 – 0.09	85%
	Post-2 – Post-1	-0.03 mV	-0.24 – 0.22	60%
Multi-dose – Single-dose	**Baseline**	**-0.07 mV**	**-0.14 – 0.01**	**95%**
	Post-1	-0.03 mV	-0.11 – 0.04	80%
	Post-2	**0.09 mV**	**0.01 – 0.17**	**99%**
	Post-3	**0.19 mV**	**0.11 – 0.27**	**100%**

Table 5-1 Posterior predictive summary for the effect of stimulation dose on MEP amplitude across time points. Bolded values indicate pd > 95%. Abbreviations: HDI, highest density interval; pd, probability of direction.

Post-1 to Post-2, MEP amplitudes decreased by 3.8% (Median: -0.03, 95% HDI [-0.24, 0.22], pd = 0.60). Between Post-2 and Post-3 time points, MEP amplitudes decreased by 2.4% (Median: -0.06, 95% HDI [-0.23, 0.10], pd = 0.77. There is no evidence for a significant difference in MEP amplitudes across time for the multi-dose condition indicating no induced potentiation occurred (**Figure 5-3B**).

Within the single-dose condition, we found that excitability was initially maintained and then decreased during the later time points. There was limited evidence for MEP changes between Baseline and Post-1 as MEP amplitudes decreased by 7.4% (Median: -0.03, 95% HDI [-0.13, 0.12], pd = 0.66, for all comparisons see **Table 5-1)**. From Post-1 to Post-2, there was some evidence for MEP differences as amplitudes decreased by 2.0% (Median: -0.14, 95% HDI [-0.36, 0.08], pd = 0.91). We found strong evidence for a reduction in MEP from Post-2 to Post-3 time points; MEP amplitudes decreased by 25.7% (Median: -0.16, 95% HDI [-0.31, -0.01], pd = 0.99 (**Figure 5-3C**).

5.5 Discussion

This study investigated the effect of multiple cPAS sessions on the motor cortical excitability of older adults. We found that relative to the single-dose condition where participants received one Hebbian-like cPAS followed by two bouts of control, non-Hebbian-like cPAS, MEP amplitudes increased over time in the multi-dose condition where participants received three bouts of Hebbian-like cPAS spaced 50 min apart. After the single-dose condition, we observed a reduction in MEP amplitudes at the time points following the two control cPAS applications in older adults, similar to our previous study in young adults (Goldenkoff et al., under review). This indicates that multiple bouts of cPAS stimulation counter the MEP-suppression effect that occurs in the hours following a single bout of cPAS. However, unlike the

cumulative increase in motor excitability following the multi-dose condition in young adults (Goldenkoff et al., under review), the size of the MEP amplitudes in the multi-dose condition remained stable after repeated spaced cPAS in older adults. This indicates an altered metaplasticity response to the cPAS priming stimulation protocol in older adults.

The finding that there was no long-term facilitation of motor activity in the multi-dose condition aligns with previous findings of reduced STDP-like synaptic plasticity in older adults (Bhandari et al., 2016; Turrini et al., 2023), suggesting a reduced ability for synapses to adapt in response to external stimuli in older adults (Cai et al., 2014; Goldsworthy et al., 2020; Porto et al., 2015; Todd et al., 2010). rTMS and paired associative stimulation (PAS) studies, have shown that both LTP- and LTD-like plasticity decreases with aging in the motor network (Fathi et al., 2010; Freitas et al., 2013; Todd et al., 2010). Notably, older adults show less response to facilitatory rTMS protocol primed by prior stimulation compared to young adults. Our findings align with findings showing an LTP-like PAS priming protocol administered prior to an additional LTP-like PAS protocol increased motor plasticity in younger, but not older adults.(Opie, Post, et al., 2017). Additionally, apart from the age-related changes in neuroplasticity mechanisms, the effects of rTMS induced in older adults might be distinct from those in younger adults due to age-related reductions in brain volume, alterations in the integrity of gray and white matter, and variations in the activity levels of neurotransmitters and other brain biochemicals (Andrews-Hanna et al., 2007; Farokhian et al., 2017; Greenwood, 2007; Seidler et al., 2010).

A limitation of this study was that we only tested one experimental stimulation protocol. It is possible that changing some parameters of the cPAS delivery (e.g., number of doses, intersession timing of stimulation, and targeted brain areas) would induce lasting motor

excitability facilitation in older adults. Although our findings indicate that three sessions of cPAS failed to induce changes in plasticity among older adults, it is possible that multiple days of rTMS or higher doses may have a lasting effect on cortical excitability. rTMS treatments for major depressive disorder are effective in adults over 65 years of age but require more treatment days and have a slower response compared to younger adults (Cotovio et al., 2022). Future studies should explore these dosing rTMS parameters in older adults beyond the three-hour time frame studied here.

Further research is necessary to better understand factors that underly the optimal interval between delivery of multiple cPAS sessions. While we found no significant increase in MEP amplitudes after repeated cPAS spaced 50 minutes apart, evidence suggests the timing between rTMS is a crucial determinant of plasticity induction in older adults (Sidhu et al., 2017). Adjusting the interpulse- or intersession-interval or intensity of stimulation may be more beneficial for older adults and patient populations. We previously found reduced facilitation in parietal-motor connections in older adults compared to young adults (Goldenkoff et al., 2021). It is plausible that these age-related changes to the parietal-motor pathways may have made cPAS less effective at inducing neuroplasticity in older adults (Bernard et al., 2013; Goldenkoff et al., 2021). Additionally, we and others have found that older adults have higher motor thresholds than younger adults and therefore may require higher intensities to activate neuronal activity in the motor network (Goldenkoff et al., 2021; McGinley et al., 2010; Sale et al., 2016).

Different stimulation target areas may better activate the motor control network within older adults. It is well documented that to carry out complex motor tasks, older adults often rely on compensatory mechanisms and activate additional cortical and subcortical brain areas to manage increased task demands and maintain adequate functional performance (Cabeza et al.,

2018; Davis et al., 2008; Seidler et al., 2010). Consequently, it is possible that PPC is not an ideal rTMS target for older adults to induce lasting changes to neuroplasticity and improve motor function (Greenwood, 2007). Additional research is needed to determine ideal stimulation parameters for healthy older adults and those with neuromotor impairments (Iriarte & George, 2018).

While it is apparent that repeated, spaced doses of Hebbian-like cPAS prevented the inhibitory effects that occur in the hours following a single dose of Hebbian-like cPAS, we found no evidence of a cumulative, dose-dependent effect on motor excitability in older adults. Our findings suggest the reduced capacity for augmenting neuroplasticity in older adults with repeated spaced cPAS in older adults. An important extension of the current study will be to assess whether priming cPAS translates to those with neurological disorders like stroke and Parkinson disease.

Chapter 6: Cerebellar Activity Influences Distal Cortical Physiology and Synaptic Plasticity in a Human Parietal-Motor Pathway Involved in Actions

6.1 Abstract

Voluntary movement control depends on plasticity in several interconnected brain regions, including the cerebellum (CB), primary motor cortex (M1), and posterior parietal cortex (PPC). While it is well established that the effects of repetitive transcranial magnetic stimulation propagate beyond the stimulation site, the impact of cerebellar stimulation on neural activity within interconnected parietal and motor areas remains largely unknown. We evaluated how intermittent theta burst stimulation (iTBS) affects a subsequent Hebbian-like cortical paired associative stimulation (cPAS) to PPC and M1. Using a within-subjects design, we administered four different single-session stimulation conditions to the CB and parietal-motor pathway of the motor network and measured the aftereffects on plasticity. We administered iTBS to the right cerebellum or visual cortex, followed by cPAS of a parietal-motor circuit. In a subset of participants, we performed two additional control conditions to assess the effect of CB iTBS alone and Hebbian-like cPAS of the PPC-M1 circuit alone. We evaluated motor-evoked potentials (MEPs) using single-pulse TMS as a measure of motor cortical excitability before and after each plasticity induction protocol. Cerebellar iTBS reduced the plasticity induction cPAS of the parietal-motor circuit, as evidenced by the decrease in MEPs. These responses were selective, as there were no activity decreases that occurred with control experiments. These findings suggest that CB activity can modify distal neural activity in a network-connected parietal-motor

circuit through heterosynaptic metaplasticity, which could be useful for neuromodulatory treatments of sensorimotor disorders characterized by aberrant plasticity.

6.2 Introduction

Cerebellar circuitry plays a crucial role in human motor control, learning, and memory, making it a promising target for neuromodulation (De Zeeuw & Ten Brinke, 2015; Grimaldi et al., 2014; Ito, 2000; Strick et al., 2009). The cerebellum (CB) receives input about motor plans and movements from the cortex (Houk & Wise, 1995; Kishore et al., 2014). Outputs from the CB inhibit motor output in the primary motor cortex (M1; (Pinto & Chen, 2001; Ugawa et al., 1995), enabling precise coordination of motor processes. Tract tracing studies in non-human primates suggest the CB interacts with other cortical regions, including the posterior parietal cortex (PPC), premotor cortex, and prefrontal cortex (Kelly & Strick, 2003; Prevosto et al., 2010). Neuroimaging studies on humans also provide evidence of interactions between the CB and the cortex (Brissenden et al., 2016; Buckner et al., 2011; Guell et al., 2018; Halko et al., 2014). The CB is connected to the parietal and frontal lobes, forming circuits for motor control. In the parietal-frontal network, the PPC plays a central role in the planning and control of goal-directed actions (Vesia et al., 2017; Vesia & Crawford, 2012; Vesia & Davare, 2011). Current theories suggest that connections between the CB and PPC are critical for accurate voluntary movements (Shadmehr & Krakauer, 2008). It is, therefore, conceivable that modulating cerebellar activity influences neural activity in downstream parietal-frontal circuits linked to motor control and adaptation (Caligiore et al., 2017).

Neuromodulation devices can manipulate brain activity to better understand specific motor circuit interactions (Hallett, 2007). Repetitive transcranial magnetic stimulation (TMS) is a type

of non-invasive neuromodulation that can directly change neural activity at the stimulation site, indirectly affecting downstream functionally connected brain regions (Siebner et al., 2009). For instance, neuroimaging research suggests that cerebellar theta burst stimulation, a form of repetitive TMS, can alter cortical communication changes in targeted cognitive and motor brain networks (Halko et al., 2014; Rastogi et al., 2017). Likewise, studies using TMS-evoked electroencephalography (EEG) potentials have shown that stimulating the CB can modify cortical activity in the parietal-motor circuit involved in motor control (Casula, Pellicciari, Picazio, et al., 2016). Although it is reasonable to hypothesize that exogenous perturbation to CB should influence distributed functional interactions and impact distal cortical physiology in motor control circuits, the idea has yet to be tested directly.

Conceptually, understanding how exogenous perturbations to cerebellar activity can affect downstream plasticity mechanisms of interconnected cortical areas governing voluntary control of skilled movement in the motor system may be used to tease apart its function. Going a step further, this inquiry could be used to develop neuromodulatory therapies to alleviate aberrant brain dynamics in neurological disorders such as stroke and Parkinson's disease (Cooperrider et al., 2020; Di Pino et al., 2014; Koch et al., 2019; Martinez-Nunez et al., 2023). To date, the effect of targeted cerebellar TMS on the collective state of neural activity and subsequent synaptic plasticity mechanisms of interconnected cortical areas in the functional network enabling goal-directed action is currently unclear.

In the current study, we examined whether cerebellar stimulation could exert a neuromodulatory effect on distant activity in a connected parietal-motor pathway involved in skilled hand action. To accomplish this, we used a modulate-and-measure approach to evaluate a targeted downstream parietal-motor plasticity response to cerebellar stimulation. We used two

repetitive TMS methods to induce long-term potentiation-like effects (LTP). The first method used intermittent theta burst stimulation (iTBS) over the CB (Huang et al., 2005). The second method, cortical-cortical paired associative stimulation (cPAS), used two coils to modulate inter-regional coupling in the parietal-motor circuit. cPAS protocols are based on the Hebbian theory of synaptic plasticity (Hebb, 1949; Markram et al., 2011) and spike-timing-dependent plasticity (Chao et al., 2015; Goldenkoff et al., 2020; Koch et al., 2013). We evaluated motor-evoked potentials (MEPs) using single-pulse TMS as a measure of motor cortical excitability before and after each plasticity induction protocol (Chen, 2000; Chen & Udupa, 2009). Given induction of cerebellar plasticity by means of iTBS can modulate the neural activity of the interconnected parietal-frontal network in the contralateral hemisphere (Casula, Pellicciari, Picazio, et al., 2016; Koch et al., 2019), we hypothesized that applying iTBS to the CB before cPAS would prevent the Hebbian plasticity effects of cPAS-induced potentiation by repeated activation of the short-latency connection between the PPC and M1.

6.3 Materials and Methods

6.3.1 Participants

Fourteen adults (10 females, ages 19-23 years) participated in the study after providing written, informed consent. Participants were screened for contraindications to MRI and TMS using standard MRI and TMS safety questionnaires (Keel et al., 2001; Rossi et al., 2011). All procedures were approved by the University of Michigan Institutional Review Board (HUM00157197 and HUM00129313) in accordance with the Declaration of Helsinki.

6.3.2 Structural MRI data acquisition

Whole-brain T1-weighted scans were acquired for all participants to define individualized TMS targets. MR data were acquired with a 3T GE scanner (MR 750) with a 32-channel head coil. Functional data for resting-state scans were obtained using a 1-shot multi-band T2*-weighted echo-planar imaging (EPI) sequence sensitive to blood oxygenation level-dependent (BOLD) contrast (TR = 1200 msec, TE = 30 msec, flip angle = 70^0, 21 cm field of view, in-plane resolution = 2.4 mm × 2.4 mm, MB acceleration = 3). Each functional volume contained 51 contiguous 2.5 mm-thick axial slices separated by a 0 mm inter-slice gap acquired in an interleaved manner.

6.3.3 Resting-state fMRI data and pre-processing

Resting-state fMRI data were preprocessed through a pipeline to correct artifacts, minimize physiological noise, and standardize and align the data for analysis. This pipeline involved slice-time correcting the data to reflect the same temporal instance and realigning all functional echo-planar imaging (EPI) volumes to the one with the minimum outlier fraction to correct for motion. We then normalized the data to the MNI152 template using a non-linear warp. The RETROICOR method (Jo et al., 2010) was used to regress noise from physiological signals such as heart-rate and respiration. We then shrank large spikes in the time series using AFNI's 3dDespike tool. We then performed nuisance regression of head-motion (3 translation and 3 rotation parameters along with their temporal derivatives), cerebrospinal fluid (CSF), and white matter signals (Glover et al., 2000; Jo et al., 2010; Van Dijk et al., 2010). Regressors associated with large motion-related spikes (framewise displacement > 0.2mm) were also included in the model (Satterthwaite et al., 2013). Functional data were then smoothed with a 4mm full width at half maximum (FWHM) kernel. No global signal regression (GSR) or

independent component analysis (ICA) denoising was applied. The output of these preprocessing steps was a residual time series used in seed-to-voxel correlation analyses (*see below*).

6.3.4 Transcranial magnetic stimulation targets

TMS targets were defined for each participant using anatomical and resting-state scans. For the PPC stimulation target, we first identified the hand knob of the left precentral gyrus on the axial and sagittal slices of the anatomical scans (Yousry et al., 1997; **Figure 6-1**, left panel). We then created a spherical region of interest (ROI) with a radius of 5mm centered on this point. From this ROI, we extracted the mean preprocessed resting-state time series. This time series was used to calculate whole-brain seed-to-voxel Pearson correlations using AFNI's 3dTcorr1D command. We next set a relatively lenient threshold of $p < 0.001$ on the resulting M1 correlation

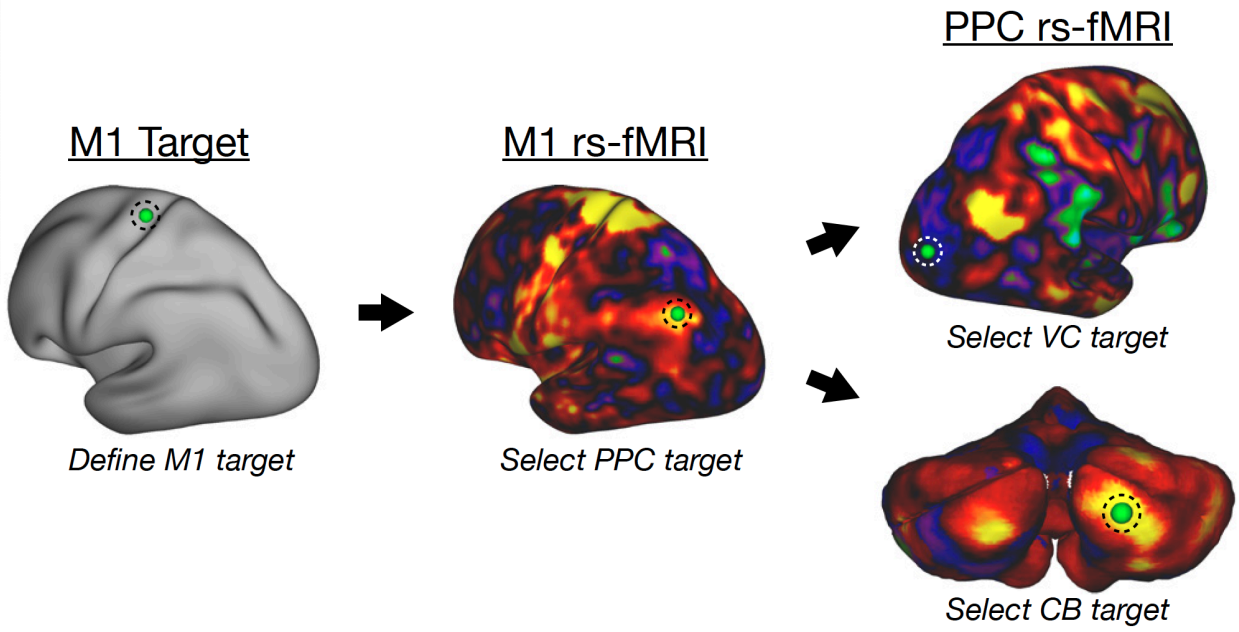

Figure 6-1 Transcranial magnetic stimulation (TMS) target selection procedure. The primary motor cortex (M1) targets were selected based on the amplitude of motor-evoked potential (MEP). A resting-state fMRI analysis was then performed with the hand knob area as a seed. The maximum correlation with the parietal lobe was selected as our (posterior parietal cortex (PPC) target. A seed was then defined for this PPC area, and an additional resting-state fMRI analysis was performed. A right hemisphere cerebellar (CB) target was selected based on maximal correlation with the PPC seed. A visual cortex (VC) target with the lowest absolute correlation with PPC was selected. Correlation maps and targets are depicted on the template (fsLR) surface for illustration purposes only. Actual targets were selected in Brainsight using native T1 space correlation maps.

map and masked out all clusters smaller than 40 contiguous voxels. The PPC stimulation site was defined as the surviving cluster that was most strongly connected with M1 in the region of the left parietal cortex (**Figure 6-1**, middle panel). A seed was then defined for this PPC area, and an additional resting-state fMRI analysis was performed. A right hemisphere cerebellar (CB) target was selected based on maximal correlation with the PPC seed using a frameless stereotactic neuronavigation system (Brainsight 2; Rogue Research Inc., Montreal, Canada). A visual cortex (VC) target with the lowest absolute correlation with PPC was selected as an active control site (**Figure 6-1**, right panel). Stimulation at this site controls for the non-specific effects of stimulation (cutaneous sensation, peripheral nerve sensation, induced current in the brain, etc.) The high-resolution T1-weighted scan for each participant was imported into Brainsight and co-registered to digitize anatomical landmarks for TMS coil placement during the experiment.

