The Efficacy of Intermittent Theta Burst Stimulation (iTBS) in Neural Facilitation and Motor Adaptation Learning

Nicia John
Department of Psychology
McGill University, Montréal
Dr. David Ostry

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I | Abstract

Intermittent theta burst stimulation (iTBS), a non-invasive brain stimulation (NIBS) technique based on the principles of theta-gamma coupling in the hippocampus, was introduced as a method to focally facilitate learning, memory, and cortical excitability in diverse brain regions. In the standard practice of using a single block of iTBS for facilitatory brain stimulation protocols, evidence shows that substantial iTBS response variability arises both between and within subjects, thereby contributing to inconsistent findings in the existing literature. Therefore, following the double-block methodology of continuous theta burst stimulation (cTBS), a NIBS technique that more reliably produces disruption of cortical activity, this thesis explores the effects of two rounds of iTBS on learning and retention in a force-field adaptation task, as well as the effects of double iTBS on motor (MEPs) and somatosensory evoked potentials (SEPs).

Two studies were conducted. In the first, an upper-limb motor learning study, participants received either one (iTBSx1) or two blocks (iTBSx2) of iTBS to either the primary motor cortex (M1), primary somatosensory cortex (S1), or a control area before training in a force-field adaptation task. To assess the consolidation of motor learning, participants returned 24 hours later for a retention test. While a single block of iTBS to S1 resulted in a significant transient decrease in learning, no significant differences in either learning or retention were observed following iTBSx2. In study two, changes in MEPs and SEPs were assessed post double iTBS. In the MEP experiment, participants received brain stimulation to either M1 or S1. There were no significant differences in MEP amplitudes across conditions. However, in the SEP protocol combining EEG and iTBS to assess differences in evoked potentials following iTBSx2 to

S1, a significant decrease in SEPs was observed. In both the MEP and SEP results, high post-stimulation response variability remained evident.

The findings from both the motor learning and event-related potential (ERP) study show that an increased number of iTBS blocks may not induce greater facilitatory effects on cortical activity. As the observed variability in responses suggests a need for a more nuanced understanding of iTBS mechanisms, this thesis demonstrates that the complex effects of iTBS on motor learning and neural excitability necessitate a more refined approach for future research.

I | Résumé

La stimulation thêta intermittente (iTBS), une technique de stimulation cérébrale non invasive (NIBS) basée sur les principes du couplage thêta-gamma dans l'hippocampe, a été introduite comme méthode pour faciliter l'apprentissage, la mémoire et l'excitabilité corticale dans diverses régions du cerveau. La pratique standard consistant à utiliser un seul bloc d'iTBS pour les protocoles de stimulation cérébrale facilitatrice montre qu'une variabilité substantielle de la réponse iTBS apparaît à la fois entre les sujets et au sein d'un même sujet, contribuant ainsi à des résultats incohérents dans la littérature existante. Par conséquent, en suivant la méthodologie à double bloc de la stimulation thêta continue (cTBS), une technique NIBS qui produit une perturbation plus fiable de l'activité corticale, cette thèse explore les effets de deux séries d'iTBS sur l'apprentissage et la rétention dans une tâche d'adaptation au champ de force, ainsi que les effets de la double iTBS sur les potentiels évoqués moteurs (MEP) et sur les potentiels évoqués somatosensoriels (SEP).

Deux études ont été menées. Dans la première, une étude sur l'apprentissage moteur des membres supérieurs, les participants ont reçu un (iTBSx1) ou deux blocs (iTBSx2) d'iTBS au niveau du cortex moteur primaire (M1), du cortex somatosensoriel primaire (S1) ou d'une zone de contrôle avant de s'entraîner à une tâche d'adaptation au champ de force. Pour évaluer la consolidation de l'apprentissage moteur, les participants sont revenus 24 heures plus tard pour un test de rétention. Alors qu'un seul bloc d'iTBS sur S1 a entraîné une diminution transitoire significative de l'apprentissage, aucune différence significative dans l'apprentissage ou la rétention n'a été observée après l'iTBSx2. Dans la deuxième étude, les changements dans les

MEP et les SEP ont été évalués après un double iTBS. Dans l'expérience MEP, les participants ont reçu une stimulation cérébrale au niveau de M1 ou S1. Il n'y a pas eu de différences significatives dans les amplitudes des MEP entre les conditions. Cependant, dans le protocole SEP combinant EEG et iTBS pour évaluer les différences dans les potentiels évoqués après iTBSx2 à S1, une diminution significative des SEP a été observée. Dans les résultats des MEP et des SEP, la grande variabilité de la réponse post-stimulation est restée évidente.

Les résultats de l'apprentissage moteur et de l'étude du potentiel lié à l'événement (ERP) montrent qu'un nombre accru de blocs iTBS n'induit pas nécessairement des effets facilitateurs plus importants sur l'activité corticale. Comme la variabilité observée dans les réponses suggère la nécessité d'une compréhension plus nuancée des mécanismes de l'iTBS, cette thèse démontre que les effets complexes de l'iTBS sur l'apprentissage moteur et l'excitabilité neuronale nécessitent une approche plus raffinée pour les recherches futures.

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Contributions of Authors

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List of Abbreviations

Abbreviation	Meaning
CA^{2+}	Calcium
CNS	Central nervous system
CS	Conditioning stimulus
cTBS	Continuous theta burst stimulation
dACC	Dorsal anterior cingulate cortex
dPFC	Dorsolateral prefrontal cortex
d-waves	Direct waves
EEG	Electroencephalography
EMG	Electromyography
ERP	Event-related potential
FDI	First dorsal interosseous
fMRI	Functional magnetic resonance imaging
ICA	Independent components analysis
ICF	Intracortical facilitation
ISI	Interstimulus interval
i-waves	Indirect waves
iTBS	Intermittent theta burst stimulation
iTBSx1	Experiment 1: One block of iTBS
iTBSx2	Experiment 2: Two blocks of iTBS
LICI	Long interval intracortical inhibition
LTD	Long-term depression
LTP	Long-term potentiation
M1	Primary motor cortex
MEP	Motor evoked potential
MS	Multiple Sclerosis
NIBS	Non-Invasive Brain Stimulation
PCC	Posterior cingulate cortex

Abbreviation	Meaning	Pages
PET	Positron emission tomography	
PMC	Premotor cortex	
dPMC	*Dorsal premotor cortex*	
PPC	Posterior parietal cortex	
ROI	Region of Interest	
S1	Primary somatosensory cortex	
SEP	Sensory evoked potential	
SICI	Short interval intracortical inhibition	
SICF	Short interval intracortical facilitation	
SMA	Supplementary motor area	
SPE	Sensory prediction error	
STG	Superior temporal gyrus	
tDCS	Transcranial direct current stimulation	
atDCS	*Anodal transcranial direct current stimulation*	
cTDCS	*Cathodal transcranial direct current stimulation*	
TMS	Transcranial magnetic stimulation	
cTBS	*Continuous theta burst stimulation*	
iTBS	*Intermittent theta burst stimulation*	
rTMS	*Repetitive transcranial magnetic stimulation*	
spTMS	*Single-pulse transcranial magnetic stimulation*	
TS	Test stimulus	
TUS	Transcranial ultrasound stimulation	

1 | Introduction

Our ability to modulate cortical activity through electrical stimulation revolutionizes the ways in which we can study the human brain. Brain stimulation techniques can be invasive, involving physical manipulation of brain tissue through surgery, or non-invasive: non-invasive brain stimulation (NIBS) techniques permit the study of human behaviour through pain-free, minimal risk technologies (Bhattacharya et al., 2021). Consequently, along with its continuous evolution, NIBS findings are often translated to clinical settings for the diagnosis and treatment of various neurological and psychological disorders (Schulz et al., 2013; Dunlop et al., 2017; Wang et al., 2023). Extensive work has been carried out to ensure the safety of using non-invasive brain stimulation tools on human participants, and procedural guidelines on their ethics and protocol are updated regularly to keep the field informed (Rossi et al., 2009; Bikson et al., 2016; Rossi et al., 2021; Buchanan et al., 2023). Therefore, it is important to further investigate the efficacy, reliability, and validity of NIBS tools to gain an increased understanding of their potential benefits and limitations across multiple contexts.

During non-invasive brain stimulation, brain regions of interest (ROIs) are temporarily disrupted to either facilitate or suppress cortical activity. Stimulation effects can be either broad—affecting multiple brain regions –or focal – influencing areas as small as a few square millimeters –changes. Several procedures, such as transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS) and transcranial ultrasound stimulation (TUS), have been developed to fulfill various research and clinical needs. This thesis specifically explores the potential of intermittent theta burst stimulation (iTBS), through TMS, to effectively facilitate upper-limb motor learning and increase cortical activity through neuronal excitation.

A standard iTBS procedure involves just over three minutes –one block– of directing three 50Hz pulses at intervals of 200ms (5 Hz) to a specific area on the scalp. Stimulation occurs intermittently with two seconds on and eight seconds off for a total of 600 pulses (190 seconds), directly stimulating the underlying cortical area of interest, and a 15-minute wait period immediately follows the three-minute block. This procedure was first used to demonstrate that iTBS can increase the amplitude of motor evoked potentials (MEPs) elicited from the right first dorsal interosseous (FDI) muscle after stimulation to the hand area of the left primary motor cortex (M1) (Huang et al., 2005). Since then, the application of one block of iTBS has been repeatedly explored as a means to enhance sensorimotor learning and to improve various cognitive functions. However, as results emerge, an area of concern arises.

When Hamada et al. (2013) obtained MEPs from the right FDI muscle before and after one block of iTBS, less than half of their participants responded to stimulation in the expected direction of MEP increase, and overall, there was no effect of iTBS on cortical activity. Participants were grouped into responders, meaning that neural activity successfully increased as a result of stimulation, or non-responders, where no change or a change in the opposite direction of excitability occurred. This finding that iTBS may not produce a significant group effect of stimulation due to variability in participants' responses is similarly evident in other instances assessing changes in cortical excitability (Katagiri et al., 2020; Leodori et al., 2021; Pellegrino et al., 2024) and motor learning (Vallence et al., 2013; López-Alonso et al., 2015). As a result, many question the current protocol's ability to induce clear and consistent cortical changes between and within participants.

To prolong the effect and strength of disruption following continuous theta burst stimulation (cTBS), the counterpart stimulation technique of iTBS that suppresses cortical activity, an advancement from the use of one block of stimulation to two blocks spaced by an inter-block wait period, which is typically set to ten minutes, was proposed (Goldsworthy et al., 2012b). Before this development, cTBS induced short-lived decreases in cortical activity that lasted less than one hour (Goldsworthy et al., 2012b) and proved highly variable among participants (McAllister et al., 2009; Ridding & Ziemann, 2010; Haeckert et al., 2021), thereby limiting the technique's capacity to effect long-term neuroplasticity – the ability of the brain to adapt to internal and external stimuli. With an additional block of cTBS, modulation of the primary motor cortex (M1) was effective in suppressing MEPs for up to several hours post stimulation (Goldsworthy et al., 2012a). Furthermore, repeated cTBS blocks to M1 and S1 were found to successfully reduce the learning, consolidation, and retention of motor learning tasks (Kumar et al., 2019; Darainy et al., 2023; Ebrahimi et al., 2024). Accordingly, this thesis seeks to explore the repeated block method used in cTBS as a potential means for decreasing the response variability inherent to current iTBS findings on motor learning and neural facilitation. Four experiments, each with new participants, were conducted.

In experiment one (iTBSx1), one block of iTBS was administered to M1, S1 or a control area before participants trained in an upper-limb force-field adaptation task. Participants then returned twenty-four hours later to test the effects of iTBS on retention of the learned force. Given the current literature, it was presumed that one block of iTBS would elicit variable increases in learning and retention in M1 and S1 participants when compared to controls. This speculation differed from that of experiment two, which followed a similar procedure of

behavioural learning and retesting. Here, two rounds of iTBS were applied to the M1 and S1 cortices.

As it is widely understood that the effects of iTBS on neural activity are greatly time sensitive, Tse et al (2018) sought to determine an optimal time interval between brain stimulation blocks that would elicit consistent changes in cortical excitability. Through an analysis of the time course of FDI MEP changes, it was proposed that a fifteen-minute post stimulation wait period following each block of a repeated iTBS protocol produces stable increases in cortical activity. Thus, for experiment two, it was hypothesized that significant increases in learning and retention using Tse et al's (2018) double-block iTBS protocol (iTBSx2) would occur in the M1 and S1 conditions. It was also considered that S1 participants would show greater learning than M1, given recent evidence that changes in S1 cortical excitability preceded that of M1 during motor learning (Ohashi et al., 2019a).

Preliminary analyses of experiment one and two prompted supplementary questions seeking to examine the effects of iTBSx2 on M1 and S1 event-related potentials (ERPs). In experiment three, two blocks of iTBS were applied to either cortex to assess changes in biceps MEPs following two rounds of brain stimulation. In experiment four, iTBSx2 to S1 provided an analysis of post brain stimulation differences in somatosensory evoked potentials (SEPs) obtained from square-wave pulse stimulation to the right median nerve. For both ERP experiments, it was considered that repeated blocks of iTBS would induce clear facilitatory effects on cortical activity that may directly translate to mechanisms of motor learning.

Overall, these experiments sought to demonstrate that increasing the amount of exposure to iTBS with two blocks of stimulation would present a more reliable and effective

methodology for facilitating cortical excitability. With associated increases in motor learning and retention, as well as decreases in response variability, an improved iTBS protocol would optimize its ability to be readily applied to diverse research studies and clinical interventions. This optimization is especially pertinent in fields such as neurorehabilitation, where the reliability and effectiveness of interventions are crucial for fostering positive recovery. Moreover, a refined iTBS protocol not only enhances its practical applicability but also contributes to advancing our understanding of mechanisms of neural plasticity.

This master's thesis consists of a literature review outlining the current landscape of brain stimulation techniques with a focus on iTBS, its foundations in neural plasticity and synaptic facilitation, and its applicability to motor learning. A manuscript of four experiments with statistical analyses of their findings follow, and a subsequent discussion places these results in context of the existing literature. Finally, a thorough conclusion summarizes the major points of this work, providing suggestions for future directions.

2 | Literature Review

2.1 Non-Invasive Brain Stimulation

Neural transmission in the human brain boasts complexity and intricacy. With the capacity to process over ten million bits of information per second, the mechanisms in the brain that induce neural efficiency are an inspiration to research exploration. Neural facilitation, the strengthening of synaptic connections by repeated neural activation, is one such process that optimizes transmission within neural circuits, contributing to our ability to learn, adapt to, and store new information (Jackman & Regehr, 2017). Non-invasive brain stimulation (NIBS) tools are useful in permitting the study of neural facilitation, and their recent developments have offered valued insights on mechanisms of learning and memory (Polanía et al., 2018; Hara et al., 2021). In general, NIBS tools are used to temporarily alter brain regions of interest (ROIs) through electrical or electromagnetic stimulation. The post stimulation differences observed are often categorized into facilitated or suppressed neural responses, as each tool's protocol can be adjusted to accomplish unique needs.