6.3.5 Transcranial magnetic stimulation

MEPs elicited by a single TMS pulse with a monophasic waveform, were recorded from the relaxed first dorsal interosseous and abductor pollicis brevis muscle in the right hand with Ag-AgCl surface electrodes in a tendon-belly arrangement. The electromyographic signal was amplified (1000x), band-pass filtered (20 Hz - 2.5 kHz; Model 2024F; Intronix Technologies Corporation, Bolton, Ontario, Canada), digitized at 5 kHz by an analog-to-digital interface (Micro 1401; Cambridge Electronics Design, Cambridge, UK), and recorded by a computer using Signal software (version 7; Cambridge Electronics Design, Cambridge, UK) for off-line analysis.

6.3.5.1 Intermittent theta burst stimulation (iTBS)

iTBS was delivered using a figure-8 coil with static cooling (MagPro MCF-B70) attached to a MagPro X-100 stimulator with MagOption (MagVenture Inc., Atlanta, GA). iTBS consisted of 10 bursts of high-frequency stimulation (a 2 s train of 3 biphasic waveform pulses at 50 Hz repeated every 200 ms) repeated every 10 s for a total of 190 s (600 pulses) (Huang et al., 2005). The iTBS coil was held tangentially to the scalp for the CB and VC stimulation with the handle directed upward at 90°. The coil was held close to the scalp for sham stimulation but angled away so no current was induced in the brain (Koch, Esposito, et al., 2020). Each participant's active motor threshold (AMT) was determined at the beginning of the experiment, defined as the minimum intensity required to produce MEPs of $\geqq 200\mu V$ in at least 5 of 10 trials while the participant maintained a 20% maximum contraction in the targeted right-hand muscle (Huang et al., 2005). This yielded a mean percentage of maximum stimulator output (MSO) intensity of 42 ± 6 across participants. To minimize participant discomfort and decrease the inter-individual difference in stimulation-induced effects in the underlying brain target, we opted to use a fixed MSO intensity of 35%, which is similar to standard iTBS protocols with 80% AMT (Huang et al., 2005) and within consensus recommendations for safety (Oberman et al., 2011; Rossi et al., 2020).

6.3.5.2 Cortical paired associative stimulation (cPAS)

Repetitive low-frequency pairs of cortical stimuli were delivered with a small figure-8 coil (D50 Alpha B.I., 5 cm diameter) to PPC and another figure-8 coil (D70^2, 7 cm diameter) to M1, each connected to a Magstim 200^2 stimulator (Magstim, Whitland, UK). cPAS consisted of 100 pairs of monophasic waveform pulses at 0.2 Hz for ~8.3 min (Goldenkoff et al., 2020; Koch et al., 2013). Coil 1 was positioned over the left PPC at a 10º angle to the midline, and coil 2 was

placed over the optimal scalp position for activation of the hand area of left M1 at a 45º angle to the midline, inducing a current in the posterior-anterior direction in the underlying cortical tissue. The interpulse interval (IPI) of the paired pulses differed for experimental conditions: PPC stimulation preceded M1 stimulation by 5 ms (Hebbian-like plasticity induction protocol) or by 500 ms (control for timing contiguity for paired associative plasticity in parietal-motor pathway) (Johnen et al., 2015; Koch et al., 2013). Measures of motor excitability for each participant were determined for the individual coils at the beginning of the experiment. Resting motor threshold (RMT) was defined as the minimum intensity required to produce MEPs of $\geqq 50\mu$V in the relaxed targeted right-hand muscle in 5 of 10 consecutive trials (Rossini et al., 1994). The intensity of the first TMS pulse (coil 1 to PPC) was set to 90% of RMT, while the second TMS pulse intensity (coil 2 to M1) was set to produce an MEP of ~1 mV in the relaxed targeted right-hand muscle. The same stimulation location and intensities for M1 and PPC were used throughout the experiment for each participant for each experimental day.

6.3.6 Experimental design

All participants underwent an fMRI scanning session a separate day before the stimulation experiments. In the main experiment, all participants received iTBS to right CB (EXP_{CB} condition) or right VC ($CTRL_{VC}$ condition) followed by cPAS. iTBS and cPAS protocols were separated by a 10-min interval. Here, we investigated whether cerebellar iTBS modulated the subsequent Hebbian-like plasticity effects produced by cPAS of interconnected parietal and motor areas. We selected VC, a region outside of the rs-fMRI connectivity network in our sample, to evaluate whether nonspecific effects of brain stimulation could have produced the effects on the subsequent induction of paired associative plasticity in the parietal-motor pathway. Each experimental condition was performed on a separate day at least five days apart. The order

was counterbalanced. During testing, participants were seated comfortably in an armchair with both hands relaxed. At the beginning of each testing session, we determined the optimal scalp position for eliciting MEPs in the targeted right-hand muscle by delivering single-pulse TMS with the D70[2] coil with minimal stimulation intensity. The lowest stimulation intensity needed to elicit a ~1 mV MEP was determined for each participant before testing. The same TMS intensity was used to examine the changes in long-term potentiation-like plasticity in M1 (Chen and

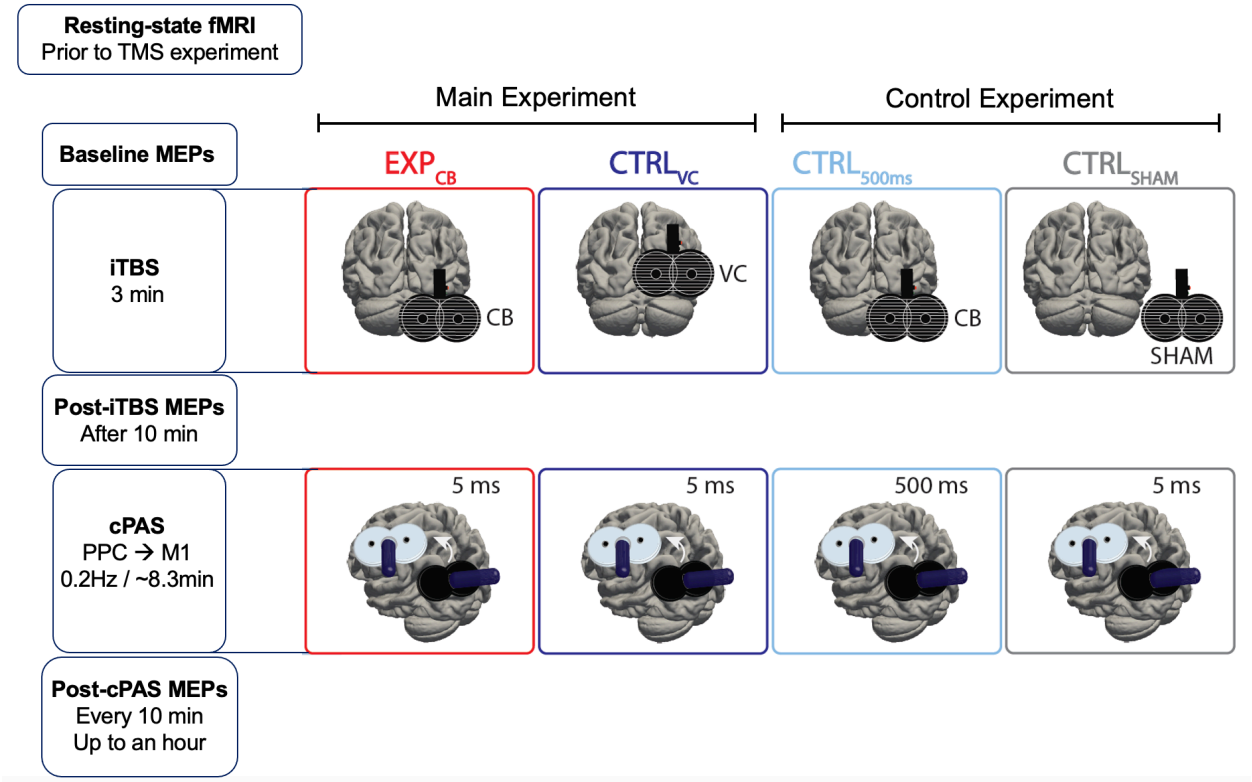

Figure 6-2 Experimental design. All participants underwent a resting-state fMRI scan before the transcranial magnetic stimulation (TMS) experiments. The main experiment included 14 subjects who underwent intermittent theta burst stimulation (iTBS) in two different conditions: EXP_{CB} (dark blue boxes) and $CTRL_{VC}$ (red boxes). The iTBS was delivered to a functionally connected cerebellar (CB) region in the EXP_{CB} condition or a non-functionally connected visual cortex (VC) region in the $CTRL_{VC}$ condition. This was followed by cortical paired associative stimulation (cPAS) to the posterior parietal cortex (PPC) and the primary motor cortex (M1) with a 5 ms interstimulus interval (ISI) at 0.2 Hz for about 8.3 min. Eight participants took part in two additional control experiments. In the $CTRL_{500ms}$ (light blue boxes) experiment, iTBS was administered to CB and cPAS with a 500ms ISI. In the $CTRL_{SHAM}$ (grey boxes) experiment, iTBS was administered with the coil held close to the scalp but angled away from it, and cPAS was given at a 5ms ISI. Motor-evoked potentials (MEPs) elicited by single-pulse TMS were measured at three different time points: baseline, 10 minutes after iTBS, and at six different time points for one hour after cPAS (at 10, 20, 30, 40, 50, and 60 min). The sessions were conducted at least five days apart from each other.

Udupa, 2009) after the different plasticity induction protocols. Each testing session included baseline (pre-iTBS), Post-iTBS, and Post-cPAS assessments (**Figure 6-2**). MEP amplitudes were measured before and 10 min after iTBS to examine the immediate effect of iTBS on motor excitability. In addition, MEP amplitudes after (10, 20, 30, 40, 50, and 60 min) the cPAS protocol were measured to examine the effect of iTBS over the 60 min following Hebbian-cPAS to PPC and M1. Twenty-four MEPs were acquired at each point in time. Single-pulse TMS was applied every 5 s. MEP amplitudes (mV) were measured peak-to-peak in a time window between 15 and 100 ms after single-pulse TMS.

We performed two additional control experiments on eight participants using the same procedures as the main experiment. One control experiment ($CTRL_{500ms}$ condition) evaluated whether cerebellar iTBS could have produced the effects on excitability in the motor cortex alone instead of an induced change in paired associative plasticity in the human parietal-motor pathway. Previous evidence shows that the induced Hebbian associative plasticity produced by cPAS depends on the timing of stimuli between PPC and M1 stimulation (e.g., IPI of <20 ms; Koch et al., 2013). We, therefore, applied the identical cPAS protocol (i.e., delivered the same number of pulses at the same frequency and intensity) to the same targeted parietal and motor areas from the main experiment but with an IPI of 500 ms (Johnen et al., 2015). One participant's data was excluded due to excessive muscle activity. The other control experiment ($CTRL_{SHAM}$ condition) verified whether the Hebbian cPAS protocol with an IPI of 5 ms between PPC and M1 delivered alone could induce the expected pattern of associative plasticity in a sample of 8 participants from the main experiment.

6.3.7 Statistical Analysis

Statistical analysis was performed using R (R Core Team, 2019; Version 3.6.1). To model the effect of cerebellar iTBS on motor cortical excitability before and after the application of cPAS, we fit a Bayesian hierarchical generalized linear model (GLM). Bayesian statistics provide numerous advantages, including making intuitive probabilistic statements about the range of credible values (e.g., parameter x has a probability of 0.95 of being in the range of 1 to 5) and incorporating prior knowledge. As MEP amplitudes are strictly positive with positive skew, we specified a Gamma likelihood function and a log link function. The model included fixed effects of stimulation condition (EXP_{CB}, $CTRL_{VC}$, $CTRL_{500\ ms}$, $CTRL_{SHAM}$) and phase (Pre-iTBS, Post-iTBS, Post-cPAS) and their interaction. The model additionally allowed intercepts to vary by subject. A posterior distribution over possible parameter values was sampled using Markov chain Monte Carlo (MCMC) sampling implemented in rstan (Stan Development Team, 2020; Version 2.21.2) via the brms package(Bürkner, 2017, 2018;Version 2.14.4). The model was specified as follows:

$$MEP_i \sim Gamma(\mu_i, shape)$$

$$\log(\mu_i) = \alpha_s + \beta_{Phase} Phase_i + \beta_{TMS} TMS_i + \beta_{Phase \times TMS} Phase_i TMS_i$$

$$\alpha_s \sim \alpha + \sigma z_s$$

$$\alpha \sim Student\_t(3, -0.1, 2.5)$$

$$\sigma \sim Student\_t(3, 0, 2.5)$$

$$z_s \sim Normal(0,1)$$

$$\beta \sim Normal(0,1)$$

$$shape \sim Gamma(1, 0.01)$$

where α_s denotes a subject-specific intercept and β_{Phase}, β_{TMS}, and $\beta_{Phase \times TMS}$ denote parameter estimates for the effect of phase, stimulation condition, and their interaction. We

specified a weakly informative prior distribution for the fixed effects (β) with a mean of 0 and a standard deviation of 1 (i.e., N(0,1)). As regression coefficients for a Gamma likelihood GLM with a log link function are interpreted as multiplicative factors rather than slopes, an N(0,1) prior indicates that *a priori*, we believe that a change in factor level (e.g. Post-iTBS to Post-cPAS) is associated with an increase or decrease in MEP amplitude by a factor between 1 and 7.1 (i.e., [exp(0), exp(1.96)]). The brms package implements a non-centered parameterization for random effects (Betancourt & Girolami, 2015), which for our model parameterizes subject-specific intercepts (α_s) using an overall intercept (α), a subject-specific offset (z_s), and a scaling parameter (σ). This parameterization decorrelates the sampling of random effects from high order hyperparameters allowing for improved sampling efficiency (Betancourt and Girolami, 2015). Default prior specifications from the brms package were used for parameters associated with subject-specific intercepts ($\alpha, z_s,$ and σ) , as well as the residual shape parameter ($shape$). By default, the location parameter for α was set to $median(log(MEP))$ and the scale parameter for α and σ was set to $max(mad(log(MEP)), 2.5)$ where mad represents the median absolute difference.

We ran four separate chains with 7000 iterations each. The first 2000 iterations were discarded as warm-ups. R-hat values were all very close to 1 (R-hat ≤ 1.001), and the effective sample size exceeded 5000 for all parameters indicating that MCMC chains had converged, and minimal autocorrelation was in the sampling. Posterior predictive checks confirmed that distributional assumptions were met and that the specified model could generate data that qualitatively resembled the actual data. For each parameter in the model, we report the median, 95% highest density interval (HDI), and the probability of direction (pd). The HDI represents the interval for which all values within that interval have a higher probability density than points

outside. Due to the log-link function, we exponentiate the median and 95% HDI values for reporting so that values represent multiplicative factors on the original response scale (e.g., a one-unit change in *x* is associated with an increase in MEP amplitude by a factor of exp(0.1) = 1.11). pd is an index of effect existence (ranging from 50% to 100%), representing the probability that an effect goes in a particular direction (e.g., pd = 0.99 indicates that effect *x* has a 99% probability of being negative). Note that pd represents the probability that the effect is negative or positive before exponentiation and the likelihood that the effect is less than or greater than one after exponentiation. We consider a pd greater than 95% to be strong evidence for an effect, a pd between 80% and 95% to provide some proof of an effect, and a pd less than 80% to indicate limited evidence for an effect.

To examine the effect of phase for each stimulation condition individually, we took draws from the expectation of the posterior predictive distribution (μ_i in the above model formula) for each stimulation condition and phase. Then, we subtracted the extracted values for one condition (e.g., Post-iTBS) from those extracted from the other condition (e.g., Post-cPAS), generating a difference distribution. We report each comparison's median, 95% HDI, and pd. We additionally computed Bayes Factors (BF) for each pairwise comparison using the BayesFactor package (Morey & Rouder, 2022). The reported BFs reflect the relative support for the alternative hypothesis of a difference between two conditions over the null hypothesis of no difference. For example, a BF of 10 indicates that the data are 10 times more likely under the alternative hypothesis than the null, whereas a BF of 0.1 (i.e. 1/10) indicates that the data are 10 times more likely under the null hypothesis than the alternative.

To characterize the effect of cerebellar iTBS across the 60 min following the cPAS protocol, we additionally fit a Gamma GLM that included fixed linear and quadratic effects of time. Intercepts were again allowed to vary by subject.

$$MEP_i \sim Gamma(\mu_i, shape)$$

$$\log(\mu_i) = \alpha_s + \beta_{Time} Time_i + \beta_{Time^2} {Time_i}^2$$

The same prior definitions as above were used for this model ($\beta \sim N(0,1)$, default brms prior specifications for the remaining parameters). We again exponentiate the median and 95% HDI values for reporting so that values represent multiplicative factors on the original response scale.

6.4 Results

Participants reported no undesirable side effects after stimulation. TMS targets for each participant are shown in stereotactic space overlaid on a template brain using Brainsight software in **Figure 6-3**. RMT was 42.0% ± 5.8% of MSO for coil 1, while the intensity to elicit an MEP

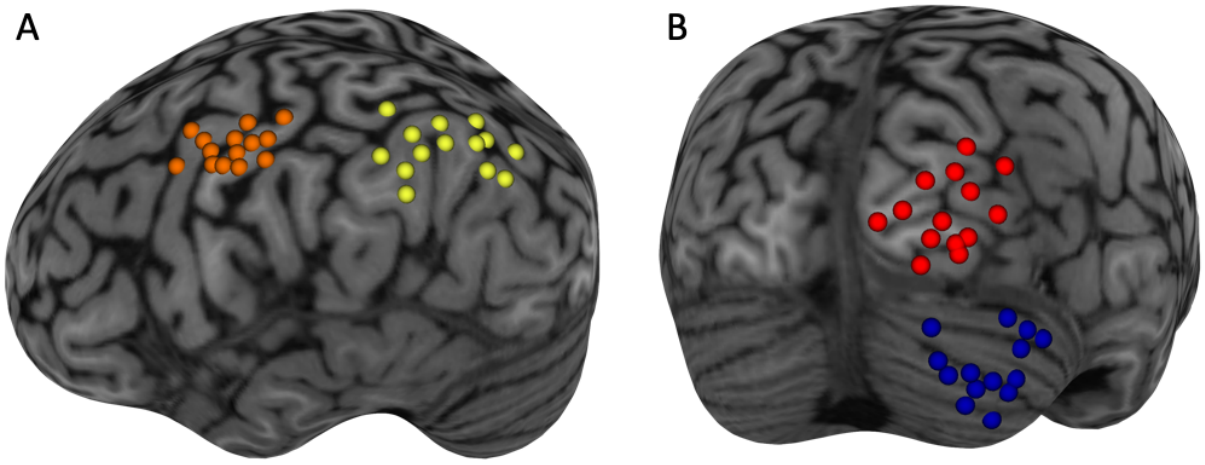

Figure 6-3 Stimulation targets for each participant are shown in stereotactic space overlaid on a template brain using Brainsight software (N=14). (**A**) Dots indicate individual locations for the primary motor cortex (M1, orange) and posterior parietal cortex (PPC, yellow) for cortical paired associative stimulation (cPAS). (**B**) Dots indicate individual locations for the cerebellum (CB, blue) and visual cortex (VC, red) for intermittent theta burst stimulation (iTBS).

amplitude of 1 mV in the targeted right-hand muscle was 49.2 ± 6.4% of MSO for coil 2 across participants.

6.4.1 Pre-iTBS, Post-iTBS and Post-cPAS

To determine the impact of cerebellar iTBS on distal cortical physiology, we first evaluated MEP amplitudes before and after the application of iTBS. We fit a Bayesian hierarchical gamma GLM to MEP amplitudes with fixed effects of phase (Pre-iTBS, Post-iTBS and Post-cPAS), stimulation condition (EXP_{CB}, $CTRL_{VC}$, $CTRL_{500\ ms}$, $CTRL_{SHAM}$), and their interaction. Post-iTBS MEP amplitudes increased 11.5% relative to pre-iTBS in the EXP_{CB} condition (Median= 1.115, 95% HDI [1.015, 1.234], pd = 98.97%; BF = 5.65). This result

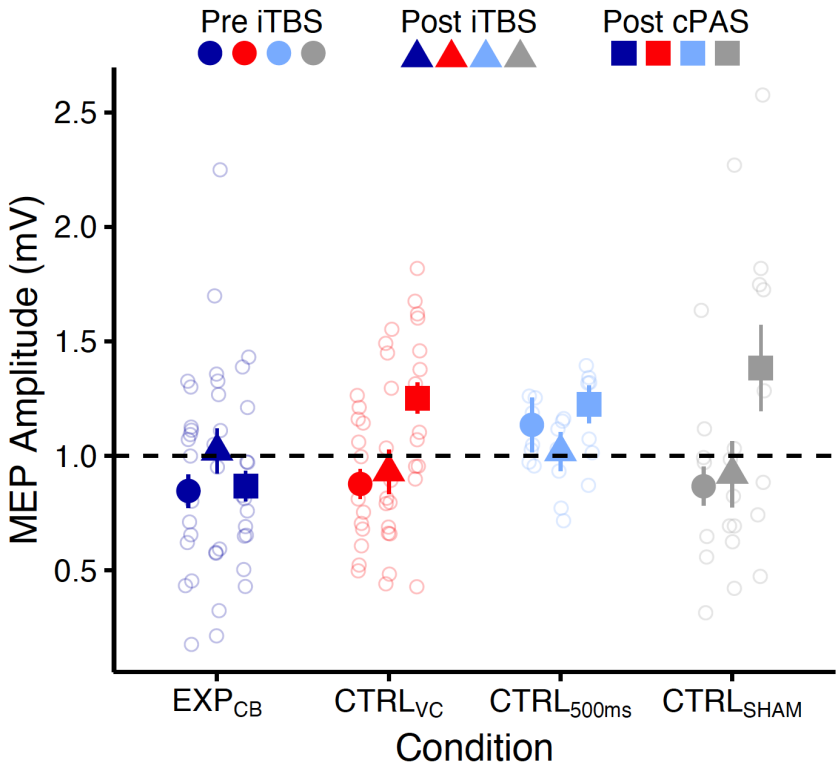

Figure 6-4 Group-averaged MEP amplitudes in millivolts at the post-iTBS (open circles) timepoint and post-cPAS (filled circles) for the EXP_{CB} (dark blue), $CTRL_{VC}$ (red), $CTRL_{500ms}$ (light blue) and $CTRL_{SHAM}$ (grey) conditions. Post-cPAS values reflect averaged MEP amplitudes collected at all six time points in the 60 minutes following cPAS. Error bars represent within-subject standard error (Morey, 2008).

indicates that the application iTBS to cerebellar nodes functionally connected PPC increased MEP amplitudes prior to the application of cPAS, consistent with prior reports (Koch, Mori, et al., 2008).

In contrast, the $CTRL_{VC}$ condition that stimulated an active control site and the $CTRL_{SHAM}$ condition in which stimulation was directed away from the scalp exhibited little evidence for a change in MEP amplitude Post-iTBS relative to Pre-iTBS ($CTRL_{VC}$: Median = 1.053, 95% HDI [0.955, 1.164], pd = 85.40%, BF = 0.17; $CTRL_{SHAM}$: Median = 1.039, 95% HDI [0.921 1.169], pd = 73.93%, BF = 0.15). The GLM analysis found some evidence of a decrease in MEP amplitude between pre- and post-iTBS timepoints in the $CTRL_{500\ ms}$ condition (Median: 0.865, 95% HDI [0.722 1.019], pd = 95.91%). However, the more targeted Bayes factor comparison revealed evidence in favor of the null hypothesis of no difference between pre- and post-iTBS (BF = 0.45).

We next examined the effect of cerebellar iTBS before and after the application of cPAS to PPC and M1. For this analysis, we collated the MEP values from all six time points following cPAS (**Figure 6-4**). In the EXP_{CB} condition, post-cPAS MEP amplitudes reduced by 8.4% relative to MEPs Post-iTBS (Median = 0.915, 95% HDI [0.843, 0.986], pd= 99.12%; BF = 39.64). In contrast, there was a 33.4% increase in MEP amplitudes following cPAS in the $CTRL_{VC}$ condition relative to the Post-iTBS MEP amplitudes (Median = 1.334, 95% HDI [1.211, 1.470], pd = 100.00%; BF = 322,776,386). This positive change in MEP amplitude was also found in the $CTRL_{500ms}$ condition; MEP amplitudes increased by 22.4% Post-cPAS relative to Post-iTBS (Median = 1.224, 95% HDI [1.079, 1.396], pd = 99.86%; BF = 13.71). This pattern of results suggests that cerebellar iTBS on its own does not inhibit M1 output directly. Instead, the suppression effect of cPAS observed after cerebellar iTBS is dependent on both the site of iTBS

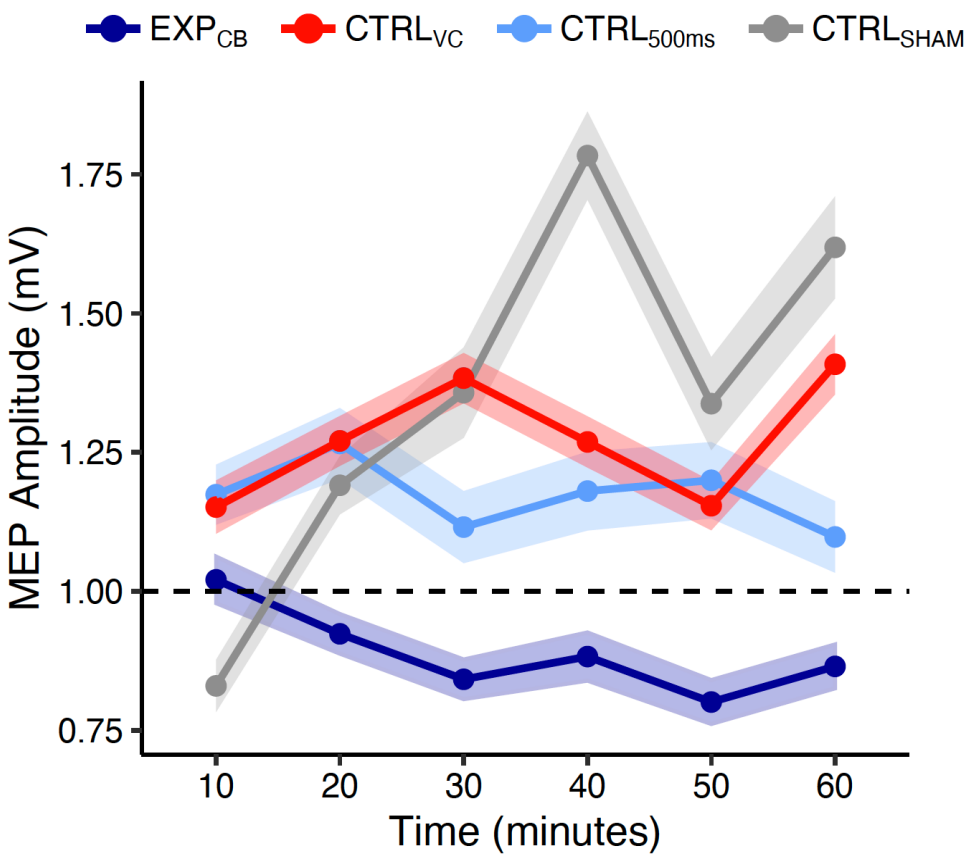

Figure 6-5 Line graph indicating group averaged MEP amplitude in millivolts every 10 min for 60min following cPAS for the EXP$_{CB}$ (dark blue circles), CTRL$_{VC}$ (red squares), CTRL$_{500ms}$ (light blue up-triangles) and CTRL$_{SHAM}$ (grey down-triangles) conditions. Shaded area represents within-subject standard error (Morey & Rouder, 2022).

and the specific timing that is thought to induce changes in PPC-M1 connectivity. Similarly, we observed a 51.4% increase in MEP values in the CTRL$_{SHAM}$ condition Post-cPAS relative to prior-cPAS (Median = 1.514, 95% HDI [1.337, 1.726], pd = 100.00%; BF = 19,269,214). This signifies that a Hebbian cPAS protocol between PPC and M1 delivered alone, with no prior neuromodulating stimulation to the cerebellum, is associated with an increase in MEP amplitude. Together, these results demonstrate that iTBS to the cerebellum, followed by Hebbian-cPAS to PPC and M1, is associated with an MEP amplitude decrease. This effect is specific to the EXP$_{CB}$ condition; MEP amplitudes in all three control conditions increased following cPAS relative to Post-iTBS.

6.4.2 Extended effects of modulatory stimulation protocols

We next examined the linear and quadratic effect of cerebellar iTBS over the 60 minutes following cPAS. MEPs were collected at 10-minute intervals for an hour following cPAS in all four conditions. An analysis of MEP amplitudes at the six time points following cPAS revealed suppression in the EXP_{CB} condition compared to the facilitation of MEPs across the three control conditions (**Figure 6-5**). We found a robust negative linear effect and positive quadratic effect across the 60 min time window in the EXP_{CB} condition (Linear: Median: 0.864, 95% HDI [0.787, 0.951], pd= 99.91%; Quadratic: Median: 1.015, 95% HDI [1.001, 1.028], pd= 98.46%) representing an initial sharp decrease in MEP amplitudes that plateaus over the 60 min time window.

In contrast, the three control conditions showed a positive linear and negative quadratic effect over time following cPAS. Modulating the visual cortex instead of the cerebellum before Hebbian cPAS ($CTRL_{VC}$) is associated with somewhat larger MEP amplitudes over time (Linear: Median: 1.063, 95% HDI [0.979, 1.155], pd= 92.20%; Quadratic: Median: 0.999, 95% HDI [0.982, 1.005], pd= 87.16%). Similarly, refraining from delivering iTBS stimulation at all, as in the $CTRL_{SHAM}$ condition, also led to an increase in MEP values Post-cPAS (Linear: Median: 1.476, 95% HDI [1.328, 1.624], pd= 100.00%; Quadratic: Median: 0.959, 95% HDI [0.946, 0.972], pd= 100.00%). Additionally, the robust negative linear effect observed in the EXP_{CB} condition was not observed when cerebellar iTBS was followed by non-Hebbian cPAS as in the $CTRL_{500ms}$ condition (Linear: Median: 1.018, 95% HDI [0.903, 1.146], pd= 62.13%; Quadratic: $CTRL_{500ms}$: Median: 0.996, 95% HDI [0.979, 1.012], pd= 68.03%;). These results demonstrate a facilitation effect of cPAS when either paired with sham stimulation or stimulation outside of the

network of interest that subsided over the 60-minute time window and neither facilitation nor suppression with cerebellar iTBS alone.

6.5 Discussion

These findings reveal cerebellar activity affects the downstream plasticity of interconnected cortical areas. Here, for the first time, we demonstrate that modifying cerebellar activity with stimulation blocks the induction of cortical associative plasticity in a distal parietal-motor pathway involved in actions. The changes in cerebellar activity induced by stimulation were selective on cortical physiology, as there were no inhibitory effects on motor associative plasticity with an active control stimulation of the visual cortex. Additionally, an increase in motor excitability was observed when cerebellar iTBS was followed by non-Hebbian cPAS, and cPAS was paired with sham stimulation. Taken together, these findings indicate the existence of causal interactions between cerebellar activity and the collective state of network activity and subsequent synaptic plasticity mechanisms of interconnected parietal-frontal areas in the motor network.

The present study is novel in that it is the first to indicate that stimulation alters plasticity in network-connected regions downstream of the targeted node through heterosynaptic metaplasticity. We have causally demonstrated the effects that cerebellar stimulation has on projections to an interconnected parietal region within the motor network. Previous research has shown that the effects of brain stimulation can propagate beyond the stimulated node (Liew et al., 2014; Beynel et al., 2020), and modulation of cerebellar excitability can alter motor activity (Gerschlager et al., 2002; Koch, Mori, et al., 2008; Oliveri et al., 2005). Casula and colleagues extend this finding to a non-motor area and demonstrated that rTMS to the lateral cerebellum

alters oscillatory activity in both M1 and PPC (Casula, Pellicciari, Ponzo, et al., 2016). Cerebellar TBS has also been shown to modulate functional connectivity in cerebral networks, mediating cognition (Halko et al., 2014; Rastogi et al., 2017) and altering temporal dynamics within the cortex (Farzan et al., 2016).

We found that $iTBS_{CB}$ prevented the plasticity induction from the Hebbian-like $cPAS_{5ms}$ to PPC and M1. However, it did not reduce MEP amplitudes following the non-STDP-like $cPAS_{500ms}$ condition. This indicates cerebellar outputs affect the interdependent connectivity between PPC and M1, possibly modulating sensory processing pathways as they transmit information, rather than directly impacting M1. This likely occurred through heterosynaptic metaplasticity along the projections from the ventral dentate nucleus to PPC and, subsequently, M1 (Bostan et al., 2013; R. P. Dum & Strick, 2003). It is possible that the cerebellum alters motor cortical plasticity through intermediate synapses within the dentate-thalamo-cortico pathway by modulating incoming afferent activity before it reaches M1 (Popa et al., 2013). This highlights the interaction between brain activity and exogenous stimulation on network physiology.

iTBS to the lateral cerebellum blocks the induction of plasticity of a cPAS protocol of the parietal-motor network, as evidenced by suppressed MEPs following the EXP_{CB} condition. It is plausible that activating the cerebellum with the excitatory iTBS protocol increased excitability within the cortical motor network. It has been proposed that cerebellar iTBS increases the excitability of inhibitory Purkinje cells, which in turn increases inhibition of the dentate nucleus. This inhibition is suggested to result in the suppression of excitatory projections within the intermediate dentate-thalamocortical pathway rather than directly at the M1 level (Grimaldi et al., 2014; Popa et al., 2013).

iTBS stimulation to the visual cortex node outside of the parietal-motor-cerebellar network did not induce the suppressive effect, as indicated by the increase in MEP amplitudes in the $CTRL_{VC}$ condition. This result suggests that effects are network-dependent and the use of individualized CB targets, based on fMRI-derived functional connectivity, may have contributed to this outcome. (Beynel et al., 2020; Fox et al., 2012).