Transcranial magnetic stimulation (TMS) operates by electromagnetic induction: a magnetic field stemming from the magnetically charged coils of a TMS device generates a current in a group of nerve cells, the electrical conductors. TMS coils are placed tangentially to the scalp, just over the brain ROI, and the centre of the magnetic field, which is the point of the strongest current, prompts focal (Hallett, 2007) changes in neural firing according to the frequency, interval, power and duration of the magnetic field (Huang et al., 2005). Numerous TMS paradigms exist.

Single-pulse TMS

When a single electromagnetic pulse is emitted from a TMS coil, neural responses undergo a brief, rapid change that can be measured in peripheral muscles. Single-pulse TMS (spTMS) was first used to elicit evoked responses from the primary motor cortex (M1) (Barker et al., 1985). With each targeted pulse over M1, descending pathways produced movements in the respective contralateral body part. These were referred to as motor evoked potentials (MEPs) and were measured through electromyographic (EMG) recordings. Since then, spTMS has become valuable to the study of brain physiology and function. For example, at varied intensities, spTMS to M1 was found to result in somatosensory and kinesthetic hand perceptions that were separate from the MEP experience (Franza et al., 2019). In other brain areas, such as to the dorsolateral prefrontal cortex (dlPFC), spTMS was found to increase cortical activity in the cingulate gyrus, caudate and thalamus based upon analyses from functional magnetic resonance imaging (fMRI) (Dowdle et al., 2018). With stimulation to the primary somatosensory (S1) and posterior parietal cortices (PPC), spTMS impaired movement reaction time in a tactile-visual matching task (Ku et al., 2015). Accordingly, spTMS continues to be an established technique for revealing insights into diverse neural processes (Farzan, 2014; Ficarella & Battelli, 2019).

Repetitive TMS

To induce changes in cortical activity that last longer than a few seconds, repetitive TMS (rTMS) techniques are employed. While the neurophysiological effects of rTMS are poorly understood, the prolonged stimulation technique was proposed to engage mechanisms of

neuroplasticity that induce long-term changes in cortical activity (Soundara Rajan et al., 2017). The use of rTMS techniques contributes to our knowledge of neuromodulation, a field of study examining the brain's ability to adapt to induced stimuli. The effects of rTMS on neuromodulatory mechanisms differ depending on factors such as the frequency, pattern, duration, and intensity of the applied stimulation (Klomjai et al., 2015). Low-frequency rTMS (< 1Hz) is understood to produce inhibitory effects on measures of cortical excitability (Fitzgerald et al., 2002; Di Lazzaro et al., 2008; Klomjai et al., 2015) while high-frequency rTMS (> 5Hz) has been shown to facilitate neuronal activity (Matsunaga et al., 2005; Holler et al., 2005; Fitzgerald et al., 2006; Klomjai et al., 2015). Both low- (LF) and high-frequency (HF) rTMS face limitations, such as slow onset effects that require multiple stimulation sessions (LF) (Edwards et al., 2019) or risk of rapid overstimulation (HF) (Cotovio et al., 2017), which may pose constraints on the efficacy of their application to clinical settings.

Recent developments of TMS explore stimulation methods based on theta rhythms in the hippocampus. With trains of consecutively repeating theta-burst pulses, a protocol termed continuous theta burst stimulation (cTBS), cTBS-rTMS is also generally found to suppress cortical activity following stimulation to numerous brain regions (*for a review, see* Wischnewski & Schutter, 2015). During intermittent theta burst stimulation (iTBS), which involves trains of pulses occurring at regular intervals that are typically configured to two seconds on and eight seconds off, the intended outcome is induced neural facilitation that leads to an increase in cortical excitability (Huang et al., 2005). Increases in evoked potentials upon iTBS brain stimulation have been reported on various occasions, such as with stimulation to M1 in participants with chronic pain (Di Lazarro et al., 2008) and stimulation to M1 in healthy older

adults (Gedankien et al., 2017). However, in both these cases, as well as in several others using the standard single-block iTBS protocol in healthy participants (López-Alonso et al., 2014; Corp et al., 2020; Katagiri et al., 2020; Leodori et al., 2021; Pellegrino et al., 2024), interindividual response variability is a concern for derived results. Further research is required to determine appropriate methodologies and applications of iTBS, the primary brain stimulation tool of this thesis *(for a continued description, see Section 2.2)*.

Paired-pulse TMS

TMS may also be delivered in paired currents that occur successively. The first pulse is a conditioning stimulus (CS) while the second is a test stimulus (TS). The effect of the TS is dependent on the intensity of the CS, as well as the time interval between the two pulses –the interstimulus interval (ISI). These variations are used to examine the dynamics of intracortical inhibition and facilitation and often seek to give an account of cortical motor circuits through stimulation to M1 (Vahabzadeh-Hagh, 2014). With a low-intensity TS following an ISI of between one and six milliseconds, M1 MEPs may decrease through interactions with inhibitory cortical circuits (Ilić et al., 2002; Shirota et al., 2010; Mrachacz-Kersting et al., 2021). This is termed short interval intracortical inhibition (SICI). However, when a high-intensity TS follows a conditioning stimulus, an opposed facilitatory effect on MEPs may be observed (short-interval intracortical facilitation, SICF) (Ilić et al., 2002; Shirota et al., 2010; Mrachacz-Kersting et al., 2021). These patterns occur by direct and indirect neural responses to stimulation, as the CS and timed TS act upon different *waves,* that is, the direct (d-waves) and indirect waves (i-waves) of a neural volley (groups of action potentials), to strengthen an inhibitory (SICI) or facilitatory (SICF) response

(Ziemann, 2020). Long-interval stimuli are also explored, though their resulting stimulation effects are more varied. When a test stimulus follows a condition stimulus with a longer ISI ranging between 50ms and 200ms, long-interval cortical inhibition (LICI) can decrease FDI MEPs during weak muscle contractions (McNeil et al., 2011). Another study showed that this effect of LICI only occurs with ISIs specifically at 100ms and 150ms (Opie et al., 2017). Finally, intracortical facilitation (ICF) methods using two successive stimuli separated by ISIs between 10ms and 15ms may produce increases in FDI MEPS with the muscle at rest (Ortu et al., 2008). Research continues to investigate neural patterns of paired-pulse TMS to underpin mechanisms of motor plasticity.

A second method of non-invasive brain stimulation produces broad changes in cortical activity. Transcranial direct current stimulation (tDCS), through its excitatory (anodal tDCS; atDCS) and suppressive (cathodal tDCS; ctDCS) variations, affects the probability that stimulated neurons will fire by altering their threshold for synaptic transmission (Nitsche & Paulus, 2000). tDCS is often used in clinical settings to alleviate the symptoms of various psychiatric disorders (Kekic et al., 2016). It may also be paired with TMS to pre-condition a cortical region before subsequent focal stimulation (Sparing & Mottaghy, 2008). This method serves to strengthen the neural response that follows TMS. While tDCS is readily used in the study of cognitive impairment (Meinzer et al., 2015), emotion regulation (Nitsche et al., 2012), pain management (Pacheco-Barrios et al., 2020) and motor learning (Buch et al., 2017), new developments for high definition tDCS are on the rise to increase the spatial resolution and reduce the current spread of this tool (Torres et al., 2013).

Finally, of recent interest is a promising NIBS technique that demonstrates success in effectively stimulating subcortical brain regions through animal studies (Kamimura et al., 2016; Kim et al., 2022) and in human participants (Wang et al., 2019; Zhang et al., 2021). Subcortical stimulation is a challenge for TMS and tDCS methods as their stimulation intensities do not adequately penetrate through multiple layers of brain tissue. Thus, focused transcranial ultrasound stimulation (TUS) involves placing an array of transducers, which emit ultrasound waves set at pre-determined frequencies and intensities, on the skull. The strategic positioning of the transducer array ensures that the ultrasound waves converge at the subcortical region of interest, offering a novel avenue for precise neuromodulation. While research is ongoing to ensure the safety of TUS in human participants (Sarica et al., 2022), recent evidence shows that TUS to the dorsal anterior cingulate cortex (dACC) and posterior cingulate cortex (PCC) induced excitatory effects on subcortical activity (Yaakub et al., 2023) without traces of lingering brain tissue damage.

In the study of motor learning and evoked potentials, focal brain stimulation provides a means to directly observe correlations between mechanisms of plasticity and brain regions of interest. Consequently, TMS is routinely administered to corticomotor ROIs for the analysis of motor skill acquisition. A wealth of research establishes the suppressive effects of cTBS on a range of motor learning tasks following stimulation to brain areas such as M1, S1, supplementary motor area (SMA), premotor cortex (PMC) and cerebellum (Platz et al., 2012; Rastoji et al., 2017; Kumar et al., 2019; Mirdamadi & Block, 2021). Further study, however, is required to highlight the role of iTBS on these processes, a central aim of this project.

2.2 iTBS and Neural Facilitation

The pulses discharged from NIBS interrupt the naturally occurring rhythmic waves of neural activity, oscillations, in the brain. Neural oscillations emerge in different frequency bands ranging from delta waves at 0.1Hz to gamma waves oscillating at 100Hz, with each being relevant to different brain functions. Appearing both in the cortex (Canolty et al., 2006) and deep in the hippocampus (Lisman & Jensen, 2013; Ponzi et al., 2023) is a distinct coupling of theta (4-8Hz) and gamma (25-100Hz) brainwaves. High-frequency gamma is modulated by the phase of slow-wave theta, and their synchronized patterning, a type of cross-frequency coupling, is understood to be a primary mechanism in the formation of working memory (Lisman & Jensen, 2013). Working memory involves the use of readily available information for the processing, planning and performance of behaviour. Extensive research proposes that mechanisms of synaptic facilitation perpetuate working memory processes (Mongillo et al., 2008; Verduzco-Flores et al., 2009; Jackman & Regehr, 2017), enabling neuroplasticity that, in turn, aids in the formation of long-term memory (Ruchkin et al., 2003).

Intermittent theta burst stimulation protocols aim to emulate the interplay of theta-gamma coupling and memory formation, thereby seeking to facilitate cortical activity and enhance subsequent learning. Huang et al (2011) argue that iTBS induces patterns of neuroplasticity similar to that of long-term potentiation (LTP), the strengthening of synaptic connections. An influx of CA^{2+} (calcium ions) is heightened during stimulation and residual CA^{2+} increases the efficacy of neuronal firing. These changes occur intermittently as stimulation is on for short bursts of two seconds and spaced at intervals of ten seconds. Upon iTBS stimulation to

the superior temporal gyrus (STG), resting-state electroencephalography (EEG) showed that iTBS successfully modulated the stimulation site by increasing the presence of theta and low-gamma coupling (Zhang et al., 2023). A similar effect was observed in the dorsolateral prefrontal cortex (dlPFC) (Chung et al., 2017), as well as in the primary somatosensory (S1) and primary motor cortices (M1) of macaque monkeys (Papazachariadis et al., 2014). Given its ability to induce theta-gamma coupling in various brain regions, iTBS has been applied to the study of evoked potentials –the brain's response to external stimulation –for further insight on the mechanisms of neural facilitation.

Using single-pulse TMS and peripheral nerve sensory stimulation, motor and somatosensory evoked potentials are obtained before and after iTBS for an examination of changes in cortical excitability. In the initial work on iTBS-induced cortical activity, post stimulation MEPs demonstrated fluctuating increases in FDI MEP amplitudes, with peak increases occurring near 5 minutes after 50Hz iTBS (Huang et al., 2005). Continued research demonstrated that increased FDI MEP amplitudes were evident 10 mins after brain stimulation using a 30Hz iTBS protocol (Wu et al., 2012), whereas variable increases emerged within 15 and 27 minutes of 50Hz iTBS (Brownjohn et al., 2014). Turning to somatosensory evoked potentials (SEPs), applying electrical stimulation to the right median nerve revealed a significant increase in cortical SEP responses at N20/P25; this was particularly evident 15 minutes after stimulation (Katayama & Rothwell, 2007; Katayama et al., 2010). Altogether, while these studies show that iTBS can induce processes of neural facilitation by increasing the amplitude of evoked potentials, the effects of iTBS appear contingent on the post-stimulation wait period following brain stimulation.

Another kind of variability unfolds as participants of iTBS studies are often grouped by whether they demonstrate an expected or unexpected response to stimulation. Respectively, the terms "responders" and "non-responders" appear regularly in the literature to characterize this interindividual variability. In an early study, iTBS was found to elicit variable changes in the biceps MEP response both within and between participants, and overall, no change in MEP amplitudes was observed at the group-level analysis (Martin et al., 2006). Concerns regarding responder variability have since been a recurrent theme in multiple studies investigating the effect of iTBS on evoked potentials (*for a review*, see Pellegrino et al., 2017). Hamada et al (2013) turn to this issue and propose that variations in the between-participant neural networks being recruited by brain stimulation pulses may account for some of the observed variability. In particular, TMS pulses may exert diverse effects on late I-wave neural inputs, influencing the capacity of synaptic connections to undergo changes in response to stimulation. The variations in post-stimulation intervals and the interindividual variability subsequent to iTBS present challenges for devising a standardized procedure that can be consistently applied across various contexts. Consequently, alternative iTBS protocols are increasingly explored.

With continuous theta burst stimulation (cTBS), a shift from the standard single-block procedure was found to improve the duration, strength, and response variability of brain stimulation effects when an additional block of cTBS was administered to the left M1 cortex (Goldsworthy et al., 2012). It was proposed that a second block of cTBS spaced by ten minutes may act on late-phase –and not early phase – neural oscillations that contribute to a suppression of cortical excitability that can last several hours. Facilitatory processes of memory formation are also associated with differences in the duration of plasticity extending from early-

and late-phase oscillations (Bikbaev, 2008). Therefore, in following the development of cTBS, iTBS findings may benefit from employing an additional stimulation block that may improve its facilitatory effects on cortical activity.

After two rounds of iTBS spaced by a 15-minute interval, FDI MEPs showed prolonged increases in MEP amplitude up to 60 minutes after stimulation (Tse et al., 2018). Moreover, the number of participants demonstrating a facilitated response increased by 20% in comparison to participants receiving one round of iTBS. While these results are encouraging, it should also be noted that when two blocks of iTBS were spaced by an interval of five minutes, an opposite effect of stimulation resulting in unchanged or inhibited MEPs in 93% of participants was produced in the same study. This, once again, demonstrates that the effects of iTBS are particularly time sensitive.

While evoked potentials provide a measure of ongoing cortical activity in response to brain stimulation, measures of motor learning can provide further details on the relationship between neuroplasticity and human behaviour. Mechanisms of neural facilitation that occur during motor learning (Rosenkranz et al., 2007; Rajji et al., 2011) have been thoroughly explored to enhance our understanding of the learning process. This review will now turn to describing the mechanisms of motor learning, and specifically that of motor adaptation learning, before expanding on the role of iTBS in skill acquisition.