The increase in MEP amplitudes following the $CTRL_{500ms}$ condition indicates that iTBS to the lateral cerebellum affects the interconnected pathway between PPC and M1 rather than inhibiting M1 output directly. As cPAS with a 500ms ISI does not induce Hebbian-like plasticity and does not affect network connectivity, this condition is similar to the effect of iTBS on the lateral cerebellum alone. The increased MEP amplitudes found following iTBS to the right CB, align with previous studies (Koch, Mori, et al., 2008; Di Lorenzo et al., 2020; Popa et al., 2010). Previous work has shown that delivering iTBS to the CB does not affect subsequent iTBS to M1 and that post-intervention MEP amplitudes increase similarly to facilitatory iTBS delivered to M1 without cerebellar preconditioning (Popa et al., 2013).

Cerebellar iTBS decreases long intracortical inhibition (LICI), suggesting that the stimulation induces a reduction of $GABA_B$ circuit activity (Casula, Pellicciari, Ponzo, et al., 2016; Koch, Mori, et al., 2008). Similarly, our findings align with previous research showing that iTBS to the node of the CB functionally connected with the default mode network enhanced network-wide cortical functional connectivity (Halko et al., 2014). This indicates that CB stimulation affects downstream cortical circuitry in addition to intra-cerebellar function.

The $CTRL_{SHAM}$ condition where sham iTBS was applied also increased MEP amplitudes. This indicates that delivering a Hebbian-like cPAS stimulation protocol where a 5ms ISI to PPC and M1 is used on its own increases cortical excitability, a finding that is in line with previous

work (Chao et al., 2015; A. N. Karabanov et al., 2013). Results from this control condition suggest that iTBS to the lateral CB interferes with the plasticity-enhancing mechanisms of paired associative stimulation to a distal cortical circuit in the motor network.

It has been well-documented that preconditioning brain activity with a prior bout of stimulation can modulate the plasticity of subsequent stimulation (Abraham, 2008; Iyer et al., 2003; Murakami et al., 2012; Siebner et al., 2004; Todd et al., 2009). It is thought that priming M1 exogenously before delivering rTMS can enhance or suppress expected effects on cortical excitability in a manner that follows homeostatic mechanisms (Iyer et al., 2003; Siebner et al., 2004). Studies have also shown that potentiation changes induced by stimulation can occur across multiple synapses (i.e., heterosynaptic metaplasticity) with remarkable specificity (Ni et al., 2014).

The way cerebellar stimulation modulates plasticity in the parietal-motor network may help elucidate mechanisms involved in skilled motor control. Recently, Huang and colleagues demonstrated that cTBS to the premotor area affected distal plasticity within M1, which in turn impaired motor learning (Huang et al., 2018). Previous research also indicates that cerebellar iTBS improves coordination and hand dexterity and increases implicit motor learning (Bradnam et al., 2016). The use of network-targeted brain stimulation has important implications for treating neuromotor impairments, as it can alter functional connectivity and induce lasting changes to motor excitability in distal brain regions after the stimulation period. Enhancing cerebellar activity with non-invasive brain stimulation may be a particularly effective way to improve motor function in patient populations (Block & Celnik, 2012; Celnik, 2015). For example, Koch and colleagues recently demonstrated that cerebellar iTBS combined with physical therapy is highly effective at improving gait and balance functions in individuals with

hemiparesis (Koch et al., 2019). The results of the present study further our understanding of how rTMS can be employed to improve motor function and lend credence to the idea that stimulation can rectify aberrant functional connections observed in patients (Fox et al., 2012; Vercammen et al., 2010).

Chapter 7: The Behavioral and Neural Effects of Parietal Theta Burst Stimulation on the Grasp Network are Stronger During a Grasping Task than at Rest

7.1 Abstract

Repetitive transcranial magnetic stimulation (TMS) is widely used in neuroscience and clinical settings to modulate human cortical activity. The effects of TMS on neural activity depend on the excitability of specific neural populations at the time of stimulation. Accordingly, the brain state at the time of stimulation may influence the persistent effects of repetitive TMS on distal brain activity and associated behaviors. We applied intermittent theta burst stimulation (iTBS) to a region in the posterior parietal cortex (PPC) associated with grasp control to evaluate the interaction between stimulation and brain state. Across two experiments, we demonstrate the immediate responses of motor cortex activity and motor performance to state-dependent parietal stimulation. We randomly assigned 72 healthy adult participants to one of three TMS intervention groups, followed by electrophysiological measures with TMS and behavioral measures. Participants in the first group received iTBS to PPC while performing a grasping task concurrently. Participants in the second group received iTBS to PPC while in a task-free, resting state. A third group of participants received iTBS to a parietal region outside the cortical grasping network while performing a grasping task concurrently. We compared changes in motor cortical excitability and motor performance in the three stimulation groups within an hour of each intervention. We found that parietal stimulation during a behavioral manipulation that activates the cortical grasping network increased downstream motor

cortical excitability and improved motor performance relative to stimulation during rest. We conclude that constraining the brain state with a behavioral task during brain stimulation has the potential to optimize plasticity induction in cortical circuit mechanisms that mediate movement processes.

7.2 Introduction

Goal-directed hand actions, such as grasping for objects, are integral to human behavior. Performing such behaviors activates a widespread network of cortical areas, including the prefrontal cortex, premotor cortex, and posterior parietal cortex (PPC; Davare et al., 2011; Fattori et al., 2017; Gallivan & Culham, 2015; Grafton, 2010; Turella & Lingnau, 2014). The primary motor cortex (M1) plays an essential role in motor control and is part of a more extensive parietal–frontal network involved in many aspects of movement planning and decision-making (Andersen & Cui, 2009; Cisek & Kalaska, 2010; Crawford et al., 2011; Kalaska et al., 1997; Vesia & Crawford, 2012). Neural inputs from PPC to motor areas in the frontal lobe are generally thought to mediate motor commands for hand movements (Fattori et al., 2017; Gallivan et al., 2018; Grafton, 2010; Turella & Lingnau, 2014). Current evidence from functional cortico-cortical connectivity measures derived from dual-site transcranial magnetic stimulation (dsTMS) indicates that inputs from PPC exert a facilitatory influence on motor output during the preparation and execution of hand movement planning, suggesting a functional parietal-motor connection that controls hand muscles (Davare et al., 2010; Gallivan et al., 2018; A. N. Karabanov et al., 2013; Koch, 2020; Koch et al., 2007, 2008; Koch & Rothwell, 2009; Vesia et al., 2013, 2017; Vesia & Davare, 2011; Ziluk et al., 2010). The plasticity of M1 associated with

voluntary movements and motor-skill learning also appears to be influenced by distributed activity in functionally related brain areas in the motor network (Buch et al., 2017; Hardwick et al., 2013; Sanes & Donoghue, 2000)., 2013; Sanes & Donoghue, 2000). However, it is unclear if other brain areas, such as PPC, can modulate this motor plasticity.

Repetitive transcranial magnetic stimulation (rTMS) can induce plastic changes in the brain (Hallett, 2007). For instance, intermittent theta burst stimulation (iTBS), a form of rTMS, can produce durable increases in motor cortical excitability for a period that outlasts the stimulation when applied to M1 (Huang et al., 2005; Suppa et al., 2016). The mechanisms of these changes are caused by processes analogous to long-term potentiation (LTP) that are also seen with skill learning (Bear & Malenka, 1994; Berardelli et al., 1998; Capocchi et al., 1992). This stimulation can directly modify neural activity at the locus of stimulation, as well as the activity of interconnected and functionally coupled brain areas (Siebner et al., 2009). These persistent effects on neural activity are primarily thought to be constrained within the functional network of the targeted region (Fox et al., 2012). Therefore, it is unsurprising that rTMS can be particularly effective for treatment-induced behavior improvements when applied to functional brain networks (Fox, 2018; Horn & Fox, 2020; Raffin & Siebner, 2014; Silasi & Murphy, 2014). Yet, the persisting effects of rTMS on enduring motor cortical excitability and behavioral outcomes are highly variable and poorly understood (Ziemann & Siebner, 2015).

The variability of rTMS-induced effects on brain and behavior responses can be partly explained by variations in ongoing activity levels of functionally specific neural populations and pathways at the time of stimulation (Bergmann, 2018; Romei, Thut, et al., 2016; Silvanto et al., 2007). For example, recordings in the visual cortex indicate that the post-stimulation response depends on

pre-stimulation activity levels (Pasley et al., 2009). Similarly, pairing rTMS with visual stimuli has shown a direction-selective plasticity induction in the visual system that biases subsequent behavioral responses for a particular motion direction (Chiappini et al., 2018). Therefore, the functional context of neural activity during stimulation appears necessary for targeting brain networks associated with specific functions.

Although we and others have shown that the PPC and associated parietal–frontal circuits of the motor planning network are essential for skilled grasp control (Davare et al., 2010, 2011; Fattori et al., 2017; Gallivan & Culham, 2015; Grafton, 2010; Turella & Lingnau, 2014; Vesia et al., 2017; Vesia & Crawford, 2012), the notion that the functional context of brain activity during PPC stimulation can modulate interactions with functionally connected motor regions to alter plasticity associated with motor control has not been directly tested. We utilized a novel approach that combines an object-driven grasp task, which selectively activates the motor control network, with iTBS to PPC. In the pilot study (Experiment 1), we investigated the immediate effects of state-dependent stimulation on electrophysiological and behavioral responses. Experiment 2 replicated the findings from the pilot study with a larger sample size and additional stimulation sessions. We predicted that applying parietal iTBS while constraining the brain state via a grasping task will be more likely to increase motor cortical excitability than an application of the same stimulation protocol during rest. We also predicted that motor performance improvement would be greater after parietal iTBS during grasp performance compared to parietal iTBS at rest.

7.3 Materials and Methods

7.3.1 Participants

We conducted two experiments involving 72 healthy, right-handed participants (Oldfield, 1971). In Experiment 1 (pilot study), we studied 24 adult participants (13 females and 11 males aged between 18 and 30). For our second experiment, we recruited 48 participants (32 females and 16 males, 18–50 years) and assigned 16 participants to each group. The sample size was determined based on prior research (Fiori et al., 2018), considering a motor performance effect size of 0.11, a desired power of 0.8, a significance level (α) of 0.05, and an estimated dropout rate of 10%. All participants provided written informed consent and underwent a TMS Adult Safety Screen to assess the potential risk of adverse reactions to TMS (Keel et al., 2001; Rossi et al., 2011). The Institutional Review Board at the University of Michigan (IRB#: HUM00157197 and HUM00186637) approved experimental procedures in accordance with the Declaration of Helsinki.

7.3.2 Electromyographic recordings

Electromyography (EMG) activity of the right hand was recorded from the first dorsal interosseous and abductor pollicis brevis muscles using surface electrodes (Ag-AgCl, 9-mm diameter). The active electrode was placed over the muscle belly, and the reference electrode over the metacarpophalangeal joint of the finger. Signals were amplified (×1000), band pass filtered (20 Hz–2.5 kHz; Intronix Technologies Corporation, Model 2024F), digitized at 5 kHz using a Micro 1,401 data acquisition interface controlled by Signal Software version 7 (Cambridge Electronic Design Ltd.), and stored on a computer for off-line analysis.

7.3.3 Transcranial magnetic stimulation

Monophasic pulses were delivered from two separate Magstim model 200^2 stimulators (Magstim) through a D70^2 (loop diameter, 70 mm) or D50 Alpha B.I. (loop diameter, 50 mm) figure-8 coil. First, motor-evoked potentials (MEPs) in the targeted relaxed right-hand muscle were elicited by delivering single-pulse TMS (spTMS) over the hand area of the left primary motor cortex (M1). The TMS coil was placed tangential to the scalp and at a 45° angle from the midsagittal line. The placement of the TMS coil was adjusted to the location where TMS produced the largest MEP from the targeted right-hand muscles. Next, the TMS coil's position was marked and registered using a standard MRI template with a frameless stereotactic neuronavigation system (Brainsight 2, Rogue Research Inc.). The resting motor threshold (RMT) was determined by the minimum stimulator output needed to obtain MEP amplitudes of at least 50 μV in five of ten TMS pulses with the D50 Alpha B.I. coil when the muscle was completely relaxed (Groppa, Oliviero, et al., 2012; Rossini et al., 1994, 2015). The intensity of the D70^2 coil was adjusted to induce MEP amplitudes of about 1 mV in at least five out of ten trials in the relaxed targeted right hand muscle.

7.3.4 Stimulation target identification

We used a function-based search-grid dsTMS technique to establish individualized left PPC locations for Experiment 1. This method uses a "hunting procedure" to target personalized functional interactions in the cortical grasping network. First, the left parietal stimulation target was selected as the P3 (left PPC) electrode position on the 10–20 electroencephalogram (EEG) coordinate system (Herwig et al., 2003; Okamoto et al., 2004) using commercially available 10–20

EEG stretch caps (g.GAMMAcap, g.tec Medical Engineering) in each participant. The P3 electrode location has been previously shown to target the inferior parietal lobule (Vesia et al., 2006, 2008, 2010, 2015). A square, 3 × 3 search grid, with positions separated by 1 cm, centered on the P3 target, was created using Brainsight (**Figure 7-1A**). A dsTMS approach with two coils was then used to identify participant-specific stimulation locations in the left PPC where parietal stimulation effectively exerts grasp-specific facilitation on M1 during an object-directed grasp task. This dsTMS technique provides a means for assessing how the behavioral context modulates the strength of interaction between PPC and M1 when the grasp-task demand recruits the parietal-motor circuit (Bestmann & Krakauer, 2015; Goldenkoff et al., 2020; Hallett et al., 2017; Koch & Rothwell, 2009; Lafleur et al., 2016; Vesia et al., 2013, 2017; Vesia & Davare, 2011). Specifically, we adopted a paradigm used previously by our group to activate the PPC-M1 circuit early in the motor plan for grasp movements (Vesia et al., 2013, 2017). Participants made one of two object-directed grasp movements to a target object with the right hand (**Figure 7-1B**). The target object was a small cylinder (2.5 cm diameter, 6.5 cm height) fixed atop a larger cylinder (7 cm diameter, 6.5 cm height), located 30 cm in front and 10 cm to the right of the starting hand position. Participants maintained visual fixation on two central LEDs in the midline for 2 s. Participants were instructed to grasp: (1) the top cylinder with a precision grip when the top LED flashed or (2) the bottom cylinder with a whole-hand grasp when the bottom LED flashed. To probe causal connectivity between the PPC and M1 in the left hemisphere, a conditioning stimulus (CS) over each PPC target in the grid was applied before delivering a test stimulus (TS) to ipsilateral M1 during reaction time (i.e., action plan phase) of the object-directed grasp such that the MEP recordings were collected before actual movement initiation (Vesia et al., 2017). TS intensity was

adjusted to induce MEP amplitudes of about 1 mV. CS preceded TS by an interstimulus interval (ISI) of 5 ms at a stimulation intensity of 90% RMT (Koch et al., 2008; Vesia et al., 2013, 2017). Approximately ten TS and CS-TS were administered randomly at each grid position. The optimal scalp position for coil placement over the left PPC was defined as the point on the grid where CS elicited the largest MEP exceeding 1.2 mV from the contralateral hand muscle of the right (response) hand in three of five consecutive trials (A. N. Karabanov et al., 2013; Oliver et al., 2009). Brainsight was used to accurately place both coils throughout the localization of the parietal stimulation target. The stimulation location for the control condition was set at the Pz electrode position, which is not part of the parietal-motor circuit responsible for grasping. The parietal rTMS location on the grid was recorded and reported in **Figure 7-2A**.

In our second experiment, the site for PPC stimulation and the cortical control stimulation locations were identified using structural MRI data on each participant. MRI data were acquired using a 3 T GE scanner (MR 750) with a 32-channel head coil. T1-weighted structural images were obtained for anatomical localization. To locate the individualized left parietal stimulation target, we generated a region of interest mask based on the superior medial parietal regions 'L_LIPv, L_7PC' using the MNI projection of the HCP-MMP1 atlas (Glasser et al., 2016). We chose a point within the anatomical mask that overlapped the center of a gyrus. We identified a target in the left visual cortex for the control stimulation group based on anatomical criteria. Notably, the visual cortical region is outside the grasping network. We determined the cortical location reached by the stimulation in each participant by projecting the coil location on the scalp onto their individual MRI using Brainsight. The resulting coordinates were reported in MNI space

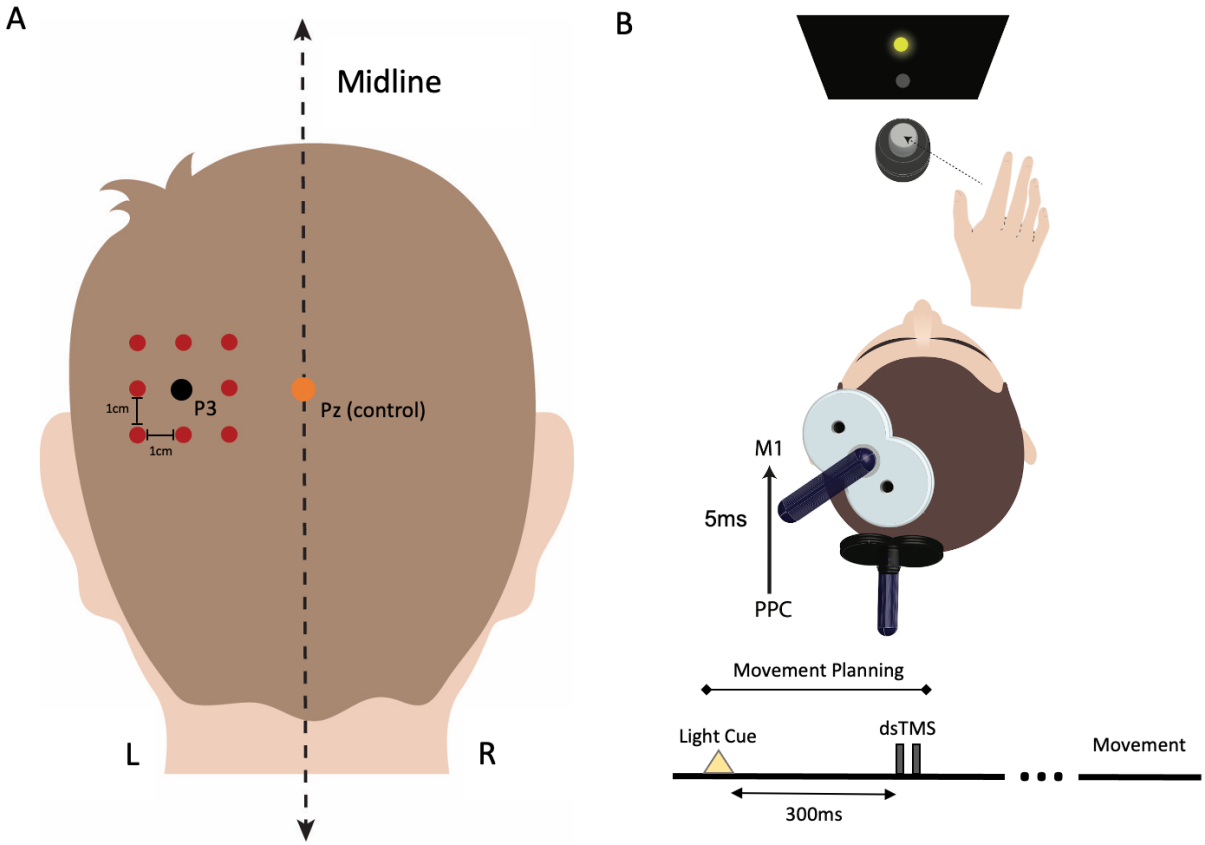

Figure 7-1 Procedure for identifying individualized left parietal stimulation locations. **(A)** The P3 electrode location was marked for each participant using the 10–20 EEG system. A 3 × 3 square search grid, with each point separated by 1 cm, was centered around P3 using Brainsight stereotactic software. The Pz electrode position was used as the stimulation location for the control condition. **(B)** During the functional localization protocol, each grid location over the parietal cortex was assessed for its maximum facilitatory effect on the primary motor cortex (M1). To identify the participant-specific location in PPC where stimulation induced the greatest facilitation in motor-evoked potential (MEP) amplitude, a dual-site, paired-pulse TMS (dsTMS) paradigm was employed using two coils. During dsTMS, participants performed an object-directed grasp task, and dsTMS was applied 300 ms after the movement cue (LED flash) occurred, coinciding with the planning phase of movement. Electromyography (EMG) was used to measure changes in MEP amplitude during the planning phase of the movement. The conditioning pulse intensity over PPC was 90% of the resting motor threshold (RMT), and the test pulse intensity over M1 was adjusted to induce an MEP of ~1 mV in the target hand muscle. The interstimulus interval (ISI) between the conditioning and test pulse was set at 5 ms. Approximately ten dsTMS pairs were delivered at each search grid location, and the location that induced the largest MEP response in three of five consecutive trials was selected as the PPC rTMS location.

(**Figure 7-2B**). To visualize the data, SimNIBS 4.0 was used to estimate the TMS-induced electric fields (Thielscher et al., 2015).

7.3.5 Theta burst stimulation

Intermittent theta burst stimulation (iTBS) to the left cortical targets was administered using a MagPro X100 with MagOption (MagVenture Inc.) and a statically cooled figure-8 coil (MCF-B70). iTBS consisted of three pulses at a frequency of 50 Hz every 200 ms for 2 s and repeated every 10 s for a total of 190 s (600 pulses; Huang et al., 2005). The conventional approach for individualizing iTBS intensity is based on the motor threshold response, which uses an intensity of 80% of the active motor threshold (AMT; Huang et al., 2005). AMT was defined as the lowest intensity required for eliciting MEP of 200 μV in five of ten consecutive trials during a 20% maximum voluntary contraction of the muscle in the right hand with the MCF-B70 coil using biphasic pulses (Huang et al., 2005). We assessed AMT for each participant to compare our stimulation intensity with previous studies that utilized the conventional approach and ensure that our stimulation intensity adhered to safety guidelines (Oberman et al., 2011; Rossi et al., 2009).

The pilot study (Experiment 1) delivered iTBS at a fixed percentage of maximum stimulator output (% MSO) of 40% to decrease the inter-individual difference in stimulation-induced effects (Vesia et al., 2010). This methodological adjustment is based on evidence demonstrating that motor threshold does not adequately characterize the underlying physiology of non-motor areas of the brain (Khammash et al., 2019; L. M. Stewart et al., 2001; Stokes et al., 2005). For Experiment 2, we administered iTBS using a personalized stimulation intensity based on the individual participant's functional neuroanatomy. This personalized approach adjusted AMT according to the distances between the scalp and the underlying cortex (for details, see Stokes et

al., 2005). The stimulation intensity was then set at 80% of the adjusted AMT for each participant ($iTBS_{PPC + Grasp}$: 37.4 ± 3.2; $iTBS_{PPC + Rest}$: 36.7 ± 2.7; $iTBS_{Control + Grasp}$: 37.4 ± 3.2).

7.3.6 Assessment of motor cortical excitability

Long-term potentiation-like plasticity in M1 was assessed by quantifying the changes in the level of motor cortical excitability with the different stimulation protocols (Chen & Udupa, 2009). A fixed percentage of maximum stimulator output was used to elicit MEPs of about 1 mV peak-to-peak amplitude using spTMS with the D70^2 coil before iTBS to PPC. Twenty-four MEPs were recorded at every assessment time point before and after (Experiment 1: 0, 15, 30, 45, and 60 min; Experiment 2: 30 and 60 min) each intervention with the 1 mV TMS intensity determined before each intervention. Stimuli were applied every 5 s.

7.3.7 Assessment of motor performance

Motor performance was assessed by examining changes in the speed to complete a widely used nine-hole pegboard manual dexterity test. The pegboard task requires dexterous control of complex movements such as multi-digit grasping and manipulating small objects (Bunday & Perez, 2012; Fiori et al., 2018; Grice et al., 2003; Mathiowetz et al., 1985). Performance of the pegboard task engages parietal–frontal brain areas in the cortical grasping network subserving sensorimotor functions (Bunday & Perez, 2012; Davare et al., 2011; Fiori et al., 2018). Participants were seated in front of a table with the start position of the right hand positioned 10 cm from the pegboard apparatus. Behavioral performance on the pegboard task was evaluated by measuring the time to complete the task using a stopwatch every time before and after (30 and 60 min) the intervention. A choice-reaction visuomotor task (CRT) was used as a control task to

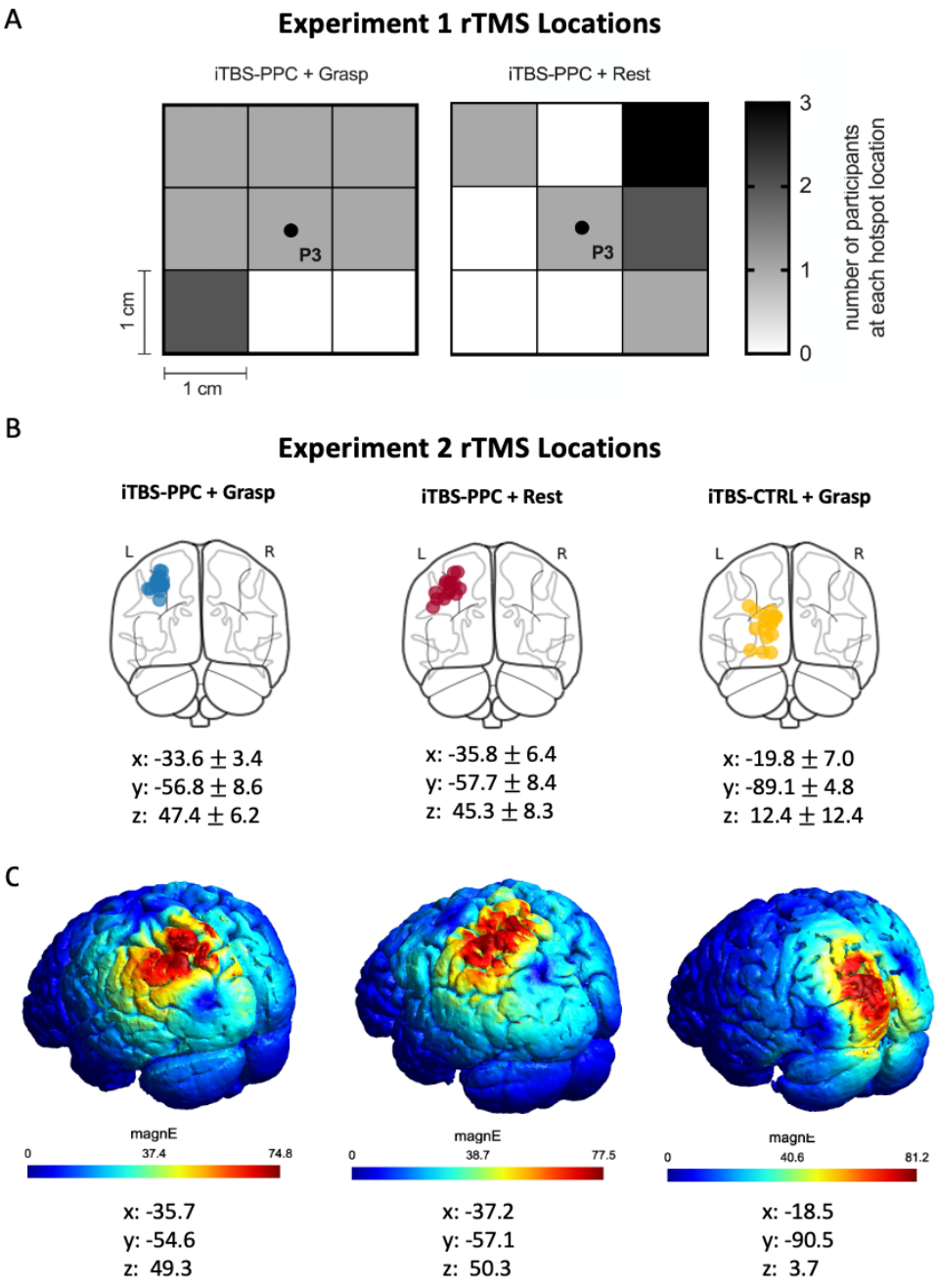

Figure 7-2 Individual rTMS locations. (A) Heat map indicating the search grid spot that was selected for the participants in the iTBS-PPC + Grasp and iTBS-PPC + Rest groups in Experiment 1. (B) In Experiment 2, structural fMRI was used to identify individualized left parietal stimulation locations for both iTBS-PPC + Grasp and iTBS-PPC + Rest groups. For the iTBS-CTRL + Grasp group, a non-correlated region was selected as the stimulation location. The stimulation locations for each participant are indicated on a standard brain, and MNI coordinates (mean ± SD) are shown for each group. (C) The electric field induced by transcranial magnetic stimulation (TMS) for one participant from each group is shown.

assess visuomotor function because it does not involve dexterous shaping and manipulating objects by the hand as required by the pegboard task (Fiori et al., 2018). Therefore, CRT is thought to be less associated with the PPC-to-M1 neural pathway. Participants were seated in front of a monitor and viewed stimuli (central number cue: '1' or '2') from 30 cm. Participants were instructed to respond by pressing the '1' or '2' key on the keyboard with the right index or middle finger. Participants were instructed to perform the task as quickly and as accurately as possible. Participants performed 40 trials at every time point before and after (30 and 60 min) the intervention. Visual stimuli were presented, and the mean reaction time (RT) of hand responses was recorded using PsychoPy (version 2021.2.3; Peirce et al., 2019). RT was defined as the interval between the visual number cue and the correct key button response. Before each experimental session, participants were familiarized with the pegboard and CRT tasks during a short training period with an instructional video (www.nihtoolbox.org) followed by a practice block.

7.3.8 Experimental design

Our study randomly assigned participants to one of three rTMS intervention groups, followed by electrophysiological measures with TMS and behavioral measures (**Figure 7-3A**). Participants in the first group received iTBS to the PPC while concurrently performing a grasping task ($iTBS_{PPC+Grasp}$). Participants in the second group received iTBS to the PPC while in an unconstrained, resting state ($iTBS_{PPC+Rest}$). Contrasting these groups allowed us to elucidate the effects of targeted TMS enhancement of parietal–frontal grasping network and motor function and the interaction between parietal iTBS and behavioral state. To test the functional specificity of stimulation to the PPC, a third group of participants received iTBS to a cortical region outside of the grasping network while concurrently performing a grasping task ($iTBS_{Control + Grasp}$).

In Experiment 1 (pilot study), 24 participants received a single session of iTBS aimed at either the PPC or Pz electrode position (**Figure 7-3B**). In the second experiment, 48 participants underwent four consecutive daily sessions of iTBS, targeting either the PPC or the cortical control site. Each assessment session tested for the effects of each iTBS protocol on motor cortical

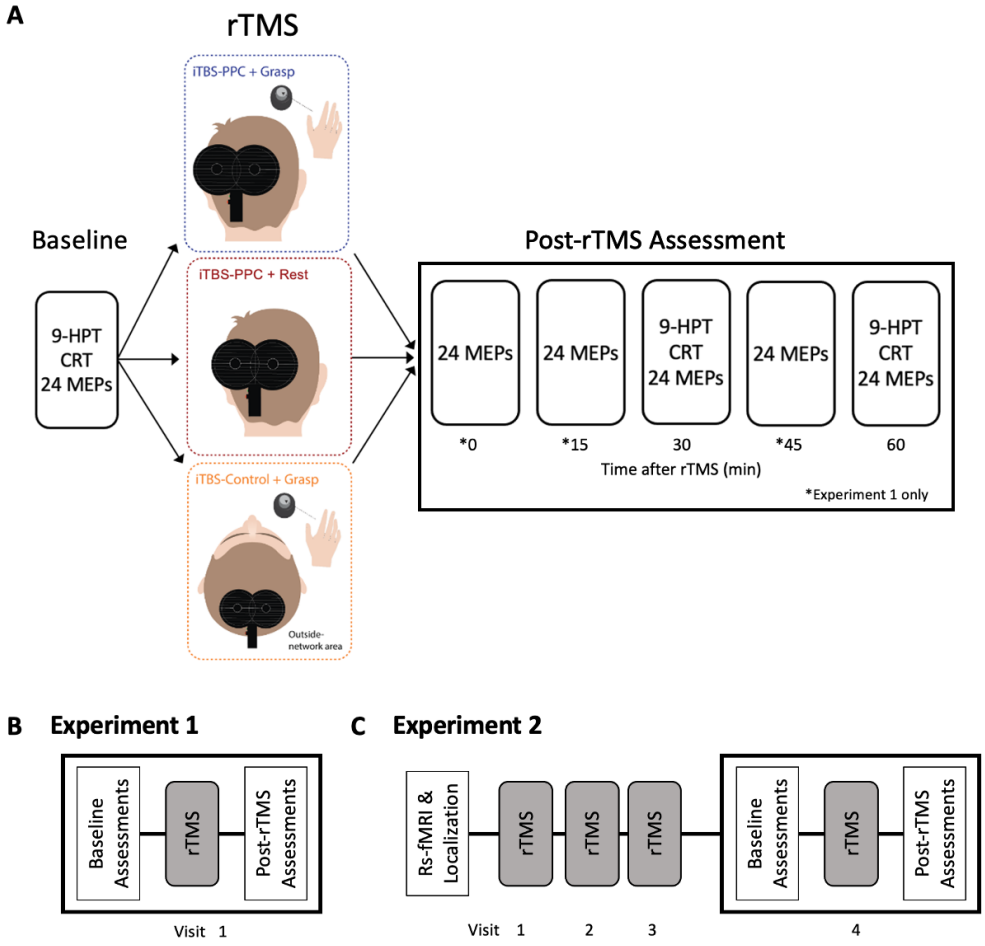

Figure 7-3 Experimental design diagram. (A) Participants were randomly assigned to one of three rTMS intervention groups. Electrophysiological and behavioral measurements were taken before (Baseline) and for an hour after the stimulation intervention. Motor-evoked potential amplitudes were measured at baseline and every 15 min for an hour after the iTBS intervention (0, 15, 30, 45, and 60 min) in Experiment 1 and after 30 and 60 min in Experiment 2. Both experiments measured behavioral performance on a nine-pegboard task (9-HPT) and choice reaction task (CRT) before and after the intervention (30 and 60 min). (B) In Experiment 1, participants underwent a single session of stimulation. (C) In Experiment 2, participants underwent a structural fMRI scan to determine the parietal stimulation location. Participants received three consecutive daily sessions of rTMS. On Visit 4, participants underwent assessments before (Baseline) and after rTMS, similar to Experiment 1.

excitability (e.g., MEPs) and behavioral performance (e.g., pegboard task and CRT). To measure changes in MEP amplitude, spTMS was applied to M1 at a fixed intensity that produced an MEP of 1 mV. In Experiment 1, we measured MEP amplitudes at baseline and every 15 min for an hour after the iTBS intervention (0, 15, 30, 45, and 60 min). In the second experiment, we measured MEP amplitudes immediately before and after (30 and 60 min) the fourth iTBS session (**Figure 7-3**) Brainsight was used to place the D702 coil over M1 throughout the experiment accurately. Both experiments assessed manual dexterity and CRT before and after the iTBS intervention (30 and 60 min).