2.3 Motor Adaptation

Consider the task of riding a bike along an uneven, winding terrain. With every stride of foot pedaling, one's exerted force and velocity shift readily from moment to moment, accommodating flexibly to incoming sensory stimuli. Execution of such a motor task, therefore, requires knowledge of a primary motor goal (Krakauer et al., 2019) and access to a repertoire of secondary adjustments that permit altered performance. With this, the base skill of cycling is preserved while slight motor alterations facilitate execution in a varied environment. This is motor adaptation.

Motor adaptation is a distinct form of motor learning as its dynamics are claimed to engage mechanisms of sensory prediction error (SPE) (Tseng et al., 2007; Uehara et al., 2018; Lee et al., 2018), that is, the motor system's inclination to minimize the difference, or error, between the online feedback of sensed movement and the planning of expected movement. The product is an interaction of feedback and feedforward mechanisms serving to update and improve motor outputs (Shadmehr et al., 2010; Mathew & Crevecoeur, 2021).

In an early study of motor adaptation, Smith and Fitch (1935) used a dart throwing task to demonstrate this phenomenon under experimental control. Participants wore prisms producing a visual distortion of 8mm to either the right or left visual field and proceeded to train in the motor task. Over the first four dart throws, a significant increase in error between the target's centre and participants' aim was observed in the direction of visual distortion. The error then declined rapidly over the next sixteen trials until decreasing significantly by the end of the training block. When the prisms were removed in a subsequent block of throws, a smaller error – one skewed in the opposite direction of original prism distortion—was similarly evident

across the first few trials, and a comparable rate of aim improvement followed until the end of the task.

It was proposed that unstable stimulus-response associations of a learned action pattern give way to the continuous transformations inherent to adaptation learning (Smith & Fitch, 1935). These adaptive processes occur rapidly (Tanaka et al., 2012; Coltman & Gribble, 2020) and can be observed on a trial-by-trial basis, making motor adaptation tasks a valuable methodology for the study of motor learning. In addition to visuomotor learning, as used in the above-described experiment, other modalities of motor adaptation learning include sensorimotor and audiomotor adaptation. While sensorimotor adaptation tasks often require the use of somatosensory feedback, such as force perturbations (Gandolfo et al., 1996; Darainy et al., 2023) or proprioceptive distortions (Cressman & Henriques, 2010) for trial-and-error learning, audiomotor tasks rely on shifts in acoustical feedback (Houde & Jordan, 1998; Shiller et al., 2009) and sound properties, such as pitch (Hahnloser & Narula, 2017) or timbre (Xu et al., 2020), to produce changes in vocal control.

Learning and Optimization in Motor Adaptation Learning

Neuroplasticity is presumably core to the progression of adaptation learning. While its two classifications, Hebbian and homeostatic neuroplasticity, are traditionally approached as separate opposing processes, many propose that they occur simultaneously on different timescales of learning (Song et al., 2000; Zenke & Gerstner, 2017). During Hebbian neuroplasticity, the strength of synaptic signals changes rapidly in response to varying levels of activity within synaptic spaces. Long-term potentiation (LTP) is a product of enhanced neural

connections while long term depression (LTD) evolves out of weakened signaling. In homeostatic plasticity, slower regulatory processes create an optimal balance of neuronal activity through negative feedback, thereby creating functional stability within a cell's internal environment. Thus, the synaptic changes perpetuated by Hebbian plasticity may function to set new baseline-levels of homeostasis (Galanis & Vlachos, 2020) that allow improvement gains in motor learning to stabilize. A newly formed skill becomes stable when it is resistant to interference from a competing skill (Dudai, 1996; Krakauer et al., 2005; Maeda et al., 2017). This phenomenon of increased stabilization is defined as motor consolidation; consolidated skills can be retrieved and reproduced during the performance and execution of a motor task.

The underlying mechanics of motor consolidation are often attributed to properties of *synaptic scaling* (Tetzlaff et al., 2013), an extension of homeostatic neuroplasticity that serves to adjust the strength of synaptic connections and prolong their stability (Chowdhury & Hell, 2018). Synaptic scaling is heavily discussed for its presence during sleep (Tononi & Cirelli, 2003; Wang et al., 2011; De Vivo et al., 2017); its process serves as evidence that learning continues beyond the online engagement of a motor task. In studies on motor consolidation, the role of sleep is considerably emphasized (Stickgold & Walker, 2007; Debas et al., 2010; Bothe et al., 2020).

The skill acquisition, consolidation and retention of motor adaptation tasks can be further explored through an analysis of neural circuitry at the level of specific brain regions of interest. Two cortical areas, the primary motor cortex (M1) and primary somatosensory cortex (S1) are ROIs key to the findings of this thesis.

2.4 Brain Regions of Interest

The M1 Tradition

Given the direct monosynaptic connections that extend from the primary motor cortex (M1) to motor neuron pools in the ventral spinal cord, it is necessary to explore M1 for its role in motor learning processes. The M1 gyrus creates the anterior border of the central sulcus and runs mediolaterally across the frontal lobe. Its internal structure is unique by the large pyramidal Betz cells that extend from its output cortical layers to muscle effector circuits along the brainstem and spinal cord.

Classical studies on the somatotopic organization of M1 were approached through the application of low electrical stimulation to the cortical surface (Schwarz, 2007). Stimulation triggered MEPs in various muscles (Schieber, 2001), and an interest grew to map out the organization of this cortical motor centre. While recent research (Hudson et al., 2017; Schieber, 2020; Gordon et al., 2023) dispute early conclusions proposing a linear organization of muscle representation in M1 (Penfield & Boldrey, 1937), an established consensus affirms that MEPs are viable tools for the study of M1 activity (Levy et al., 1984).

In a ballistic pinch task, gains in motor performance were associated with increases in MEP amplitudes of the flexor policis brevis (FPB) muscle during the first 60 minutes of motor training, but remained unchanged after participants fully learned the new skill (Muellbacher et al., 2001). These increases in MEPs suggested that M1 contributes to the activity of effector-specific ballistic movements during motor learning. However, during the refinement stages of a precision motor task, FDI MEP amplitudes were found greatest during late and not early learning of a finger force control task (Ohashi et al., 2019). In the Ohashi study, achieved motor

learning was not correlated with changes in MEP amplitudes, and it was proposed that M1 cortical excitability is dependent on the repetitive use of task-specific muscles. Findings on the effector- and task-specific role of M1 in motor learning appear repeatedly in the literature (Saucedo Marquez et al., 2013; Wang et al., 2015).

In the context of skill optimization during motor adaptation learning, consolidation mechanisms may be partially independent of M1 activity (Baraduc et al., 2004; Richardson et al., 2006; Kumar et al., 2019). This finding may be attributed to various conclusions that motor adaptation is not purely a factor of motor processes, but additionally manifests as a result of perceptual learning mechanisms (Howard, 1971; Darainy et al., 2013; Ohashi & Ito, 2019). Therefore, the study of facilitatory brain simulation and motor adaptation should involve an assessment of both motor and perceptual components of motor learning to capture differences between mechanisms of skill acquisition and consolidation.

Beyond M1's projections to the spinal cord and motor effectors, the cortical region is linked directly and indirectly to additional brain areas involved in motor adaptation learning. Among these are the cerebellum, a key player in the processing of sensory prediction error (Tseng et al., 2007; Statton, 2018; Popa & Ebner, 2019); basal ganglia, a subcortical region providing reinforcement for successful motor performance (Seidler et al., 2006; Doyon et al., 2009); dorsal premotor cortex (dPMC), which supports the feedforward planning and selection of motor trajectories (Tzvi et al., 2020; Sugiyama et al., 2022) and posterior parietal cortex (PPC), a cortical area holding mechanisms for the online adjustments of motor performance during adaptation (Della-Maggiore et al., 2004; Newport & Jackson, 2006; Schintu et al., 2023).

Sensorimotor Adaptation: An S1 View

Though functionally different from M1, an M1-like somatotopic organization is similarly observed in S1's organization of sensory afferents (Penfield & Boldrey, 1937). The S1 gyrus is the primary input centre of peripheral somatosensory information in the parietal lobe. It sits posterior to the central sulcus and can be subdivided into three parallel-running streams of sensory information. According to Brodmann's atlas, these areas are termed Brodmann's areas 1, 2, 3a and 3b. Areas 3a and 3b receive proprioceptive and cutaneous information respectively, while areas 1 and 2 use multimodal processing to integrate cutaneous and proprioceptive cues.

The direct neural pathways appearing between the M1 and S1 cortices (Cash et al., 2015; Edwards et al., 2019) provide a continued means for analyzing the ways in which somatosensory information informs motor control. A series of electrophysiology rodent studies demonstrates that the S1 connections branching into layers 2/3 and 5 of M1 (Mao et al., 2011; Petrof et al. 2015; Yamawaki et al., 2021) provide inputs of ongoing movements for the updating of subsequent motor commands (Rocco-Donovan et al., 2011; Yamawaki et al., 2021). This results in a highly integrated loop of online sensorimotor updating, a course of events necessary for motor adaptation learning.

When a group of participants was administered two blocks of cTBS to either the primary motor (M1) or primary somatosensory (S1) cortices, adverse effects to the retention and relearning of an upper-limb force-field adaptation task were found prominent following disruption to S1 (Kumar et al., 2019). These effects were observable in a retention task occurring 24 hours after initial learning and were significantly different from the 24-hour retention and relearning kinematics of the M1 and control stimulation groups.

Despite the established implications of M1-S1 ties, the contribution of S1 functioning in motor adaptation processes is largely under researched. A parallel course of study in somatosensory perceptual learning highlights that S1 undergoes Hebbian-like plasticity in the presence of new sensory stimuli (Pleger et al., 2003; Hodzic et al., 2004; Pacchiarini et al., 2017). Thus, a proposed link between perceptual and motor adaptation learning shares that perceptual processes of S1 may improve the sensitivity of afferent receptors to tactile stimuli, thereby changing the manner in which S1 mechanisms correspond to M1 and its output commands (Darainy et al., 2013). More recently, a budding wave of findings through force-field and visuomotor adaptation tasks (Mathis et al., 2017; Mirdamadi & Block, 2020; Ebrahimi et al., 2024) have presented remarkable evidence for the contributions of S1 in its capacity for enabling effective motor skill learning, consolidation, and retention.

2.5 iTBS and Motor Learning

The variability in the effects of iTBS on cortical activity, as observed in studies on evoked potentials, is similarly apparent in studies on motor learning. While the application of one block of iTBS has been shown to enhance learning in various behavioural tasks, inconsistencies between findings reveal that stimulation-based neural facilitation may depend on task-specific factors, individual differences, brain regions of interest or other unexplored variables.

With a skilled motor task involving the interaction of multiple motor competencies, that is, the sequential visuomotor isometric pinch force tracking task, iTBS to hand area of left M1 did not induce differences in cortical excitability or motor learning, which was measured by

changes in displacement error during the tracking of a visual cursor (López-Alonso et al., 2018). In another study examining motor performance with the ballistic finger abduction task, one block of iTBS was found to induce LTD effects on M1 cortical excitability, which in turn decreased the dependent variable of peak acceleration (Stökel et al., 2015). Additional research on the effects of iTBS to M1 show that brain stimulation may enhance motor learning over multi-day fine motor task training sessions (Platz et al., 2018), impair implicit motor sequence learning (Wilkinson et al., 2010) and decrease performance in a finger tapping task (Shirota et al., 2017).

In the context of upper-limb motor adaptation, there is no available data on the effects of iTBS to M1 or S1. However, successful findings demonstrating facilitatory responses following iTBS to the cerebellum have recently emerged. In stroke patients, cerebellar iTBS was found to significantly enhance online learning in a visuomotor task (Koch et al., 2020), and similar findings were achieved when applying stimulation to the cerebellum (Kaethler et al., 2023) and dorsolateral prefrontal cortex (dlPFC) (Song et al., 2020) in healthy controls. These findings suggest that the mechanisms involved in cerebellar neural facilitation may be more closely aligned with the induced effects associated with one block of iTBS. Additional research is required to further investigate the mechanisms of neural facilitation in other motor cortical areas and to decrease the iTBS response variability evident from post-stimulation evoked potentials. This thesis achieves this objective by employing an upper-limb force-field adaptation task to examine the effects of neural facilitation after applying either one or two blocks of iTBS to the M1 and S1 cortices.

2.6 Conclusion

Non-invasive brain stimulation (NIBS) techniques are widely used in the study of neuromodulation. Specifically, findings derived from applications of transcranial magnetic stimulation (TMS) have contributed substantial knowledge on the methods by which cortical activity can be suppressed or facilitated. Consistent with the facilitatory processes that are inherent to theta-gamma coupling in the cortex and hippocampus, TMS neural facilitation techniques such as intermittent theta burst stimulation (iTBS) aim to increase cortical activity and enhance neural excitability that promotes efficient neural transmission, fosters synaptic plasticity, and optimizes learning and memory processes in a range of contexts.

Measurements of evoked potentials and behavioural learning demonstrate that iTBS is capable of inducing such effects. However, sizeable differences in its after-effect occur at group-level, interindividual and intraindividual analyses, making a standardized iTBS technique difficult to attain. Recent research proposes that increasing the number of stimulation of blocks in applications of iTBS may decrease the variability associated with current protocols. This method of two rounds of spaced iTBS is yet to be explored in the context of motor learning.

Studies on motor adaptation are valuable to unraveling various processes of motor skill acquisition, as its inherent trial-by-trial changes in motor performance can be distinctly studied. Mechanisms that underlie motor adaptation include Hebbian plasticity, homeostatic plasticity, and synaptic scaling. These contribute to shaping the acquisition, consolidation, retention, and recall required for the successful learning and optimization of motor adaptation tasks.

Numerous brain regions play a role in the development of adaptation learning, including the primary motor cortex (M1), primary somatosensory cortex (S1), cerebellum, basal ganglia,

dorsal premotor cortex, and posterior parietal cortex. Several brain stimulation studies reveal the contribution of each. Of dominant focus in current literature is the role of M1 in adaptation learning. However, various studies examining the time course of M1 cortical excitability during learning demonstrate that M1 processes may primarily reflect the activation of effector-specific muscles during task learning and not mechanisms that particularly encode learning. During motor adaptation, where sensory modalities are important to acquiring the motor task (e.g. visuomotor adaptation, force-field adaptation, and audiomotor adaptation), perceptual contributions may be crucial to the learning and stabilization of behaviour. Accordingly, the mechanisms of S1 plasticity should be additionally explored.