7.3.9 Statistical analysis

Separate one-way analyses of variance (ANOVA) were used to confirm that the three groups ($iTBS_{PPC + Grasp.}$, $iTBS_{PPC + Rest}$, $iTBS_{Control + Grasp}$) did not differ in age or motor cortical excitability at baseline. MEP amplitudes were measured peak-to-peak for maximum and minimum values in the time window between 10 and 50 ms after spTMS (Carson et al., 2004; Fujiyama et al., 2016; Vesia et al., 2018). Changes in motor cortical excitability across Time and Intervention group were tested by fitting a linear mixed-effects model. The transformed MEP amplitude was used as the dependent variable, with the Intervention group and Time as fixed effects and subject as a random effect. Before including the data in the model, outlier MEP amplitudes that deviated by more than 3 units from the absolute median were removed for each subject. In total, 3.5% of all MEPs were excluded in Experiment 1, and 4.2% were excluded in Experiment 2 (Leys et al., 2013). MEP amplitudes were further transformed to account for their non-normal distribution. In Experiment 1, a power transformation of $x^{-0.16}$ was used, while in Experiment 2, a power

transformation of $x^{0.017}$ was applied. The model was then tested using type II Wald F tests with Kenward–Roger degrees of freedom correction.

Changes in motor performance were quantified by expressing mean time as a symmetric percentage change from the baseline of the time to complete the pegboard task and mean reaction time on the CRT for each participant. For the pegboard task, symmetric percentages were subjected to an order norm transformation to meet normality assumptions. Then, a linear mixed-effects model was fitted with transformed symmetric percent change as the dependent variable, Intervention group ($iTBS_{PPC + Grasp}$, $iTBS_{PPC + Rest}$, $iTBS_{Control + Grasp}$), and Time (30, 60 min) as fixed effects, and subject as a random effect. Similarly, for reaction time, values were log-transformed for normality. A linear mixed-effects model was fitted with transformed reaction time as the dependent variable, Intervention group and Time as fixed effects, and subject as a random effect. After fitting each model, type II Wald F tests with Kenward– Roger degrees of freedom correction were used to test for differences. In addition, Games-Howell *post hoc t*-tests were performed on pairwise comparisons of groups to account for unequal variances between groups and control for multiple comparisons' Type I error rate (Games & Howell, 1976). Analyses were performed using IBM SPSS Statistics Version 26.0 (IBM Corp., Armonk, NY, United States) and R (R Core Team, Vienna, Austria, 2022). Data are given as mean ± standard error of the mean (SEM). The threshold for statistical significance was set at $p \leq 0.05$. Where appropriate, partial η squared (η^2) values were computed as a measure of effect size. Cutoffs for effect sizes of ≥0.01, ≥0.06, and ≥ 0.14 are considered small, medium, and large, respectively (Cohen, 1992).

7.4 Results

All participants tolerated the experimental procedures. As shown in **Table 7-1** we found no significant difference between the three groups in age or measures of motor cortical excitability at baseline (**Figure 7-4**).

Experiment 1

	iTBS-PPC + Grasp	**iTBS-PPC + Rest**	**iTBS-Control + Grasp**	**Statistical Comparison**
Age (years)	24.0 ± 3.4	21.5 ± 2.1	24.5 ± 3.3	F(2,21) = 2.31 p=0.12
AMT (% MSO) (MagPro MCF-B70 coil)	41.6 ± 8.0	41.7 ± 8.0	39.1 ± 6.7	F(2,19) = 0.29 p=0.76
RMT (% MSO) (Magstim D50 B.I coil)	45.6 ± 8.6	46.9 ± 12.1	44 ± 9.3	F(2,21) = 0.16 p=0.85
$SI_{1\ mV}$ (% MSO) (Magstim D70^2 coil)	44.5 ± 6.7	47 ± 9.7	44.8 ± 9.7	F(2,21) = 0.19 p=0.82

Experiment 2

	iTBS-PPC + Grasp	**iTBS-PPC + Rest**	**iTBS-Control + Grasp**	**Statistical Comparison**
Age (years)	26.4 ± 8.6	26.8 ± 8.3	27.8 ± 8.3	F(2,45) =0.10 p=0.90
AMT (% MSO) (MagPro MCF-B70 coil)	39.5 ± 5.4	37.9 ± 3.9	40.4 ± 6.2	F(2,40) =0.82 p=0.45
RMT (% MSO) (Magstim D50 B.I coil)	43.1 ± 5.6	44.5 ± 9.6	50 ± 10.9	F(2,45) =2.67 p=0.08
$SI_{1\ mV}$ (% MSO) (Magstim D70^2 coil)	46.1 ± 7.3	47 ± 9.1	51.3 ± 11.7	F(2,45) =1.36 p=0.27

Table 7-1 Group values for age and stimulator intensities. Data are presented as mean ± SD. Transcranial magnetic stimulation (TMS) intensity (expressed as a percentage of the maximum stimulator output, % of MSO) of active motor threshold (AMT) and resting motor threshold (RMT). $SI_{1\ mV}$ refers to the percentage of MSO required to produce a ~ 1 mV motor-evoked potential (MEP). Separate one-way analyses of variance (ANOVA) were used to confirm that the three groups did not differ in age or motor cortical excitability at baseline.

7.4.1 Effects of the brain state during parietal stimulation on downstream motor cortical excitability

To test the hypothesis that manipulating the behavioral state during stimulation to PPC would affect motor plasticity associated with motor control, we compared changes in the excitability of the motor cortex by measuring the size of TMS-induced MEPs in the three stimulation groups.

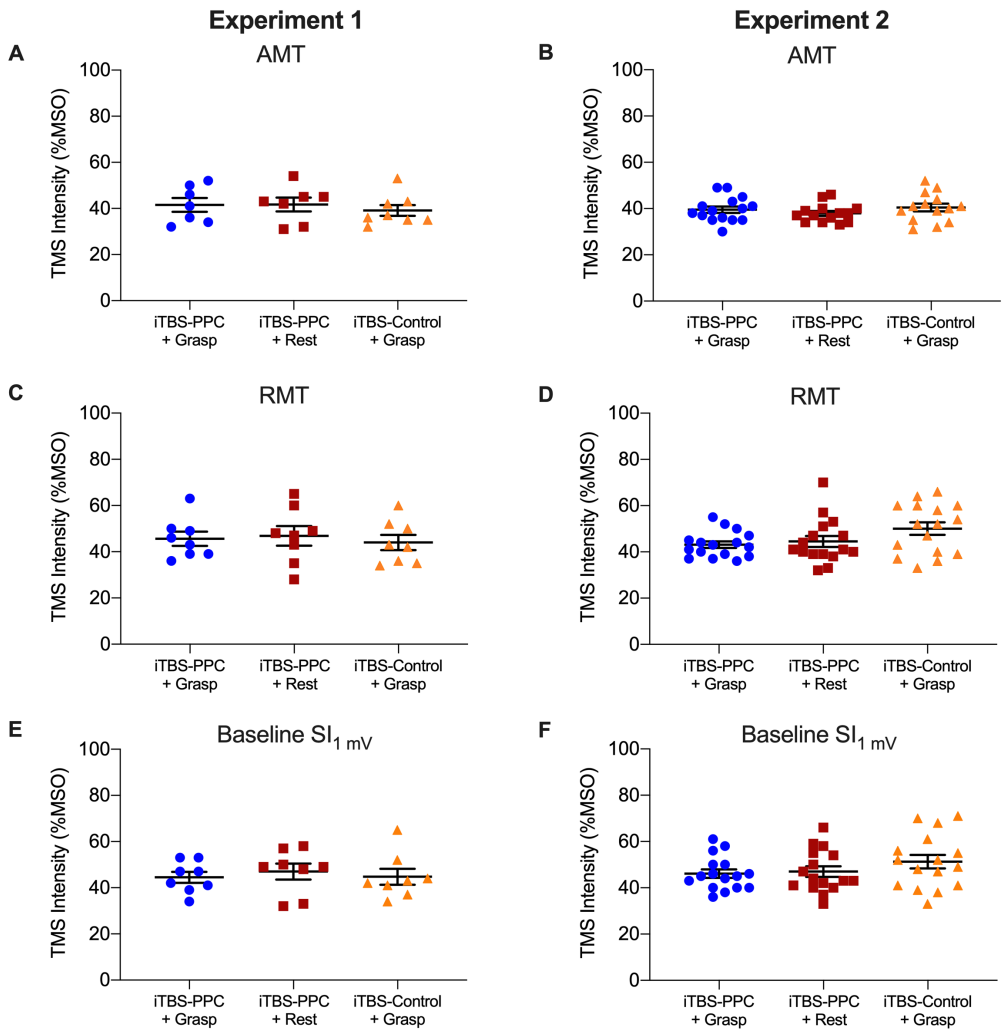

Figure 7-4 Individual values for baseline stimulator intensities. Column scatter plots showing the (A-B) transcranial magnetic stimulation (TMS) intensity (expressed as a percentage of the maximum stimulator output, MSO) of active motor threshold (AMT), (C-D) TMS intensity of resting motor threshold (RMT), and (E-F) TMS intensity eliciting 1 mV MEPs at baseline, for each participant for the $iTBS_{PPC + Grasp}$ group (blue circles) and $iTBS_{PPC + Rest}$ group (red squares) and $iTBS_{Control + Grasp}$ group (orange triangles) for each experiment.No differences were found between groups (for statistics, see **Table 7-1**).

7.4.1.1 Experiment 1

There were significant main effects of the Intervention group ($F_{2,21} = 4.17, p = 0.029, \eta_p^2 = 0.28$) and Time ($F_{5,3192.2} = 3.33$, p = 0.005, $\eta_p^2 = 0.005$) and a significant Time × Intervention group interaction ($F_{10,3192.2} = 5.66$, p < 0.001, $\eta_p^2 = 0.02$) on the MEP amplitudes; **Figure 7-5A**). Post hoc analyses revealed that MEP amplitudes for the $iTBS_{PPC + Grasp}$ group were significantly different from baseline MEPs at 30 min ($p < 0.0001$), and the difference in amplitudes from immediate post-stimulation to 30 min was also significant ($p = 0.002$). For the $iTBS_{PPC + Rest}$ group, MEP amplitudes were significantly different from baseline immediately after stimulation ($p < 0.0001$), at 30 min ($p = 0.03$), and 45 min ($p = 0.03$). Further *post hoc* analyses demonstrated that there were significant differences in MEP amplitude for the $iTBS_{PPC + Grasp}$ group at every time point following baseline compared to both the $iTBS_{PPC + Rest}$ and $iTBS_{Control + Grasp}$ groups (all comparisons $p < 0.0001$, except between $iTBS_{PPC + Grasp}$ and $iTBS_{Control + Grasp}$ immediately post-stimulation, where $p < 0.001$. There were no significant differences in MEP amplitudes between $iTBS_{PPC + Rest}$ and $iTBS_{Control + Grasp}$ at any time point. Closer inspection of the individualized normalized data showed highly consistent increases in the percentage change of MEP amplitudes across participants at 30 min and 60 min post-stimulation for the $iTBS_{PPC + Grasp}$ group (MEP change (%) increased for 7 out of 8 participants at 30 min; sign test $p = 0.07$; MEP change (%) increased for 6 out of 8 participants at 60 min; sign test $p = 0.29$; **Figure 7-5B,C**). Conversely, neither $iTBS_{PPC + Rest}$ (MEP change (%) increased for 1 out of 8 participants at 30 min; sign test $p = 0.07$; MEP change (%) increased for 3 out of 8 participants at 60 min; sign test $p = 0.73$) nor $iTBS_{Control + Grasp}$ (MEP change (%) increased for 2 out of 8 participants at both 30 min and 60 min; sign test $p = 0.29$) affected the magnitude of change in the MEP at these time points.

7.4.1.2 Experiment 2

In line with the pilot experiment's findings, Experiment 2 revealed significant main effects of the Intervention group ($F_{2,44}$= 5.64, p = 0.007, η_p^2 = 0. 2) and Time ($F_{2,3188.3}$= 26.91, p <0.0001, η_p^2 = 0.02) and a significant Time × Intervention group interaction ($F_{4,3188.3}$ = 22.95, p < 0.0001, η_p^2 = 0.03) on MEP amplitudes (**Figure 7-5D**). *Post hoc* tests indicated significant differences in MEP amplitudes for the $iTBS_{PPC + Grasp}$ group from baseline at 30- and 60-min post-stimulation ($p < 0.0001$). MEP amplitudes for $iTBS_{PPC + Rest}$ significantly differed between baseline and 60 min post-stimulation ($p = 0.002$) and between 30- and 60-min post-stimulation ($p = 0.03$), but not between baseline and 30 min post-stimulation. Conversely, no significant differences in MEP amplitudes were observed between any time points for the $iTBS_{Control + Grasp}$ group. Further *post hoc* tests revealed no significant differences in MEP amplitudes among groups at baseline. However, at both 30- and 60-min post-stimulation, the $iTBS_{PPC + Grasp}$ group showed significantly different MEP amplitudes compared to both $iTBS_{PPC + Rest}$ and $iTBS_{Control + Grasp}$ ($p < 0.0001$). At 60 min post-stimulation, the MEP amplitudes between the $iTBS_{PPC + Rest}$ and $iTBS_{Control + Grasp}$ groups also were significantly different ($p < 0.0001$).

The individualized normalized data showed consistent increases in the percentage change of MEP amplitudes from baseline across participants at 30 min and 60 min post-stimulation for the $iTBS_{PPC}$ + Grasp group (MEP change (%) increased for 15 out of 16 participants at 30 min; sign test p < 0.0005; MEP change (%) increased for 16 out of 16 participants at 60 min; sign test p < 0.0001; **Figure 7-5E,F**). Conversely, neither $iTBS_{PPC + Rest}$ (MEP change (%) increased for 10 out of 16 participants at 30 min; sign test p = 0.45; MEP change (%) increased for 12 out of 16 participants at 60 min; sign test p = 0.08) nor $iTBS_{Control + Grasp}$ (MEP change (%) increased for 6 out of 16 participants

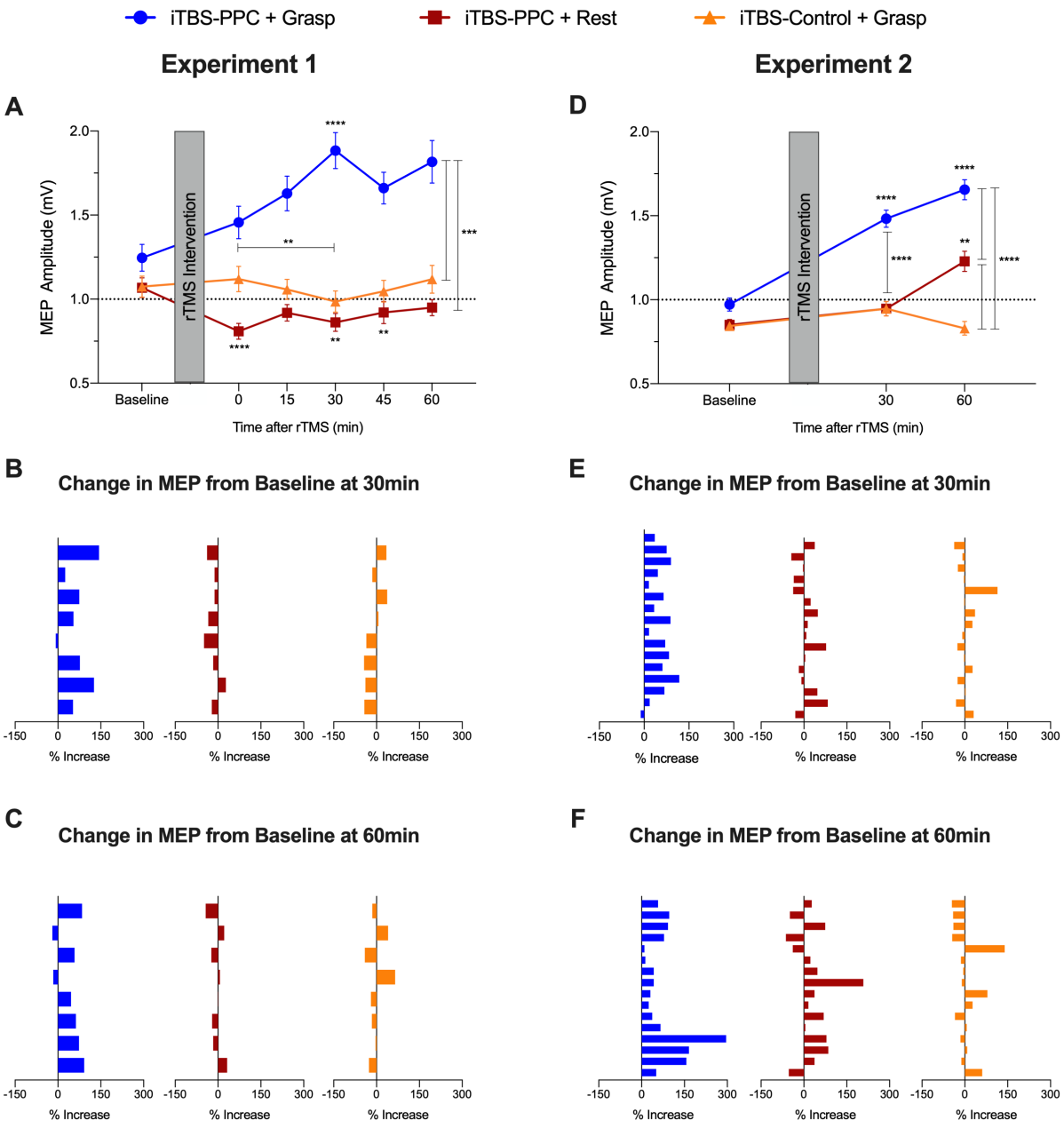

Figure 7-5 Motor cortical excitability findings. Group averaged motor evoked potential (MEP) amplitude (mV) for **(A)** Experiment 1 and **(D)** Experiment 2. Percentage change from baseline of MEP amplitude for each participant **(B)** 30 min and **(C)** 60 min post-stimulation in Experiment 1. Percentage change from baseline of MEP amplitude for each participant **(E)** 30 min and **(F)** 60 min post-stimulation in Experiment 2. Error bars denote the standard error of the mean (SEM). Asterisks indicate significant *post hoc* comparisons, $*p \leq 0.05$, $**p \leq 0.01$, $***p \leq 0.001$, $****p \leq 0.0001$.

at 30 min; sign test $p = 0.45$; and MEP change (%) increased for 7 out of 16 participants at 60 min; sign test $p = 0.8$) affected the magnitude of change in the MEP at these time points.