When combining iTBS with motor learning inquiries, similar instances of variability in findings on motor performance saturate the literature. This is particularly true for findings describing M1-induced neuroplasticity. More consistent effects of iTBS are seen with stimulation to the cerebellum within upper limb visuomotor adaptation studies. As inputs to the cerebellum are tightly integrated with the activity of cortical motor areas, further research is required to pinpoint the effect of iTBS on motor adaptation upon stimulation to additional brain regions of interest. Accordingly, this thesis provides an exploration on the after-effects of administering either one or two blocks of iTBS to M1 and S1 before participants learn a force-field adaptation task, and subsequent experimental work on the effect of double-block iTBS on evoked potentials highlights new considerations for the study of neural facilitation.

3 | Materials and Methods

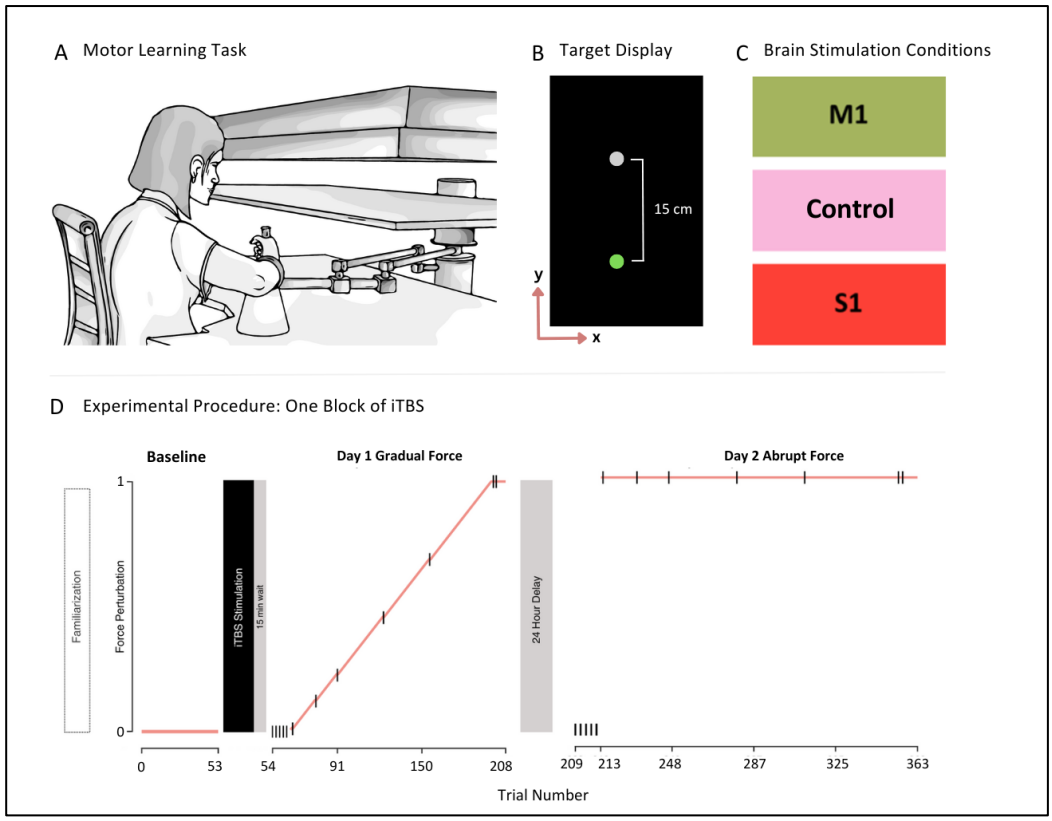
Ethics

This study was approved by McGill University Faculty of Medicine Institutional Review Board. All participants provided written informed consent before participation.

Participants

One hundred and twenty-three right-handed participants aged 18 to 40 years (89 female and 34 male, M=23.11 years, SD= 4.12 years) engaged in either an upper-limb motor learning task or an event-related potential (ERP) study. Participants were healthy and reported no underlying neurological conditions. Motor learning participants had no past experience of motor adaptation training with a robot arm.

iTBS in Upper-Limb Motor Learning



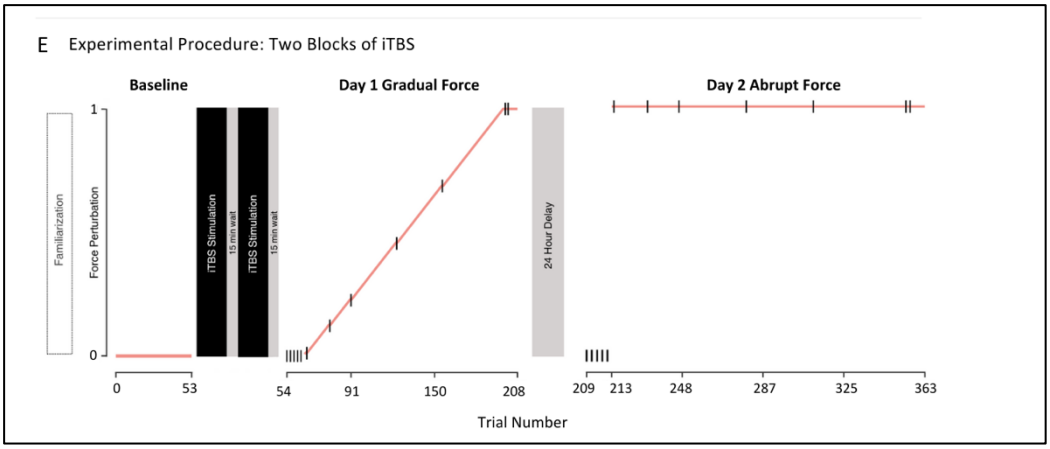


Figure 1.0 ***Upper Limb Motor Learning Study.*** **A** *Motor Learning Task* Participants were comfortably seated in a motor manipulandum chair where a visual display of the force-field adaptation task was presented. The right arm was placed on an air sled to facilitate movement. **B** *Target Display* The start and end target points, placed 15cm apart on the y axis, were displayed using an LCD screen. The start position turned green to signal the start of each new trial. **C** *Brain Stimulation Conditions* Three brain stimulation conditions were used throughout this study: M1, S1, and occipital cortex control. **D** *Experimental Procedure: One Block of iTBS* The motor learning task involved familiarization (20 trials) and baseline trials (53 trials) that preceded one block of iTBS stimulation. After a 15-minute post-stimulation period, participants engaged in a gradual learning block of the force-field task (155 trials) where a force perturbation of 0 is 0N and a perturbation of 1 is 15N. Twenty-four hours later, participants returned for a retention test involving abrupt force loads (155 trials). In both the day one and day two tasks, error-clamp trials were interspersed identically throughout learning and retention served as non-kinematic measures of learning. **E** *Experimental Procedure: Two Blocks of iTBS* Participants followed the same task as described in *C* but received two blocks of iTBS stimulation. Each block was followed by a 15-minute wait period.

Behavioural Task

Participants performed a point-to-point reaching task while holding the handle of a robot arm (InMotion2, Interactive Motion Technologies, Figure 1.0). The handle was fitted with a force-torque sensor (ATI Industrial Automation) for measuring movement-generated forces, and a semi-silvered mirror reflecting a mounted display screen was placed just below eye level for visualization of the point-to-point targets. Targets were displayed as 20mm white circles aligned to participants' body midline. The start position was set 30cm from the body, with the target position 45cm away (Fig.1B). The mounted mirror obstructed participants' view of their right arm and the robot handle, and an air sled supported the participants' elbow. Hand position was recorded with two 16-bit optical encoders operating at 400Hz and presented to participants on the display screen.

To initiate a trial, the robot moved the participants' right hand to the start position, and after a 500ms delay, the cursor turned from red to green, signifying that the participant was to move directly to the end target. At the end target, colour-coded signals provided feedback of movement duration: blue signaled slow movement (i.e. lasting over 1000ms), red was too fast (i.e. below 800ms) and green indicated optimal timing (i.e. between 800ms and 1000ms). To conclude each trial, the robot moved the participant back to the start position.

The behavioural task occurred over two days with sessions conducted approximately 24 hours apart. On day one, participants engaged in a motor learning session that began with a familiarization block consisting of 20 trials. This was followed by a baseline phase of 50 null-field trials, where there was no perturbation, and a learning phase of 143 force-field training trials. During the learning phase, a velocity-dependent load with a gain of 15 N was introduced gradually on a trial-by-trial basis. The force was applied as follows (Equation 1.0):

$$\begin{bmatrix} f_x \\ f_y \end{bmatrix} = \begin{bmatrix} 0 & d \\ -d & 0 \end{bmatrix} \begin{bmatrix} v_x \\ v_y \end{bmatrix}$$

Equation 1.0 *Applied Force During Motor Adaption Learning*

The lateral and sagittal directions are denoted by x and y, respectively. The commanded force applied to the robot is represented by f_x and f_y, while hand velocities according to the Cartesian coordinates system are denoted as v_x and v_y. The coefficient d (N.s.m−1), determining the strength of the force field, was $0 < d \leq 15$. An additional three error-clamp (or channel) trials were conducted in the baseline block, while an additional twelve were conducted

within the learning phase. The error clamp trials reduced kinematic error during point-to-point reaching by restricting movement to straight-line paths. Their rigid-force channel walls (spring coefficient = 4000N/m; damping coefficient = 40N/m) captured participants' exerted force, allowing for a force-based measure of learning. The baseline block's channel trials provided a measure of baseline forces before brain stimulation. During learning, five of the error-clamp trials were placed at the beginning of training to record participants' baseline exerted forces after brain stimulation, and the remaining seven were distributed randomly throughout the training block. The last two error-clamp trials were conducted just before the end of training, at trials 146 and 148, to provide a final measure of learning. The indices of the error-clamp trials were identical between participants.

A 24-hour post-training delay was implemented to facilitate consolidation of the motor task. On the second day, participants underwent 143 relearning trials configured to abruptly introduce the force-field load at 15N. Twelve error-clamp trials, positioned identically to those in day one's learning sessions, were also included in this block. The first five error-clamp trials on day two were used as a measure of retention, and the remaining seven assessed relearning.

Brain Stimulation

Two brain stimulation motor learning experiments were conducted. In both, brain stimulation was administered before participants learned the behavioural task. The iTBS stimulation protocol used in both experiments involved three pulses at 50Hz at intervals of 200ms to the brain region of interest. These bursts were on for two seconds at a time, occurring every 10 seconds, to create a total of 600 pulses in the span of three minutes (Huang et al.,

2005). Three minutes of stimulation was equivalent to one block of iTBS. Experiment one involved a single block of iTBS followed by a 15-minute post-stimulation wait period (iTBSx1). Experiment two involved two blocks of iTBS stimulation separated by 15 minutes. These two blocks also preceded a 15-minute post-stimulation wait period (iTBSx2) (Tse et al., 2018).

Participants were randomized into one of three brain stimulation conditions: M1, S1 and Control. There were 15 participants in each condition of experiment one (iTBSx1) and 16 participants in each condition of experiment two (iTBSx2). The number of participants included was based on previous work in our lab, in which 12 participants per condition were sufficient to see effects of cTBS on motor memory retention in a force field learning task (Kumar et al., 2019).

A handheld 70mm Magstim butterfly coil (Magstim200 stimulator) was used to perform stimulation in the brain area corresponding to each experimental condition. The Brainsight Neuronavigational tool was used to position the stimulating coil with the participant's head co-registered to the MNI152 (Montreal Neurological Institute) brain. To record surface EMG responses, Ag/AgCl surface electrodes were positioned over the biceps brachii. EMG responses were recorded using the Brainsight frameless stereotactic system's (Rogue Research) EMG unit, where signals are amplified at a factor of 13,500, bandpass filtered between 16Hz and 550Hz and digitized at 3kHz with a 12-bit resolution for visualization.

Participants held their right forearm at a 90° angle in the supine position to provide measurement of an active motor threshold (AMT), the lowest intensity of stimulation output required to produce an observable and consistent biceps muscle contraction. The lifted position facilitated a motor response, a motor evoked potential (MEP) to single pulse stimulation, as

participants simply held their forearm against gravity. The specific target area for iTBS in the M1 and S1 conditions was identified by defining the point at which single-pulse TMS to M1 elicited at least five out of ten biceps MEPs >200μV in peak-to-peak EMG amplitude. The single pulse TMS (spTMS) intensity that elicited this response was determined as the AMT (stimulation intensity, M=55.03% of maximum stimulator output, SD=7.86%), and iTBS stimulation intensity was then set to 80% AMT.

A virtual scalp marker set this MEP cortical landmark as the iTBS hotspot in the M1 condition. In the S1 condition, a scalp marker was set 2cm posterior to this hotspot, allowing iTBS to be centred over S1. Finally, control condition participants received brain stimulation either at the vertex of the skull in the iTBSx1 experiment or over the medial occipital lobe in the iTBSx2 experiment. Control locations were changed due to concerns that vertex stimulation may not be a neutral control stimulation site due to its proximity to areas potentially involved in sensorimotor learning.

To ensure that participants in all conditions generated a comparable amount of force in the lifted arm position, twenty participants performed a maximum voluntary contraction (MVC) test before continuing to the brain stimulation block of their respective experimental conditions. MVC measures were obtained from participants' right arm in three conditions: at rest (*pos1*), during elevation of the forearm against gravity (*pos2*), and during maximal biceps contraction (*pos3*). Each test was repeated three times, and BrainSight EMG recordings provided a measure of peak EMG amplitudes. Peak EMG amplitude in microvolts was averaged for each condition across the three repetitions, and baseline EMG was subtracted from *pos2* and *pos3*. Peak EMG amplitude during elevation of the forearm against gravity (*pos2* peak amplitude, M = 19.76μV,

SD = 11.44μV) was expressed as a percentage of peak EMG amplitude during maximal biceps contraction (*pos3* peak amplitude, M = 484.96μV, SD = 265.79 μV). Supporting the arm against gravity in *pos2* was thus 4.32% (SE = 0.44%) of MVC. Given the relatively low variability of the estimates, it was concluded that participants generated a comparable amount of biceps activity during MEP acquisition across brain stimulation groups and that MEP amplitudes, which were used to set iTBS stimulation intensity, were not substantially affected by differences in biceps activation.

M1 and S1 Event-Related Potentials

MEP Experiment

Changes in MEPs from before to after brain stimulation were assessed in twenty additional participants who received two blocks of iTBS to either M1 (n=10) or S1 (n=10). MEPs were acquired following S1 stimulation to confirm that the effects of receiving iTBS to S1 were due to the targeted stimulation and not a consequence of indirect effects on M1. A 15-minute wait period occurred after each stimulation block. As in the motor learning experiments, participants held their forearm at a 90˚ angle to generate a biceps AMT. The M1 hotspot was virtually marked as the point for iTBS stimulation in the M1 condition. The S1 condition received brain stimulation 2cm posterior to the M1 hotspot. iTBS intensity on the Magstim stimulator was set at 80% AMT at both stimulation sites, and EMG responses were recorded using the Brainsight EMG unit. Fifteen MEPs (AMT stimulation intensity, M=51.8% of maximum stimulator output, SD=5.23%) were recorded before and after iTBS in each condition to obtain mean MEPs at each time point.