Together, these results indicate that the influence of PPC stimulation on motor cortical excitability depended on both the behavioral task being performed and the time at which the assessment was administered. Furthermore, this result reinforces that increased motor cortical excitability resulted from stimulation targeting a specific parietal-motor pathway. Critically, it is apparent that inducing functional activation in the cortical grasping network through a causal behavioral manipulation during parietal stimulation reliably alters downstream motor plasticity.

7.4.2 The effects of brain state during parietal stimulation on motor performance

7.4.2.1 Experiment 1

We examined the participants' motor performance on a pegboard test after (30 and 60 min) each rTMS intervention. There was a significant main effect of the Intervention group ($F_{2,21} = 11.54$, $p < 0.001$, $\eta_p^2 = 0.52$), no main effect of Time ($F_{2,42} = 1.68$, $p = 0.20$, $\eta_p^2 = 0.07$), and a significant interaction between Time and Intervention group ($F_{4,42} = 7.31$, $p < 0.001$, $\eta_p^2 = 0.41$), on the symmetric percentage change from baseline of mean time to complete the pegboard task (**Figure 7-6A**). Post hoc analyses showed that motor performance significantly improved at each time of measurement for the $iTBS_{PPC + Grasp}$ group compared to the $TBS_{Control + Grasp}$ (30 min, $p = 0.004$; 60 min: $p = 0.002$) and at the 60 min for the $iTBS_{PPC + Rest}$ group ($p = 0.003$). The time to complete the pegboard task decreased for the $iTBS_{PPC + Grasp}$ group, as shown by post hoc analyses indicating a significant symmetric percentage change from baseline in motor performance at 30

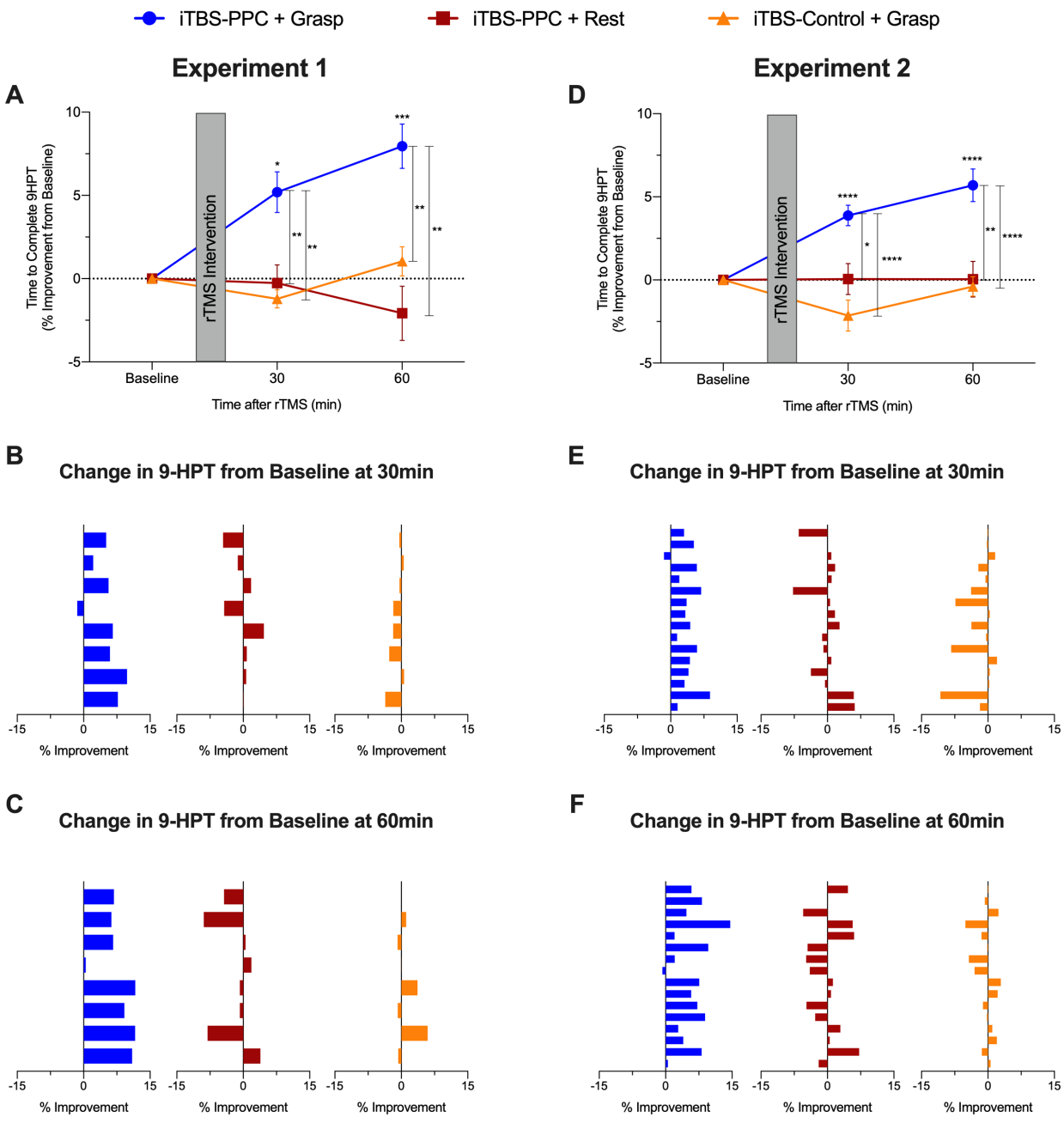

Figure 7-6 Functional dexterity findings. Group averaged percentage change from baseline to complete the nine-hole pegboard manual dexterity test (9-HPT) for (A) Experiment 1 and (D) Experiment 2. Positive values indicate a performance improvement. Mean percentage change from baseline to complete 9-HPT for each participant (B) 30 min and (C) 60 min post-stimulation in Experiment 1. Mean percentage change from baseline to complete 9-HPT for each participant (E) 30 min and (F) 60 min post-stimulation in Experiment 2. Error bars denote the standard error of the mean (SEM). Asterisks indicate significant post hoc comparisons, *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, ****$p \leq 0.0001$.

min ($p = 0.03$) and 60 min ($p < 0.001$). Notably, there was no significant difference in the symmetric percentage from baseline in motor performance at each time point for the $iTBS_{PPC + Rest}$ or the $iTBS_{Control + Grasp}$ groups (all comparisons $p \geq 0.15$).

Improvements in the percentage change from baseline in the time taken to complete the pegboard task were highly consistent across participants in the $iTBS_{PPC + Grasp}$ group (7 out of 8 participants' motor performance improved at 30 min; sign test $p = 0.07$; 8 out of 8 participants motor performance improved at 60 min; sign test $p = 0.008$) but not in the $iTBS_{PPC + Rest}$ group (4 out of 8 participants motor performance improved at 30 min; sign test $p = 1.27$; 3 out of 8 participants motor performance improved at 60 min; sign test $p = 0.73$) or the $iTBS_{Control + Grasp}$ group (2 out of 8 participants motor performance improved at 30 min; sign test $p = 0.29$; 3 out of 8 participants motor performance improved at 60 min; sign test $p = 0.73$; **Figures 7-6B,C**).

7.4.2.2 Experiment 2

The improvements in manual dexterity observed in Experiment 1 were replicated in Experiment 2. We found significant main effects of both Intervention group ($F_{2,45} = 20.98$, $p < 0.001$, $\eta_p^2 = 0.48$) and Time ($F_{2,90} = 3.87$, $p = 0.02$, $\eta_p^2 = 0.08$), as well as a significant Time × Intervention group interaction ($F_{4,90} = 7.61$, $p < 0.001$, $\eta_p^2 = 0.25$) on the symmetric percentage change in the time to complete the pegboard task from baseline (**Figure 7-6D**). Post hoc tests confirmed that the $iTBS_{PPC + Grasp}$ group showed significant differences from the other intervention groups, and their performance improved over time. Specifically, the $iTBS_{PPC + Grasp}$ group showed significantly different symmetric percentage changes in performance at both 30- and 60-min post-stimulation when compared to either of the other groups ($iTBS_{PPC + Rest}$, 30 min: $p = 0.01$, 60 min: $p = 0.002$; $iTBS_{Control + Grasp}$, 30 min: $p < 0.001$; 60 min: $p < 0.001$). Similar to the findings in

Experiment 1, only the $iTBS_{PPC + Grasp}$ group displayed improvements in performance over time, with their symmetric percentage change in time to complete the pegboard task being significantly different from baseline at both 30 and 60 min ($p < 0.001$). In contrast, neither of the other groups showed significant differences at either time (all comparisons $p > 0.07$).

Improvements in the percentage change from baseline in the time taken to complete the pegboard task were highly consistent across participants in the $iTBS_{PPC + Grasp}$ group (15 out of 16 participants' motor performance improved at both 30 and 60 min; sign test $p < 0.0005$) but not in the $iTBS_{PPC + Rest}$ group (10 out of 16 participants motor performance improved at 30 min; sign test $p = 0.45$; 8 out of 16 participants motor performance improved at 60 min; sign test $p = 1.2$) or the $iTBS_{Control + Grasp}$ group (5 out of 16 participants motor performance improved at 30 min; sign test $p = 0.21$; 7 out of 16 participants motor performance improved at 60 min; sign test $p = 0.8$; **Figures 7-6E,F**). Thus, motor improvement occurred reliably only when the functional state of

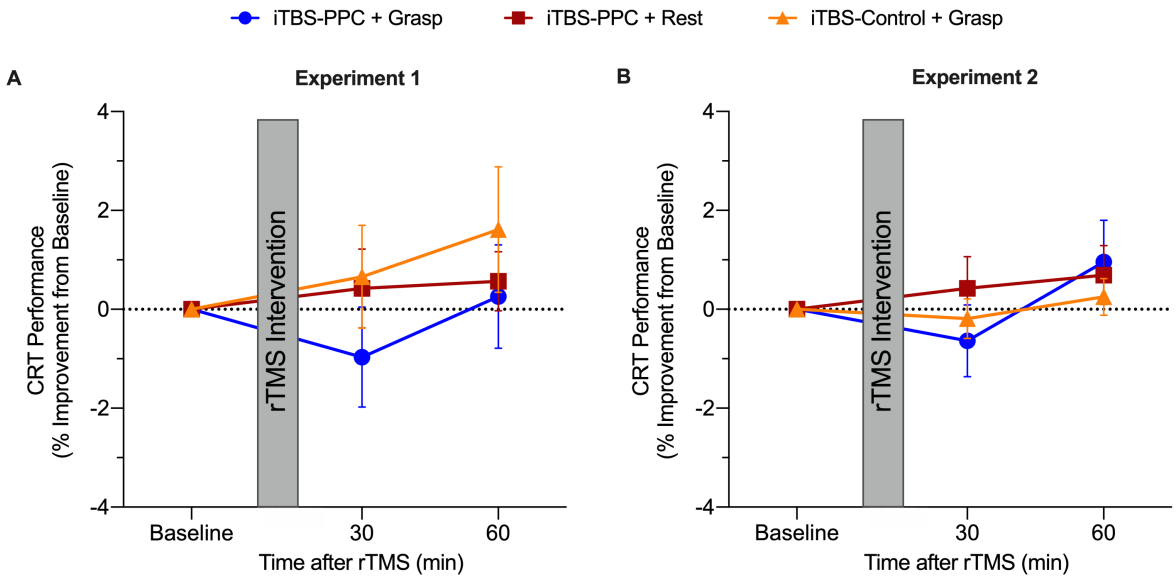

Figure 7-7 Group averaged percentage change from baseline for the choice-reaction visuomotor task (CRT) for 30- and 60-min post-stimulation for **(A)** Experiment 1 and **(B)** Experiment 2. Positive values indicate a performance improvement. Error bars denote the standard error of the mean (SEM).

the grasp network was engaged with a motor task during the administration of parietal stimulation, not for either control condition. These results underscore the consistent benefits of state-dependent parietal stimulation on manual dexterity across both experiments.

To assess the specificity of the effects of stimulation on motor performance, we compared reaction times for a control visuomotor CRT task that does not involve dexterous hand shaping and object manipulation in both experiments. Across both experiments, no significant differences in visuomotor performance were found across intervention groups or time. In the pilot experiment, after fitting and testing a linear mixed-effect model, there were no main effects of Time ($F_{2,42} = 1.42$, $p = 0.25$, $\eta_p^2 = 0.06$) or Intervention group ($F_{2,21} = 0.03$, $p = 0.97$, $\eta_p^2 < 0.001$), and no significant interaction ($F_{4,42} = 0.60$, $p = 0.67$, $\eta_p^2 = 0.05$; **Figure 7-7A**). Similarly, in the second experiment (**Figure 7-7B**), there was no significant main effect of Time ($F_{2,902} = p = 0.07$, $\eta_p^2 = 0.06$), Intervention group ($F_{2,45} = 1.60$, $p = 0.21$, $\eta_p^2 = 0.07$), or interaction ($F_{4,90} = 0.81$, $p = 0.52$, $\eta_p^2 = 0.03$). These findings are consistent with the hypothesis that the effect of parietal stimulation on motor performance is specific to planning and execution states for object-directed grasps rather than a general attention or performance benefit. Motor improvement was selective for skilled object-directed grasps and occurred reliably only when the targeted cortical motor planning network was engaged with a motor behavior at the time of parietal stimulation.

7.5 Discussion

The current study describes brain and behavior responses to intermittent theta burst stimulation to PPC applied during two distinct endogenous states of neural activity in the motor system (i.e., brain state at rest versus during action planning and execution). Delivering iTBS

to PPC when the cortical grasp network is engaged with a motor task increases the downstream excitability of an interconnected M1 region responsible for fine-motor action and concomitantly improves skilled motor performance for up to an hour. These findings demonstrate that the effects of parietal network-targeted stimulation are brain-state dependent and can influence motor plasticity beyond the stimulated region with high specificity to improve skilled motor control of hand actions immediately after stimulation.

It has been commonly found that there is a large degree of variability in brain activity and behavioral responses following rTMS (Corp et al., 2020; Nicolo et al., 2015; Ozdemir et al., 2020, 2021; Ridding & Rothwell, 2007; Ziemann & Siebner, 2015). For motor control, most work has examined the neural effects of rTMS on a brain at rest (Bergmann et al., 2016; Siebner et al., 2009). However, recent work has proposed that this variability can be partially explained by state-dependent effects, in which the stimulation response depends on the ongoing level of brain activity during stimulation (Bergmann, 2018; Bradley et al., 2022; Pasley et al., 2009; Romei, Thut, et al., 2016; Silvanto et al., 2008). In our study, we show that the direction of change in excitability is influenced by the physiological state of the targeted parietal-motor grasp network during stimulation. Our results suggest that PPC's facilitatory influence during grasping may cause recurrent excitation, leading to long-term potentiation-like changes in cortical excitability when stimulated. In contrast, stimulating during periods of PPC-mediated inhibition, such as during rest, may reduce neural activation, resulting in less potentiation. This explanation aligns with studies indicating that the ongoing activity level at the time of stimulation influences corticospinal excitability (Bestmann, Harrison, et al., 2008; Bestmann & Krakauer, 2015; Naros et al., 2020; Schaworonkow et al., 2019; Zrenner et al., 2018) and is consistent with recent

cortico-cortical TMS findings showing remote excitability effects of the parietal cortex on motor cortex reverse in direction with the motor state (Koch et al., 2008; Vesia et al., 2013, 2017).

The current findings also align with TMS's neural and behavioral effects when manipulating sensory, attentional, and cognitive states. Recent findings also have demonstrated that co-administration of low frequency rTMS to the motor cortex with motor training can enhance motor plasticity and improve motor skills in both damaged and intact brains (Buetefisch et al., 2004, 2011, 2015; Revill et al., 2020; Thabit et al., 2010). In addition, cognitive manipulations that direct attention to the hand during rTMS have been shown to produce larger increases in motor cortical excitability (Conte et al., 2007; Stefan et al., 2004). Other approaches have been used to modulate brain excitability before TMS by selectively preconditioning a specific neuronal population using either stimulation (Ni et al., 2014; Opie et al., 2019; Siebner et al., 2004) or behavioral adaptation (Silvanto et al., 2007) protocols. For instance, perceptual adaptation has been shown to augment the TMS-induced neural representation of observed motor behavior (Rotenberg et al., 2014). Our current results extend these prior findings on state-dependent motor responses to rTMS to provide novel physiological evidence that engaging the parietal– frontal network for goal-directed hand movements during parietal stimulation can affect cortical motor output for up to an hour.