SEP Experiment

Ten new participants engaged in an EEG-TMS experiment to assess possible changes in SEP amplitude following two blocks of iTBS to S1. To find the S1 stimulation point, surface electrodes were, once again, placed over the biceps brachii to record MEPs from single-pulse TMS to M1 (AMT stimulation intensity, M=50.4%, SD=8.87%), and the S1 marker was placed 2cm posterior to the M1 hotspot. To record SEPs, a BioSemi 64-channel EEG cap (10/20 layout) was used to acquire data from the thirty-two channels over participants' left hemisphere. EEG was recorded at 2048Hz and visualized with BioSemi ActiView (BioSemi, Amsterdam, Netherlands). The BioSemi ground electrodes, CMS and DRL, were positioned on either side of electrode POz. During acquisition, the EEG signal was referenced to electrode TP7, which sits just behind the left ear.

Participants were asked to remain seated during SEP recording, sitting as still as possible with their eyes closed for a three-minute block of baseline EEG acquisition. This served as a measure of resting state cortical activity. Given the surface inaccessibility of the biceps musculocutaneous nerve, SEPs were then acquired from the more superficial median nerve that innervates the forearm, wrist and hand. This procedure was adopted since the biceps, forearm and wrist representations are spatially adjacent in S1 (Gordon et al., 2023). A reusable bar electrode was positioned over the right median nerve at the wrist to elicit an evoked S1 response, a somatosensory evoked potential (SEP). Using an isolated square-wave stimulator, square-wave pulses with a duration of 0.2s were delivered in two blocks, each at 3Hz for 3 mins

(Ohashi et al., 2019), for a total of 1,080 pulses. For each participant, the amplitude of stimulation was set just below the threshold of muscle contraction at the wrist. This amplitude remained constant across median nerve stimulation blocks. With this procedure, six minutes of SEPs were acquired before and after two blocks of iTBS (iTBSx2).

Data Analyses

Behavioural Data Analysis

Participants' hand position and their exerted force were recorded at 400Hz. A zero-phase lag Butterworth filter was used to low-pass hand position data at 40Hz, and a measure of velocity was obtained by differentiation of the position data. To analyze the movement path between target points, movement start and movement end were scored at 5% of peak velocity. Movement path data provided a measure of perpendicular deviation from the straight-line trajectory between target points. This served as a kinematic dependent measure.

The dependent measure used to assess learning in error clamp trials involved calculating a regression coefficient. On each trial, the applied force over time was regressed on the ideal force over time, where the latter was calculated using Equation 1.0, as a function of velocity. Therefore, the regression coefficient, provides a force-based measure of adaptation that is relative to the ideal expected force, the amount of force required to fully compensate for the perturbation. The regression coefficient was obtained using the following equation (Equation 2.0), where actual force is denoted by f_A and ideal force is denoted as f_I. The time, t, captures forces up to peak velocity and b_0 is the intercept.

$$f_A(t) = bf_I(t) + b_0$$

Equation 2.0 *Adaptation Regression Coefficient of Actual Force Relative to Ideal Force*

Three error-clamp trials were placed in the baseline block to capture participants' baseline forces, and the first five error-clamp trials on day two were averaged in each condition to create an adaptation coefficient for retention. Furthermore, the end of day one learning and day two relearning were represented by the mean of the last two error-clamp channel trials. Comparisons across conditions were statistically quantified with an ANOVA, and post-hoc tests for pairwise comparisons were corrected with the Tukey HSD.

In analyses of perpendicular deviation, twenty consecutive kinematic trials formed a subset at each of the following experimental phases: the end of day one learning, the beginning of day two retention, and the end of day two relearning. An ANOVA was performed to compare values at each phase.

MEP Analysis

MEPs were recorded at an EMG sampling rate of 5Hz from surface electrodes placed over the biceps brachii muscle. The peak-to-peak MEP response was assessed between 10ms and 90ms following stimulation onset, and MEPs were visualized with Brainsight's EMG unit. In the event-related potential experiment involving the effect of iTBS on MEPs, the dependent variable of MEP amplitude is the peak-to-peak EMG magnitude. Data visualization in the *Results* section of this analysis presents MEPs with a 6^{th} order low-pass and zero-phase filter with a cut-off frequency of 20Hz. An analysis of pre- and post-stimulation amplitudes was done with a paired samples t-test.

SEP Analysis

SEPs were elicited from the right median nerve using a square-wave pulse stimulator, and analyses of SEP amplitudes were conducted using EEG data at CP3, which corresponds to event-related potentials of hand area S1 (Ohashi et al., 2019). EEG signals were recorded at 2048Hz and resampled to 1024Hz during analysis. The continuous raw EEG signal was then notch filtered at 60Hz and band pass filtered between 1 and 100Hz, before being re-referenced to the average of six selected channels: C1, C3, C5, CP1, CP3 and CP5. Independent components analysis (ICA) cleaning was used to remove a recurring stimulation artifact. The data analysis focused on the interval between -10ms to 70ms following stimulation onset, and the data were normalized by subtraction of baseline values between -10ms and 0ms. The peak-to-peak amplitudes of the P20/N25 SEP component (Tsuji et al., 1988; Politof et al., 2021) were averaged across participants to provide a mean SEP before and after brain stimulation. A paired samples t-test was used for statistical analysis.

Removal of Data

Two participants, subject number 15 in the S1 condition and number 14 in Control, were removed from the iTBSx1 experiment. These participants produced forces greater than three standard deviations from the group mean force compensation level and, therefore, overcompensated for the loads throughout training and retraining. Fourteen participants remain in each of these conditions.

4 | Results

To explore the efficacy of iTBS in motor adaptation learning and neural facilitation, two studies, each with two experiments, were conducted. In study one, *iTBS in upper-limb motor learning*, participants received either one (n = 43) or two (n = 48) blocks of iTBS stimulation before participating in a force-field adaptation task. In study two, *iTBS on M1 and S1 event-related potentials*, changes in MEP and SEP amplitudes were assessed after two blocks of iTBS.

iTBS in Upper-Limb Motor Learning

The single stimulation (iTBSx1) and double stimulation (iTBSx2) block experiments each took place over two days of performing a velocity-dependent force-field adaptation task. Participants were seated in the chair of a robotic manipulandum setup and were instructed to make reaching movements between point-to-point targets on a reflected visual display. To begin, on day one, participants performed a series of familiarization and null-field trials where the force-field remained off. The null trials were used as a measure of baseline motor performance before adaptation learning. iTBS to the primary motor cortex (M1), primary somatosensory cortex (S1) or a control area at either the vertex of the skull (iTBSx1) or the medial occipital lobe (iTBSx2) was administered immediately after baseline trials. A 15-minute post-stimulation wait period followed each iTBS block. Participants subsequently completed a learning phase in which force-field loads were introduced gradually up to 15N across trials. Gradual force-field training minimizes participant awareness of the load with the goal of engaging implicit processes of motor learning. Therefore, the use of this perturbation was designed to minimize participants' use of explicit strategies during initial training.

Twenty-four hours later, participants returned to complete a retention test followed by a relearning phase. Here, the force-field load was introduced abruptly at 15N. By employing abrupt loads on day two, as opposed to reusing the gradual loads introduced on day one, differences in performance during relearning could not be masked by incremental increases in load level. Error-clamp trials, characterized by high stiffness-force channel walls, were interspersed throughout both the learning and relearning phases to measure participants' exerted force. In each training phase, five error-clamp trials were placed at the beginning of the training block, five were positioned intermittently during the task and two were placed near the end. The following results provide the findings of experiment one (Fig. 1C), where one block of iTBS preceded learning, and experiment two (Fig. 1D), where two blocks of iTBS preceded learning.

Experiment 1: One Block of iTBS

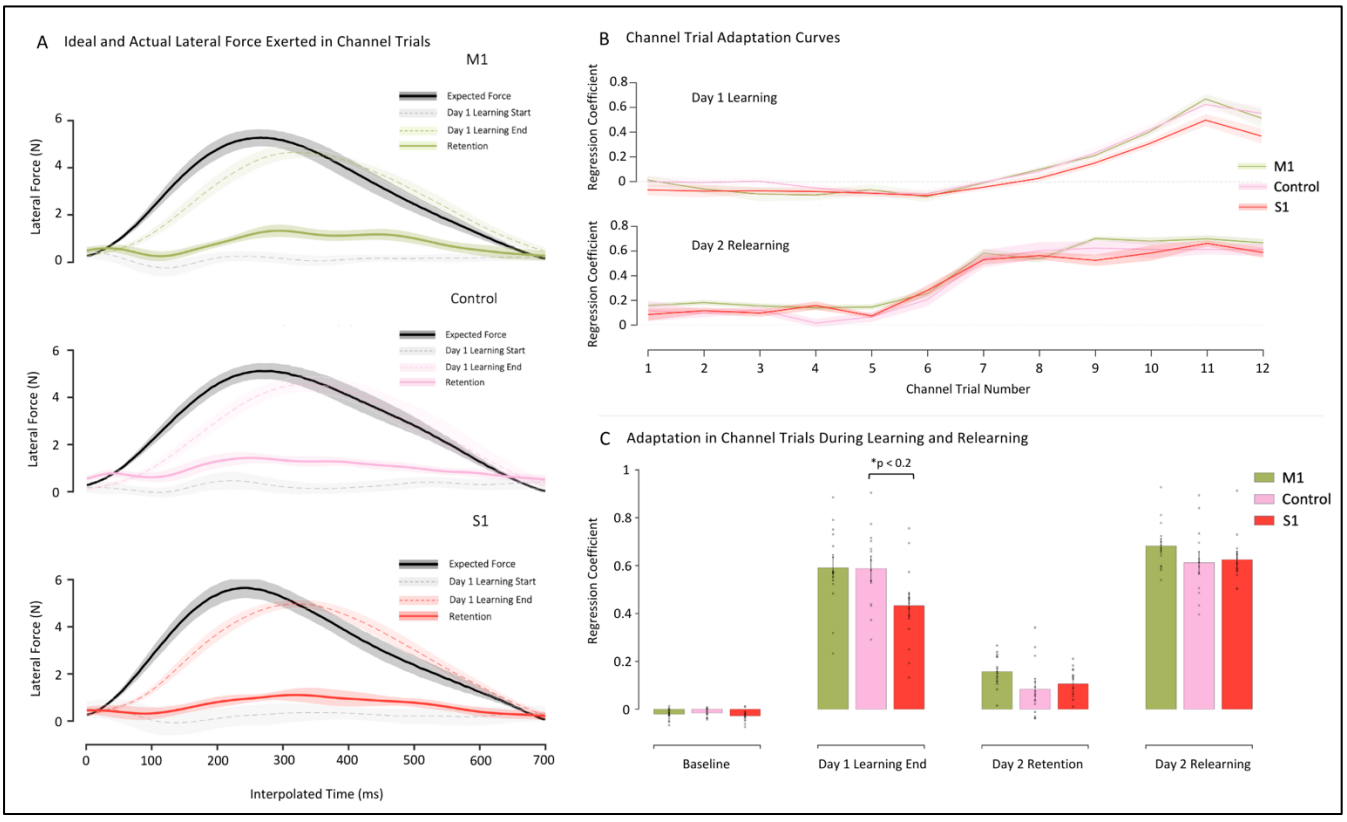


Figure 2.0 ***Experiment 1: Channel Trials.*** **A** *Expected and Actual Force in Channel Trials* Lateral force curves from participants' movements between point-to-point targets during the beginning and end of day one learning, as well as the beginning of day 2 retention. The black curve represents the expected force required to fully compensate for the load. Time between targets is represented as interpolated time(ms). **B** *Channel Trial Adaptation Curves* Learning and Relearning curve plots over the twelve channel trials on day one and two respectively. The first five channels were positioned at the start of the block. The second five were positioned intermittently and the last two were placed at the end. Learning is measured by the regression coefficient of actual force regressed on expected force up to peak velocity. A regression coefficient of one reflects complete compensation for the expected force. **C** *Adaptation in Channel Trials During Learning and Relearning* Using the same segmentation of channel trials described in B, a summary plot shows the mean of each group of channels across conditions. Three channel trials were conducted in the baseline phase. Day 1 Learning is mean of the last two channel trials on day one. Day 2 Retention is a mean over the first five channel trials on day two. Day 2 Relearning is the mean of the last two channel trials on day two.

Figure 2 shows participants' force-based performance during error-clamp trials over day one and day two learning. In Figure 2A, mean actual and ideal force profiles are plotted for each brain stimulation condition over the duration of point-to-point reaching. Time, measured in milliseconds, was standardized to 700 points for each trial through interpolation, ensuring a consistent number of data samples representing the duration of movement across all trials. The mean lateral force profile required to fully compensate for the load, referred to as the *Ideal force,* averaged 5.34N across conditions, with peak force expected near 250ms. Mean actual force is presented in subsets of channel trials reflecting participants' lateral force exertion. The first five channel trials on day one depict lateral force exerted during *Day 1 Learning Start*, the last two on day one depict lateral force exerted at *Day 1 Learning End*, and the first five on day two capture the *Retention* of day one learning. There are no observable differences in force exertion between experimental conditions (stimulation sites) at the beginning of learning, as the actual exerted force remains near zero in all conditions. All participants sufficiently learned to compensate for the load by the end of day one [M = 88% of ideal force, SD = 0.22], and actual peak force occurred within 350ms of movement start. Along with the absence of observable differences across groups at *Day 1 Learning End*, the *Retention* force profile indicates that participants performed with similar levels of force exertion upon returning 24 hours after day one training.

Figure 2B presents the regression coefficient of actual force regressed on ideal force up to peak velocity for the twelve channel trials present in both *Day 1 Learning End* and *Day 2 Relearning*. A slope of one indicates complete compensation. During the initial five channel trials on day one, the adaptation regression coefficient remained near zero before the gradual load was introduced on a trial-by-trial basis. During learning, as seen from channels six to ten, learning curves for all conditions reveal that participants gradually increased their force exertion until the end of training at trials 11 and 12, where the load reached maximum at 15N. Interestingly, it becomes evident that at channel seven (trial 8/155 total trials), S1 participants began to consistently compensate for the load at a slower rate than M1 and Control. This difference was retained until the end of learning, where channels 11 and 12 show that S1 participants achieved less force compensation. One block of iTBS to S1, therefore, resulted in a transient deficiency in performance during the learning process. Despite this, on day two, participants in all conditions demonstrated similar amounts of retention (channel trials 1 to 5) and rates of relearning (trials 6 to 12) across channel trials.

Figure 2C summarizes the learning curve plots by averaging over channel trials at the level of condition and experimental phase. *Baseline* is representative of forces exerted during the three channel trials conducted in the pre-stimulation baseline block. *Day 1 Learning End* reflects a mean of the last two channel trials on day one. *Day 2 Retention* reflects a mean over the first five channel trials on day two, and *Day 2 Relearning* reflects the last two channel trials on day two. As previously seen in the learning curves plot (Fig.2B), differences in learning appear at the end of day one (Fig.2C), as S1 participants exerted less force – and, therefore, a smaller adaptation coefficient – by the end of initial training. This adverse effect of one block of

iTBS to S1 did not persist to day two retention or relearning, and no notable differences in the regression coefficient were found among conditions, indicating that iTBSx1 did not influence task consolidation.

To analyze these findings, a one-way ANOVA compared conditions at each experimental phase: Day 1 Learning Start, Day 1 Learning End, Day 2 Retention and Day 2 Relearning. When considering lateral force compensation (Fig. 2A), there were no significant differences among experimental conditions (stimulation sites) at the start of day one learning (a baseline measure) [$F_{2,40}$=0.460, p = 0.635, n^2 = 0.022], the end of day one learning [$F_{2,40}$=0.884, p = 0.421, n^2 = 0.042] nor the beginning of day two relearning, that is, retention [$F_{2,40}$=1.306, p = 0.282, n^2 = 0.061]. Using measures from the adaptation regression coefficient (Fig.2B-2C), it was seen that while the end of day one learning was significantly greater than learning start for all conditions [paired-sample t-test; t(42)= -23.288, p < 0.001, d=-3.551], S1 participants performed with significantly less compensation by the end of initial training (Fig. 2C) [$F_{2,40}$=4.017, p = 0.026, n^2 = 0.167]. This statistical difference was not maintained 24 hours later during day two testing. Instead, all participants produced comparable amounts of retention at the beginning of day two [$F_{2,40}$=2.803, p = 0.073, n^2 = 0.123]. Furthermore, participants quickly relearned the task at a comparable rate (Fig.2B) and no significant difference in the adaptation coefficient at the level of condition was produced by the end of day two relearning (Fig. 5C) [$F_{2,40}$=1.480, p = 0.240, n^2 = 0.069].

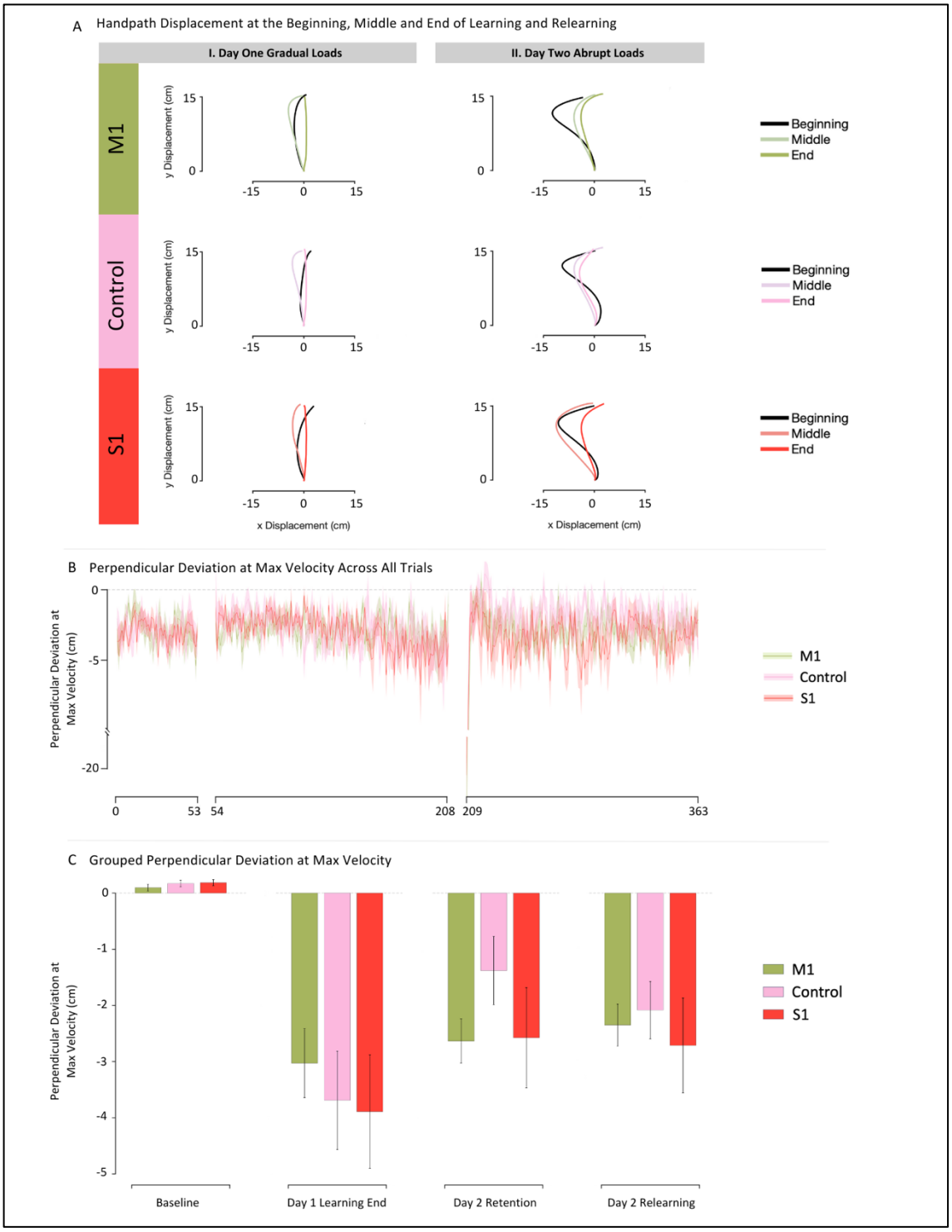


Figure 3.0 ***Experiment 1: Perpendicular Deviation (PD) at Maximum Velocity.*** **A** *Hand Path Displacement at the Beginning, Middle and End of Learning and Relearning.* Representative hand paths from the beginning, middle and end of gradual adaptation on day one and abrupt adaptation on day two for each condition. Each hand path is a single trial and hand position is displayed as displacement in cm. Day one: beginning, trial number 70/363; middle, trial number 133/363 and end, trial number 155/363. Day Two: beginning, trial number 228/363; middle, trial number 288/363 and end, trial number 363/363. **B** *Perpendicular Deviation at Maximum Velocity Across all Trials* Channel trials were removed to produce visualization of hand path kinematics from baseline (trials 0 to 53) to day one training (trials 59 to 208) to day two relearning (trials 209 to 363). Perpendicular deviation (PD) measured the amount of deviation from straight-line hand paths at peak movement velocity. PD at 0 indicates complete compensation for the force while negative values indicate less compensation, that is, deviation moving in the same direction of the force perturbation. **C** *Grouped Perpendicular Deviation at Max Velocity* A summary plot of PD during baseline, day one learning, day two retention, and day two relearning. Twenty consecutive non-channel trials were grouped at each phase to produce a mean perpendicular deviation for each condition.

Figure 3.0 presents findings obtained from calculations of perpendicular deviation at maximum velocity (PD), a measure assessing learning and relearning through kinematic data derived from non-error-clamp trials. In Figure 3A, representative hand paths at the beginning, middle and end of day one learning (trials 70, 133 and 155, respectively) and day two relearning (trials 228, 288 and 363, respectively) demonstrate differences in movement paths during gradual force-field learning (Fig.3A-I) and abrupt force-field learning (Fig.3A-II). On both days, the force perturbation moved the limb towards the left.

During initial training, when participants encountered the load gradually, movements between target points remained relatively straight throughout the learning block as incremental trial-by-trial changes in load permitted progressive force correction (Fig. 3A-I). However, on day two, when the load was introduced abruptly, participants initially produced broad, curved movements at the beginning of relearning (Fig 3A-II) and gradually re-adapted towards producing straight-line pathways by the end of day two. It is seen that by the end of relearning, in all conditions, participants do not fully compensate for the load with straight-line hand paths.

As movements with greater deviation from the straight-line point-to-point trajectory demonstrate less learning due to less force compensation, Figure 3B illustrates the PD in all non-channel trials across baseline (trials 1 to 53), day one training (trials 59 to 208) and day two relearning (trials 214 to 363). Here, a value of 0 indicates complete force compensation. Participants perform similarly during baseline while the force-field is inactive. On day one, gradual learning with incomplete compensation continues throughout training, and there are no discernable differences in performance between conditions. Twenty-four hours later, participants do not expect the abrupt force-field load and show extreme deviation over the first

few trials. Subsequently, relatively quickly, retention of day one's gradually learned load appears as participants adapt their hand paths to compensate for the perturbation. Minimal differences can be observed between conditions. Particularly, Control participants appear to perform with slightly greater compensation in comparison to M1 and S1 over the first half of the relearning block (trials 214 to 363) (Fig.3B). This suggests that one block of iTBS may have diminished force compensation in a subset of participants in the M1 and S1 conditions.

Figure 3C provides a summary plot of perpendicular deviation at max velocity by stimulation site, as well as by the following experimental phases: Baseline, Day 1 Learning End, Day 2 Retention, and Day 2 Relearning. At each phase, twenty consecutive non-error-clamp trials were grouped to provide a mean PD value that characterizes force compensation at each time point. As previously noted, the perturbation was off during the baseline block. By the end of initial training on day one, small differences among conditions appear obscured by inter-individual variability in participant performance. While high variability persists across trials on day two, mean PD during *Day 2 Retention* suggests that Control participants performed with less perpendicular deviation than M1 and S1 participants. However, by the end of *Day 2 Relearning*, kinematics in the Control condition appear to slightly decline towards a PD comparable to the M1 and S1 participants, who show little change in PD between *Day 2 Retention* and *Day 2 Relearning*.

A one-way ANOVA was used to analyze differences in PD, which is the mean of twenty consecutive kinematic trials, between conditions at each experimental phase. There were no significant differences in perpendicular deviation at max velocity at the end of day one learning (Fig.3C) [$F_{2,40}$=0.274, p = 0.762, n^2 = 0.013]. A similar non-significant effect occurred on day two,

where participants in the M1, S1 and Control conditions produced varied hand-path trajectories throughout retention (first 20 trials on day two) and relearning (last 20 trials on day two) [$F_{2,40}$=1.081, p = 0.349, n^2 = 0.051 during *Day 2 Retention*; [$F_{2,40}$=0.252, p = 0.779, n^2 = 0.012 during *Day 2 Relearning*].