The state dependency of neuronal responses to rTMS also can be found in interconnected brain areas (Siebner et al., 2009). Indeed, it is well established that the effects of stimulation propagate beyond the stimulation site to impact functionally specific brain networks (Beynel et al., 2020; Fox et al., 2012; Lynch et al., 2022; Siebner et al., 2009). Importantly, the effects of stimulation on brain networks can be influenced by the activation state of interconnected regions

within the functional network (Blankenburg et al., 2008, 2010; Moisa et al., 2012; Ruff et al., 2006, 2008). It is possible that the ongoing activity and inherent excitability of neurons can influence the spread of neural excitation within the targeted area and to other regions in the brain. As a result, synchronizing neural firing patterns with stimulation can strengthen connections between neurons and facilitate state-specific changes in the brain (Siebner et al., 2022). For example, activating the motor system with a behavioral task, such as the performance of an isometric hand grip during premotor cortex stimulation, influences contralateral cortex activity (Bestmann, Swayne, et al., 2008). Cortico-cortical interactions that can be probed with two TMS coils over two connected brain areas have shown dynamic changes in excitability(Goldenkoff et al., 2020; Hallett et al., 2017; Koch & Rothwell, 2009; Lafleur et al., 2016; Van Malderen et al., 2022)2016; Van Malderen et al., 2022). Furthermore, our previous dsTMS experiments show that PPC regions involved in encoding hand movements exert an inhibitory influence on motor output at rest. Interestingly, this net inhibitory drive at rest in PPC is facilitated during the preparation of a grasping movement (Vesia et al., 2013, 2017). We, therefore, reasoned that capitalizing on the physiological state of the brain using multi-focal TMS methods can selectively target active neurons when delivering stimulation to the parietal location to enhance the specificity of excitation to the connected motor regions. This approach may increase the excitability of specific neural pathways associated with movement by modulating the connections between pre- and post-synaptic neuronal activities through Hebbian mechanisms (Hebb, 1949; Markram et al., 2011) , inducing LTP-like changes in synaptic strength (Suppa et al., 2016). In the current study, intermittent theta burst stimulation may have induced long-lasting changes in cortical excitability by modulating calcium influx via the post-synaptic membrane, resulting in LTP-like effects on

cortical synapses (Hebb, 1949; Huang et al., 2011; Markram et al., 2011; Suppa et al., 2016). The underlying mechanisms of the brain-state-dependent TMS effects on motor function observed in our data may be activity-dependent plasticity, whereby control over the cortical state with a voluntary movement during stimulation boosts the response in the activated brain network (Siebner et al., 2009); *cf.* (Paulus & Rothwell, 2016). The current results add to prior research demonstrating that theta burst stimulation to premotor (Huang et al., 2018) and PPC (Premji et al., 2011) regions can impact downstream cortical motor plasticity. Altogether, these findings demonstrate that the effect of stimulation on downstream motor cortical excitability depends on the current state of excitation of the connected brain region being stimulated within the functional network.

The present findings also demonstrate that this state-dependent modulatory effect can improve behavior immediately after stimulation. For example, we found that theta burst stimulation to the grasping network selectively improves skilled motor performance when the network is active relative to when it is at rest. This result is consistent with previous work in the visual domain, indicating robust state-dependent effects when pairing stimulation with neural activity functionally tuned to visual motion stimuli (Chiappini et al., 2018). One possible mechanism of the immediate state-dependent effect is that selective neural representations and pathways underlying the perceptual and behavioral processes are more susceptible to stimulation (Bradley et al., 2022; Pasley et al., 2009; Romei, Thut, et al., 2016; Silvanto et al., 2008). Future neuroimaging work is necessary to characterize the neural basis of this neural response, particularly at mesoscale brain circuits that subserve voluntary motor control.

The convergence of the current neurophysiological and behavioral findings strongly suggests that variability in neural activity levels at the time of stimulation contributes to the variability of the responses to rTMS in the motor system. In the current study, the group-averaged data showed that applying theta burst stimulation during a constrained high-activity state through a causal behavioral manipulation improves motor function immediately after stimulation rather than using the same pulse train during spontaneous neural activity discharge while participants are at rest. A closer inspection of individual results clearly shows two distinct patterns diverging based on the functional context of neural activity during stimulation. The group that received brain-state dependent parietal stimulation showed significant and consistent increases in both excitability and performance in all participants. In contrast, the effects of stimulation on motor plasticity and motor performance changes varied in magnitude and direction across individuals within the control conditions. This implies that variations in resting-state brain activity may influence individual differences in TMS responses and can be reduced by task manipulations (Bergmann, 2018; Romei, Thut, et al., 2016; Siebner et al., 2009, 2022; Silvanto et al., 2008; Silvanto & Pascual-Leone, 2008). This relationship may explain, in part, the considerable individual variation in brain and behavior responses within healthy and patient population studies reported in brain stimulation research. Such state-dependent TMS methods can identify novel neural paths to modify the output of the motor cortex and possibly translate into therapeutic approaches that underpin hand control for neurological disorders with aberrant plasticity. Notably, motor impairments after stroke often can be explained by abnormalities in parietal–frontal circuits subserving the integration of sensory input with motor commands, thus demonstrating network-level dysfunction of neural interactions for sensorimotor control (Grefkes & Fink, 2011; Guggisberg et al., 2019). Most therapeutic

stimulation has focused on frontal motor circuits (Morishita & Hummel, 2017), encompassing the primary motor cortices, premotor cortices, and supplementary motor areas. Here, we focused on interactions between PPC, a higher-order area significantly involved in action-related processes, and frontal motor areas (Andersen & Cui, 2009). Even though these network effects are relevant to therapeutic response (Fox et al., 2014; Horn & Fox, 2020), few studies have focused modulatory stimulation on the PPC component, an important 'brain hub' (Grefkes & Fink, 2011, 2014; Grefkes & Ward, 2014) of a well-characterized parietal–frontal grasping network (Davare et al., 2011; Grafton, 2010; Turella & Lingnau, 2014; Vesia & Crawford, 2012). This is important because higher levels of functional connectivity in parietal–frontal circuits in the motor system have been related to more favorable motor outcomes after stroke (Schulz et al., 2015, 2016).Given that the current results provide evidence for parietal contributions to motor function, we propose that targeting higher motor areas such as PPC with rTMS, primarily when functionally engaged with other interconnected frontal cortical regions, might be a better alternative for stroke patients with greater sensorimotor impairments (Plow et al., 2015, 2016). Further research is needed to determine the relevance of the proposed rTMS approach in clinical settings.

The current study has some limitations worth noting. First, the number of female participants in Experiment 2 was greater than males. Recent work has highlighted the influence of sex on the brain and behavior responses to TMS (Hanlon & McCalley, 2022). This may relate to various biological metrics, such as the distance between the scalp and cortex, gray matter density, and estradiol and progesterone levels. Still, sex is unlikely to account for the current results because it would be counterbalanced across the intervention groups. In addition, we personalized

stimulation intensity based on each participant's neuroanatomy to minimize variance in cortical target site intensities (Stokes et al., 2005). It is also important to consider that the current study did not implement a sham control. We, therefore, cannot rule out the TMS-induced placebo effects on brain and behavioral outcomes (Boucher et al., 2021). We would expect, however, variance in brain and behavior responses in all intervention groups. Yet, our results showed clear and consistent effects of brain-state dependent parietal TMS on motor excitability and manual dexterity, with notable differences between intervention groups. Future research could benefit from including sham TMS to better differentiate the effects of time on motor function.

In summary, our findings demonstrate that brain-state-dependent stimulation of a higher-order node in the cortical grasping network can alter motor cortical excitability beyond the stimulation site, leading to improved motor control of hand movements for up to an hour. Whether these changes in brain and behavior persist beyond the one-hour period we tested remains to be seen. Similarly, because multiple consecutive days of stimulation can produce long-lasting cumulative effects (Freedberg et al., 2019, 2020; J. X. Wang & Voss, 2015), future studies should investigate the duration and magnitude of state-dependent changes on motor function caused by multiple-day stimulation, which could be particularly relevant to a clinical cohort. As our data indicate, rTMS results could be more consistent by controlling the behavioral state at the time of stimulation to induce network-specific plasticity in the motor system. It may prove useful to employ this methodological approach to optimize targeted neuromodulation strategies with practiced movements for treating a wide range of neurological disorders marked by movement dysfunction, such as stroke and Parkinson's disease.

Chapter 8: Conclusion

8.1 Summary

Through a series of studies in this dissertation, I researched the underlying mechanisms of rTMS and its interactions with the motor control network, the variability in outcomes of its application, and proposed methodological improvements aimed at enhancing its lasting effects on brain and behavior outcomes. While many of the studies presented here probe the mechanisms by which rTMS modulate brain activity and behavioral outcomes in young healthy adults, I also examined how plasticity mechanisms change with age and may consequently impact the interaction of rTMS with brain activity in a motor control network in older adults. Ultimately, these findings underscore the complexity of motor control processes in the human brain and the nuanced effects that rTMS can have on neural networks across the lifespan.

8.1.1 Network based rTMS stimulation

Traditional rTMS protocols have primarily stimulated the primary motor cortex (M1) to investigate or enhance motor control, as it produces movement execution commands. However, this approach overlooks the complexities of the human motor network and the integrated activities of distinct neural regions that collectively orchestrate motor planning, initiation, and execution (Plow et al., 2015; Raffin & Siebner, 2014).

Alternatively, I presented a broader approach that encompasses different nodes within the motor network, such as the cerebellum (CB) and posterior parietal cortex (PPC). This method accounts for the dynamic interactions of various cortical, subcortical, and cerebellar regions and

makes use of the downstream plasticity effects that occur from rTMS-induced current spread along axons and modulation of neural oscillatory activity (Liew et al., 2014). In **Chapter 2** (Goldenkoff et al., 2020), I discussed how to use rTMS in a paired-pulse, dual-coil approach to probe parietal-motor interactions and transiently strengthen synaptic efficiency between two interconnected brain areas in the reach-to-grasp motor network. This method is important because it can reveal causal relationships between brain regions of a functional network and behavior at a systems level (Chouinard & Paus, 2010; Hallett et al., 2017; Lafleur et al., 2016). I used the dual-coil functional connectivity assessment in **Chapter 3** (Goldenkoff et al., 2021) to examine how connections between the PPC and M1 change in older adults. My findings indicate that faciliatory mechanisms between these brain areas are reduced with age. This finding informs a later study, **Chapter 5** (Goldenkoff et al., in prep), which investigates the plasticity effects of cortical paired associative stimulation (cPAS) in older adults.

Taken together, I demonstrated that multifocal stimulation, i.e., activating several different nodes within a network to enhance the effects of stimulation, is an important factor in optimizing the effects of rTMS interventions.

8.1.2 Dosing quantities of rTMS stimulation

Multiple, repeated sessions of rTMS are more likely to produce enhanced and sustained effects on neural plasticity than a one-off session (Nettekoven et al., 2014; Nyffeler et al., 2006). Repeated exposure to stimulation supports incremental synaptic changes to synaptic plasticity that build up over time and facilitate lasting modifications to neural circuit connectivity. In **Chapter 4** (Goldenkoff et al., under review), I demonstrated this dose-dependent effect within the parietal-motor network and showed the potential for repeated spaced doses of cPAS to cumulatively increase motor excitability in young adults. The study presented in **Chapter 4**

spaced the bouts of cPAS 50min apart, which corresponds with ideal intervals for the improvement of motor learning (Smolen et al., 2016). Providing adequate breaks between rTMS sessions can facilitate additive plasticity as the down periods allow the brain to consolidate the induced synaptic changes to long-term potentiation (Goldsworthy et al., 2012).

However, because it is well established that older adults have a reduced capacity for plasticity and altered parietal-motor connectivity (as demonstrated in **Chapter 3**), **Chapter 5** (Goldenkoff et al., in prep) investigated how repeated multi-dose cPAS protocol would affect motor excitability in older individuals. The study found no increases in potentiation after repeated spaced cPAS, indicating a reduced additive metaplastic response in older adults. However, the reduction in motor excitability after applying a single dose of cPAS was countered by the delivery of multiple doses.

In summary, these results indicate that effects of rTMS are dose-dependent in young adults and suggest that further research is required to understand how number of rTMS sessions interact with the plasticity alterations associated with aging.

8.1.3 Controlling the brain-state during rTMS stimulation

The efficacy of rTMS is not only contingent on the parameters of the stimulation itself but also on the dynamic state of the brain at the time of intervention, and variability of rTMS-induced effects can be partly attributed to neural activity within targeted neural populations during stimulation (Bergmann, 2018). Therefore, modulating the brain stats by preconditioning with a bout of priming stimulation or employing task-specific engagement during stimulation could amplify the efficacy and functional specificity of rTMS interventions. I delved deeper into the impact that manipulating the brain state has on the outcomes of rTMS in the final chapters of the dissertation.

In **Chapter 6** (Goldenkoff et al., in prep), I showed how a bout of priming stimulation to a node in the motor network modulates the effects of subsequent stimulation delivered to downstream brain regions. Specifically, intermittent theta burst stimulation (iTBS) applied to the right cerebellum reduced the effect of subsequent parietal-motor paired associative stimulation on motor plasticity. This study suggests that by stimulating a cerebellar target in the motor network, it is possible to modify the brain's activity state and regulate plasticity induction in a downstream parietal-motor circuit, which is involved in reach-to-grasp actions.

The brain state can also be manipulated by engaging the participant in a task that activates the targeted network (Chiappini et al., 2018; Romei, Thut, et al., 2016). In **Chapter 7** (Goldenkoff et al., 2023), I showed that controlling the brain state during parietal iTBS with a grasping task enhances downstream motor excitability and performance. This likely occurs because the action primes neuronal populations and lowers the activation threshold required to induce excitation in the motor network involved in reach-to-grasp control, making the motor network more responsive to stimulation. When designing interventions that use rTMS, it is crucial to consider the current state of the brain. To improve the effectiveness and specificity of stimulation outcomes, therapeutic protocols should synchronize stimulation with ongoing brain activity or adjust the brain state with prior stimulation or task engagement.

8.2 Limitations and future directions

A limitation of this study is its generalizability. Participants were mostly recruited from the University of Michigan campus and the surrounding Ann Arbor area, representing a population of predominantly white, highly educated, and higher socioeconomic status individuals compared to the national average (DePietro, 2023). Therefore, the effects of rTMS observed may not generalize to more diverse demographic groups. Future research should aim to include a

broader range of participants, including wider age ranges, representation of more race and socioeconomic backgrounds, and neurodiverse individuals (Peebles et al., 2023). This knowledge can be used to individualize therapeutic interventions to meet the needs of each patient and improve their motor symptoms.

Further research is also needed to better tailor rTMS protocols to specific populations, including older adults and patients with varying degrees of motor impairments. Because of the increased prevalence of neurodegenerative conditions like stroke and Parkinson's Disease in this population, understanding how rTMS protocols influence synaptic plasticity in older individuals is crucial for the translation of these approaches to therapeutic interventions. We need to gain a deeper understanding how factors like age, disease severity, physiological variations, and individual differences in brain structure and function affect responsiveness to rTMS to improve personalization of treatment approaches. Research should also explore how rTMS can be effectively integrated with other rehabilitation therapies, such as physical therapy and cognitive-behavioral therapy, because addressing multiple facets of motor impairment could improve motor recovery interventions and make them more tailored to individual patients' needs (Evancho et al., 2023).

Another limitation of these studies is the reliance on changes to motor evoked potential (MEP) amplitudes as the primary pre/post-intervention measurement probes. There is well-documented MEP inter-trial variability, and many factors significantly affect MEP amplitude, including prior and concurrent muscle activation and number of repeated pulses delivered (Darling et al., 2006; Kiers et al., 1993). Also, MEPs likely reflect net inhibitory and excitatory inputs to the entire descending pathway and do not capture the localized cortical effects that do not project to the spinal neurons (Rocchi et al., 2018). While some of the studies discussed here

utilize behavioral changes to evaluate rTMS effectiveness, future research should integrate MEP measurements with functional assessments, kinematic metrics, neuroimaging, and electroencephalography to gain a holistic understanding of rTMS impact. Combining multiple measurement approaches can provide a more detailed view of how rTMS modulates neural network connectivity, alters real-time brain dynamics, affects movement execution, and impacts activities of daily living (Bergmann et al., 2016).

Third, this dissertation did not examine the long-term functional outcomes of rTMS interventions targeting the motor control network. I monitored brain and behavioral modulations for up to a few hours after stimulation. However, for rTMS to be effectively translated into clinical practice, we need to better understand the persistent effects that remain days, weeks, and months afterwards. Future research should aim to evaluate the lasting effects of network-focused, dose-optimized, and brain-state tailored rTMS therapy. Such studies are crucial for understanding therapeutic outcomes' durability and identifying potential long-term side effects.

8.3 Implications for brain research and rehabilitation

The findings from this dissertation have implications for both basic science and the translation of rTMS into clinical practice. For basic science, this research enhances our understanding of the neural mechanisms underlying motor control and the effects of rTMS on brain and behavior. It provides a deeper insight into how different components of the motor control network interact, causally influence plasticity in other brain regions, and respond to targeted interventions. Ultimately, this research contributes to the broader field of neurophysiology and neurorehabilitation research by helping to elucidate the role of interconnected neural circuits involved in motor control, with a specific focus on goal-targeted reach-and-grasp actions.

For the translation to therapy, this work underscores the potential of rTMS as a customizable and effective treatment for motor impairments, particularly those resulting from stroke or other neuromotor disorders. This research paves the way for more personalized rTMS protocols and opens new avenues for maximizing the efficacy of rTMS by demonstrating the importance of focusing stimulation within specific networks, optimizing stimulation dose, and considering the brain state during stimulation. The ability to tailor interventions to individual patient needs could significantly enhance recovery outcomes, making rTMS a more viable and widely accepted therapeutic option in clinical settings. Eventually, the outcomes of this research may help develop neurorehabilitation strategies to improve recovery of motor skills lost to brain injury or disease.

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