Experiment 2: Two Blocks of iTBS

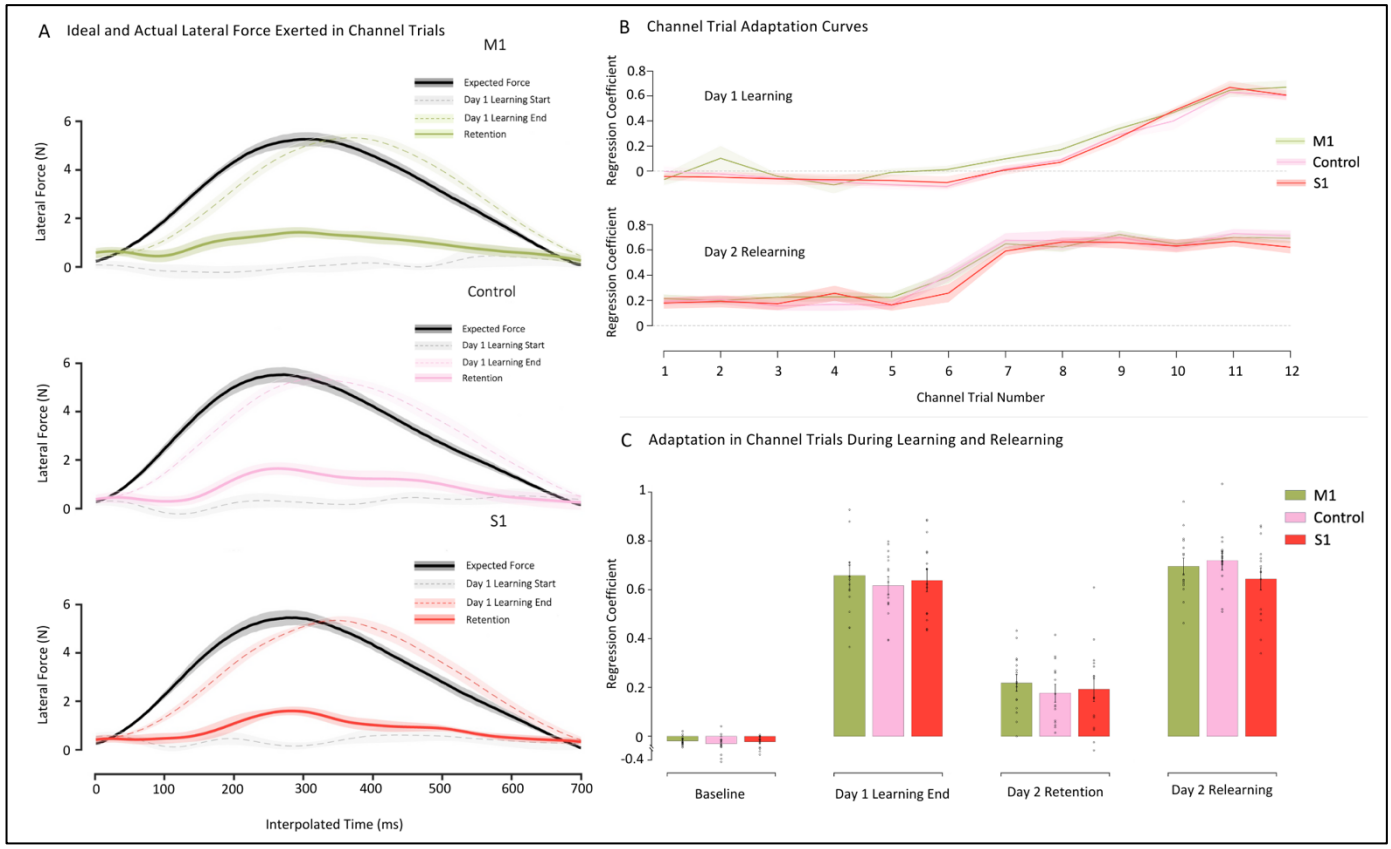


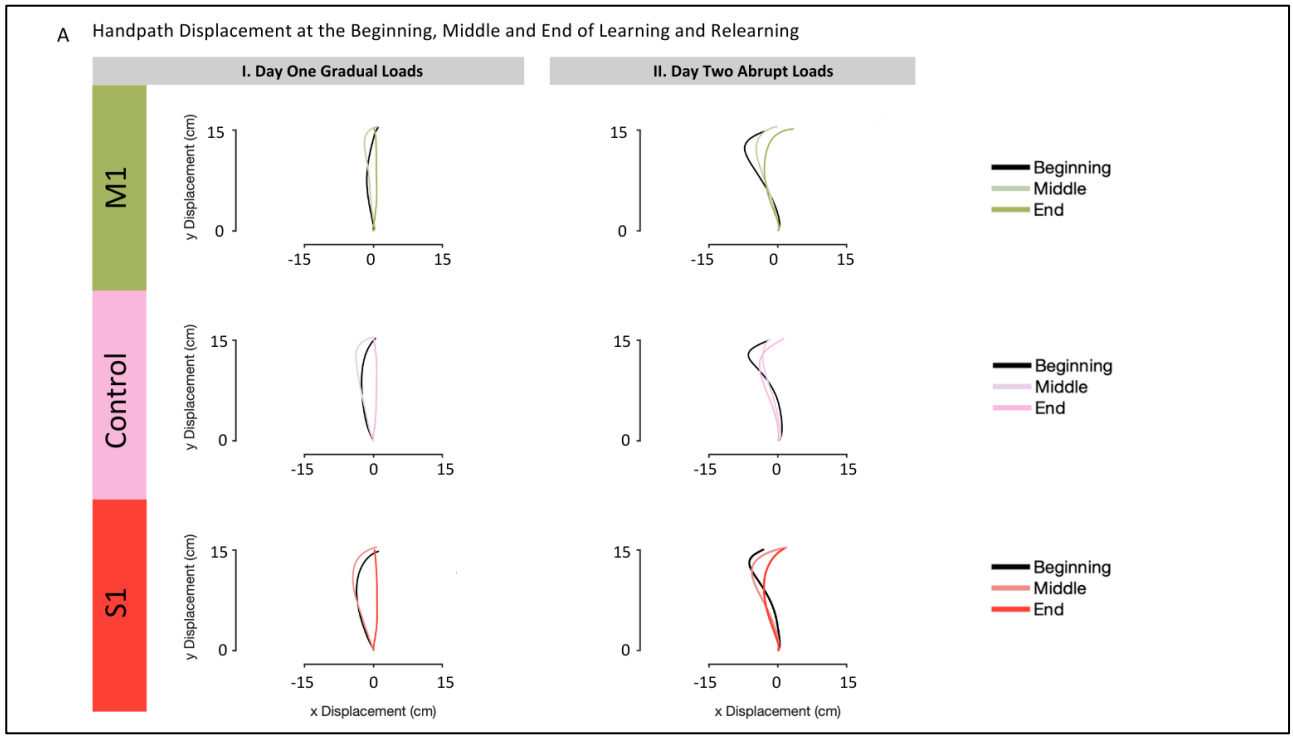
Figure 4.0 ***Experiment 2: Channel Trials.*** **A** *Expected and Actual Force in Channel Trials* Lateral force curves from participants' movements between point-to-point targets during the beginning and end of day one learning, as well as the beginning of day 2 retention. The black curve represents the expected force required to fully compensate for the load. Time between targets is represented as interpolated time(ms). **B** *Channel Trial Adaptation Curves* Learning and Relearning curve plots over the twelve channel trials on day one and two respectively. The first five channels were positioned at the start of the block. The second five were positioned intermittently and the last two were placed at the end. Learning is measured by the regression coefficient of actual force regressed on expected force up to peak velocity. A regression coefficient of one reflects complete compensation for the expected force. **C** *Adaptation in Channel Trials During Learning and Relearning* Using the same segmentation of channel trials described in B, a summary plot shows the mean of each group of channels across conditions. Three channel trials were conducted in the baseline phase. Day 1 Learning is mean of the last two channel trials on day one. Day 2 Retention is a mean over the first five channel trials on day two. Day 2 Relearning is the mean of the last two channel

Experiment two explores the effect of two blocks of iTBS on force-field adaptation learning, and Figure 4.0 displays the associated results obtained from channel trials, presented similarly to experiment one (Fig.2). In Figure 4A, mean actual and ideal force are presented for each condition: M1, S1, and Control, where brain stimulation targeted the medial occipital lobe. As in experiment one, twelve error-clamp, channel, trials were conducted on both day one and two. Thus, the mean actual force exerted by participants averages over the first five channel trials on day one, *Day 1 Learning Start*; the last two on day one, *Day 1 Learning End;* and the first five on day two, *Day 2 Retention*. Participant forces remained near zero at the start of day one, before the gradual load was introduced, and as displayed in *Day 1 Learning End*, all participants sufficiently learned the task by exerting a close to ideal amount of force to compensate for the load by the end of initial training. By the start of day two, no apparent differences occurred between conditions, suggesting that participants' learning and retention of the learned lateral force was not differentially affected by two rounds of iTBS.

When considering the regression coefficient up to peak velocity, a similar overall effect can be inferred. Figure 4B shows day one and day two learning curves for each condition across channel trials. In the first five channels on day one, compensation for the load was not required. However, during learning (channels 6 to 10), as the load gain increased from zero to 15N, M1 participants adapted to the load at a faster rate than S1 and Control. Two blocks of iTBS may have, therefore, induced a short-lasting transient effect on M1 learning. Nonetheless, this M1 difference subsided by the end of day one, as channels 11 and 12 depict similar adaptation coefficients across all conditions.

Figure 4C, once again, groups channel trials by experimental phase for an analysis of force-based performance between conditions. Here, M1 and S1 participants do not differ from Control in their achieved adaptation on day one nor on day two.

Through a one-way ANOVA, it was shown that across stimulation sites, all participants achieved the same amount of learning by the end of the day one training block (Fig. 4B), as there were no significant differences in the regression coefficient (Fig.4C) [$F_{2,45}$=0.25, p = 0.782, n^2 = 0.011]. An expected decrease in learned adaptation occurred over day two retention trials and relearning was restored by the end of the task (Fig.4B-C); however, there were no differences between conditions during day two retention [$F_{2,45}$=0.36, p = 0.703, n^2 = 0.016] or day two relearning [$F_{2,45}$=1.304, p = 0.281, n^2 = 0.055].



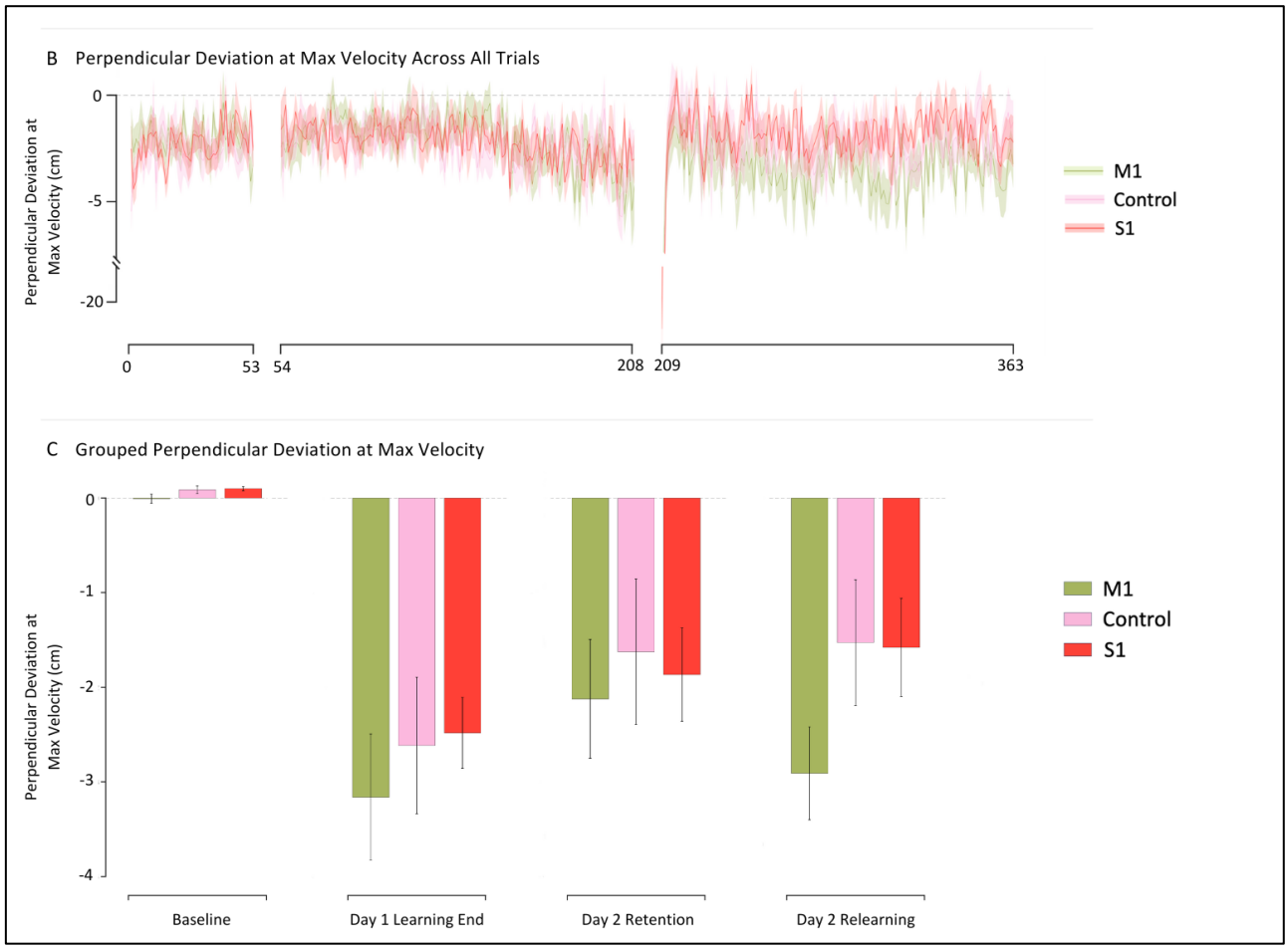


Figure 5.0 ***Experiment 2: Perpendicular Deviation at Max Velocity.*** **A** *Hand Path Displacement at the Beginning, Middle and End of Learning and Relearning.* Representative hand paths from the beginning, middle and end of gradual adaptation on day one and abrupt adaptation on day two for each condition. Each hand path is a single trial and hand position is displayed as displacement in cm. Day one: beginning, trial number 70/363; middle, trial number 133/363 and end, trial number 155/363. Day Two: beginning, trial number 228/363; middle, trial number 288/363 and end, trial number 363/363. **B** *Perpendicular Deviation at Maximum Velocity Across all Trials* Channel trials were removed to produce visualization of hand path kinematics from baseline (trials 0 to 53) to day one training (trials 59 to 208) to day two relearning (trials 209 to 363). Perpendicular deviation (PD) measured the amount of deviation from straight-line hand paths at peak movement velocity. PD at 0 indicates complete compensation for the force while negative values indicate less compensation, that is, deviation moving in the same direction of the force perturbation. **C** *Grouped Perpendicular Deviation at Max Velocity* A summary plot of PD during baseline, day one learning, day two retention, and day two relearning. Twenty consecutive non-channel trials were grouped at each phase to produce a mean perpendicular deviation for each condition.

Figure 5.0 illustrates perpendicular deviation at maximum velocity across day one and day two kinematic trials. Representative hand path trajectories (Fig. 5A) from the beginning, middle and end of both gradual learning on day one and abrupt relearning on day two are plotted for all conditions. As in experiment one, participants similarly began and ended day one learning with little deviation from a straight-line path, while on day two, participants learned to

adapt to the abrupt load with less PD. In Figure 5B, PD during baseline (trials 1 to 53) and day one learning (trials 59 to 208) show minimal differences between brain stimulation conditions. However, on day two (trials 214 to 363), throughout relearning, M1 participants appear to use less force compensation than participants in S1 and Control. This suggests that two blocks of iTBS may have affected the consolidation process of M1 participants.

Finally, Figure 5C further describes PD performance in experiment two by averaging over PD data from twenty non-channel trials at each experimental phase: the last 20 at the end of day one learning, the first 20 at the beginning of day two (retention), and the last 20 on day two (relearning). Participants perform with varied hand path trajectories within each condition throughout day one and day two. *During Day 2 Relearning*, a visual discrepancy, as similarly seen in Figure 5B, can be observed among M1, S1 and Control participants.

Overall, for the data shown in Figure 5C, there were no differences in perpendicular deviation at maximum velocity across conditions by the end of day one learning, the beginning of day two retention, nor the end of day two relearning (Fig.5C) following a one-way ANOVA performed at each experimental phase [$F_{2,45}$=0.329, p = 0.722, n^2 = 0.014 for *Day 1 Learning*; $F_{2,45}$=0.142, p = 0.868, n^2 = 0.006 for *Day 2 Retention*; $F_{2,45}$=1.813, p = 0.175, n^2 = 0.075 for *Day 2 Relearning*]. It can be presumed that the inter-individual variability across conditions affects the statistical significance of the visual M1 trend appearing at the end of day two (Fig.5B-C) [Relearning PD: *M*= -2.908, *SD*= 2.033 for *M1*; *M*= -1.579, *SD* = 2.138 for *S1*; *M*=-1.527, *SD*=2.743 for *Control*].

Differences Between One and Two Blocks of iTBS in Learning, Retention and Relearning

The number of iTBS blocks administered during brain stimulation periods elicited varied effects on the cortical areas under investigation. Multivariate ANOVAs were conducted on three dependent variables, namely, lateral force, the adaptation coefficient, and perpendicular deviation at maximum velocity, within each condition (M1, S1 and Control) of the upper-limb motor learning experiments. Post-hoc independent samples t-tests were used to follow up on MANOVA significances. The tables below present the differences between each of the behavioural measures over the course of learning, retention and relearning, for the iTBSx1 versus iTBSx2 experiments.

Lateral Force

Preliminary MANOVA Pillai tests revealed effects of one versus two blocks of iTBS on lateral force in the M1, S1 and Control conditions [Pillai's Trace = 0.301, $F_{3,27}$=3.882, p = 0.020 for *M1*; Pillai's Trace = 0.257, $F_{3,26}$=2.992, p = 0.049 for *S1*; Pillai's Trace = 0.271, $F_{3,26}$=3.228, p = 0.039 for *Control*]. Subsequent one-way ANOVAs were assessed for each brain stimulation area and follow-up post-hoc t-tests describe the derived effects at varied phases of each experiment with a Tukey HSD correction. Post-hoc tests are presented in Table 1.0. The following description provides an analysis of significant differences observed in M1, S1 and then Control participants.

Between the two M1 conditions, participants receiving two blocks of iTBS used significantly more force by the end of day one learning than those receiving one block of stimulation [t(29)= -3.535, p < 0.001, d=-1.270]. In S1 participants, an effect of iTBS block approaches significance at the end of day one learning, where significantly more force was

observed for the iTBSx2 group [$t(28)= -2.024$, $p = 0.053$, d=-0.741 for *day 1 end*]. In addition to this, S1 participants showed significant differences between iTBS experiments in terms of day two relearning [$t(28)= -2.318$, $p = 0.028$, d=-0.848 for *day 2 start*]. Here, iTBSx2 resulted in greater lateral force exertion. Finally, in the Control conditions, where participants were stimulated in different brain regions, post-hoc t-tests show that one round of iTBS stimulation to the vertex, in experiment one, significantly diminished lateral force production by the end of day one learning in comparison to medial occipital lobe stimulation, conducted in experiment two [$t(28)= -2.885$, $p < 0.007$, d=-1.056]. This could imply that stimulating the medial occipital lobe might have served as a more neutral approach to achieving experimental control.

Table 1.0 *t-Tests Comparing Lateral Force Exerted in M1, S1 and Control During Experiments iTBSx1 and iTBSx2*

	Mean Difference	SE	*df*	*t*	*d*	p_{Tukey}
Conditions: M1 (iTBSx1) and M1 (iTBSx2)						
Day 1 Learning Start	-0.138	0.350	29	-0.393	-0.141	0.697
Day 1 Learning End	-0.601	0.170	29	-3.535	-1.270	**0.001**
Day 2 Retention	-0.127	0.228	29	-0.556	-0.200	0.582
Conditions: Control (iTBSx1) and Control (iTBSx2)						
Day 1 Learning Start	0.059	0.277	28	0.213	0.078	0.833
Day 1 Learning End	-0.736	0.255	28	-2.885	-1.056	**0.007**
Day 2 Retention	-0.069	0.286	28	-0.239	-0.088	0.813
Conditions: S1 (iTBSx1) and S1 (iTBSx2)						
Day 1 Learning Start	-0.177	0.317	28	-0.557	-0.204	0.582
Day 1 Learning End	-0.343	0.169	28	-2.024	-0.741	0.053
Day 2 Retention	-0.508	0.219	28	-2.318	-0.848	**0.028**

Adaptation Regression Coefficient

There was no significant effect of one versus two stimulation blocks in the M1 conditions when considering the adaptation regression coefficient [Pillai's Trace = 0.117, $F_{4,26}$=0.861, p = 0.500]. However, further one-way MANOVAs revealed that learned adaptation in the S1 and Control groups differed depending on the number of iTBS blocks participants received [Pillai's Trace = 0.335, $F_{4,25}$=3.152, p = 0.032 for *S1*; Pillai's Trace = 0.324, $F_{4,25}$=2.996, p = 0.038 for *Control*]. Post-hoc t-tests are displayed in Table 2.0. The following description provides statistical results derived from regression coefficient analyses from the baseline, day one learning end, and day two phases.

There were no differences in participants' baseline exerted forces during channel trials at the level of iTBS block [t(29)= -0.277, p = 0.783, d=-0.100 for M1; t(28)= 1.410, p = 0.169, d=0.516 for *Control*; t(28)= -0.578, p = 0.68, d=-0.211 for *S1*]. At the end of day one learning, *iTBSx2* S1 participants learned to compensate for the force perturbation with greater expected force than iTBSx1 S1 participants[t(28)= -3.381, p = 0.002, d=-1.237]. This was not true for comparisons between the control conditions [t(28)= -0.530, p = 0.600, d=-0.194]. However, it was found that over the course of day two's trials, control participants receiving one block of stimulation to the vertex demonstrated significantly less retained and relearned adaptation on day two than that observed for *iTBSx2* control participants [t(28)= -2.126, p = 0.042, d=-0.778 for retention; t(28)= -2.238, p = 0.033, d=-0.819 for *relearning*]. This suggests that iTBSx1 may have impaired the consolidation processes of participants receiving vertex stimulation. In S1 participants, achieved retention and relearning occurring 24 hours after initial training did not

differ between iTBS protocols [[$t(28)$= -1.769, p = 0.088, d=-0.143 for retention; $t(28)$= -0.390, p = 0.699, d=-0.143 for *relearning*].

Table 2.0 *T-Tests Comparing the Adaptation Regression Coefficient in M1, S1 and Control During Experiments iTBSx1 and*

	Mean Difference	SE	*df*	*t*	*d*	p_{Tukey}
Conditions: M1 (iTBSx1) and M1 (iTBSx2)						
Baseline	-0.008	0.029	29	-0.277	-0.100	0.783
Day 1 Learning	-0.067	0.068	29	-0.979	-0.352	0.336
Day 2 Retention	-0.062	0.035	29	-1.740	-0.625	0.092
Day 2 Relearning	-0.014	0.041	29	-0.328	-0.118	0.745
Conditions: Control (iTBSx1) and Control (iTBSx2)						
Baseline	0.061	0.043	28	1.410	0.516	0.169
Day 1 Learning	-0.029	0.054	28	-0.530	-0.194	0.600
Day 2 Retention	-0.093	0.044	28	-2.126	-0.778	**0.042**
Day 2 Relearning	-0.108	0.048	28	-2.238	-0.819	**0.033**
Conditions: S1 (iTBSx1) and S1 (iTBSx2)						
Baseline	-0.020	0.035	28	-0.578	-0.211	0.568
Day 1 Learning	-0.206	0.061	28	-3.381	-1.237	**0.002**
Day 2 Retention	-0.086	0.049	28	-1.769	-0.648	0.088
Day 2 Relearning	-0.019	0.050	28	-0.390	-0.143	0.699

Perpendicular Deviation at Maximum Velocity

Finally, there was no significant effect of iTBS block on perpendicular deviation in learning, retention or relearning for any of the brain stimulation areas between experiments iTBSx1 and iTBSx2. A MANOVA revealed that an additional iTBS stimulation block did not significantly change a specific cortical area's response as assessed kinematically in this task [Pillai's Trace = 0.173, $F_{4,26}$=3.882, p = 0.276 for *M1*; Pillai's Trace = 0.115, $F_{4,25}$=0.812, p = 0.529

for *S1*; Pillai's Trace = 0.090, $F_{4,25}$=0.616, p = 0.655 for *Control*]. Table 3.0 shows t-test comparisons between one and two iTBS blocks for all conditions.

Table 3.0 *T-Tests Comparing Perpendicular Deviation at Max Velocity in M1, S1 and Control During Experiments iTBSx1 and iTBSx2*

	Mean Difference	SE	*df*	*t*	*d*	p_{Tukey}
Conditions: M1 (iTBSx1) and M1 (iTBSx2)						
Baseline	0.106	0.078	29	1.349	0.485	0.188
Day 1 Learning	0.132	0.940	29	0.140	0.050	0.890
Day 2 Retention	-0.511	0.777	29	-0.658	-0.237	0.516
Day 2 Relearning	0.558	0.645	29	0.865	0.311	0.394
Conditions: Control (iTBSx1) and Control (iTBSx2)						
Baseline	0.085	0.071	28	1.186	0.434	0.246
Day 1 Learning	-1.076	1.165	28	-0.923	-0.338	0.364
Day 2 Retention	0.245	1.035	28	0.236	-0.086	0.815
Day 2 Relearning	-0.557	0.885	28	-0.629	-0.230	0.534
Conditions: S1 (iTBSx1) and S1 (iTBSx2)						
Baseline	0.087	0.056	28	1.540	0.564	0.135
Day 1 Learning	-1.409	1.062	28	-1.327	-0.486	0.195
Day 2 Retention	-0.711	1.021	28	-0.696	-0.255	0.492
Day 2 Relearning	-1.136	0.999	28	-1.136	-0.416	0.265

iTBS on M1 and S1 Event-Related Potentials

The variability of findings in the upper-limb motor experiments brought into question whether iTBS can elicit consistent effects on cortical activity. Given the wealth of existing literature on the effects of a single block of iTBS on ERPs, the following experiments sought to uniquely examine the effects of two blocks of iTBS (iTBSx2) on MEPs and SEPs after stimulation

to either the primary motor or primary somatosensory cortex. In experiment three, the mean of fifteen MEPs was obtained before and after stimulation to M1 (n=10) (Fig. 6A) or S1 (n = 10) (Fig. 6E) using the evoked EMG response from the biceps, the primary muscle of the behavioural motor adaptation task, as the dependent variable. In Experiment four, iTBSx2 was applied to S1 following an EEG acquisition block of SEPs resulting from square-wave pulse stimulation to the median nerve. A second block of EEG data was obtained after brain stimulation to quantify associated changes in SEPs. The EEG channel CP3, which sits right over the left hemisphere hand area of S1, was of interest. While EEG data from the entire left hemisphere was obtained, an analysis of all 32 channels was beyond the scope of this thesis.

Experiment 3: Two Blocks of iTBS on MEPs

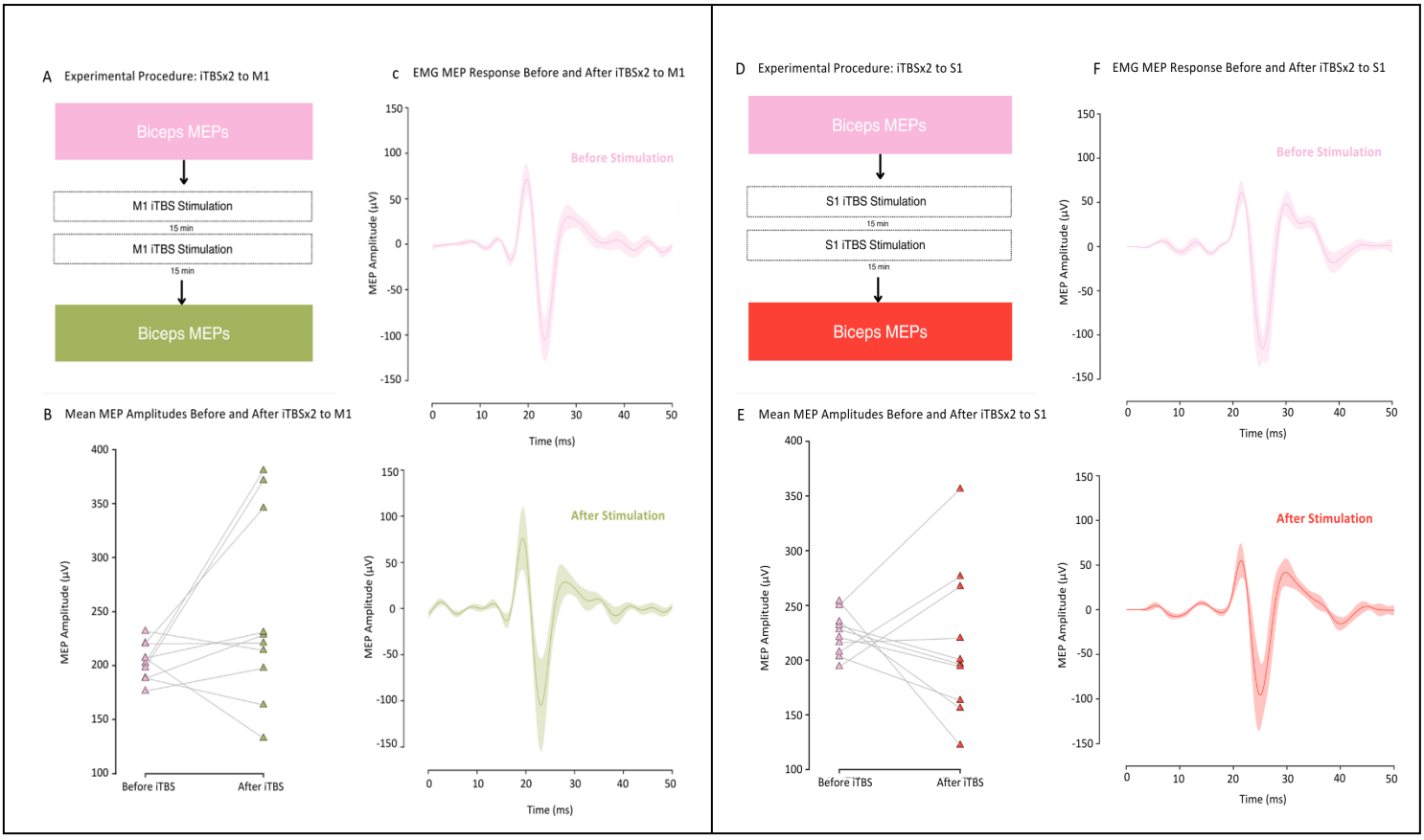


Figure 6.0 ***Two Blocks of iTBS on MEPs.*** **A** *Experimental Procedure: iTBSx1 to M1.* The mean of biceps MEPs were obtained before and after two blocks of iTBS. **B** *Mean MEP Amplitudes Before and After iTBSx2 to M1.* MEP amplitude was quantified as the absolute peak-to-peak value of EMG recordings. Individual participant means are plotted before and after iTBSx2 to M1. **C** *EMG Response Before and After iTBSx2 to M1.* MEPs were observed between 10 and 50ms of stimulation onset (0ms). The mean MEP waveform across participants is displayed before stimulation (pink) and after stimulation (green). **D** *Experimental Procedure: iTBSx2 to S1.* The mean of biceps MEPs were obtained before and after two blocks of iTBS. **E** *Mean MEP Amplitudes Before and After iTBSx2 to S1* MEP. amplitude was quantified in the same way as *B*. Individual participant means are plotted before and after iTBSx2 to S1. **F** *EMG Response Before and After iTBSx2 to S1.* The mean MEP waveform across participants is displayed before stimulation (pink) and after stimulation (red).

Figure 6.0 displays the protocol and changes in MEPs following two blocks of iTBS to either the M1 (Fig.6A) or S1 (Fig.6D) cortices. Fifteen MEPs were acquired from ten participants both before and after stimulation. Average MEPs were computed to produce a mean peak-to-peak MEP amplitude for each participant (Fig.6B). It can be observed that three of ten participants responded with particularly increased MEPs following iTBSx2 to M1. MEP waveform plots at each time point (Fig.6C) reflect that after stimulation, evoked responses between participants were highly variable when compared to pre-stimulation MEPs. Prior to M1 stimulation, the mean amplitudes were observed to be 203.87μV [SD=17.089] (Fig.6B), and after receiving two blocks of brain stimulation, the mean amplitude increased to M = 248.486μV with a standard deviation of SD=86.799. Levene's test for homogeneity of variances demonstrates that iTBSx2 significantly increased the variability of MEP responses following M1 stimulation [$F_{1,18}$= 15.291, $p < 0.001$]. Overall, with a paired-samples t-test, there was no significant change in MEP magnitude after iTBSx2 to M1 (Fig. 6B) [$t(9)$= -1.639, p = 0.136, d= -0.518] .

Furthermore, to ensure that any effect of receiving brain stimulation to S1 was solely because of targeted stimulation, and not a result of activity spread from M1, MEPs were recorded pre and post iTBSx2 to S1 (Fig. 6D). Mean MEPs calculated before and after stimulation display a broad range of responses from increased to decreased MEPs (Fig. 6E). However, with a mean peak-to-peak amplitude of 223.81μV [SD = 19.582] before stimulation and a mean of

215.09μV [SD = 68.535] after stimulation (Fig. 6F), there was no significant difference in MEP change following S1 brain stimulation [$t(9)$= -1.639, p = 0.716, d= 0.474]. Following a Levene's test, iTBSx2 increased the variability of the MEP response in S1 participants [$F_{1,18}$=7.155, p < 0.002]. The increased variability in MEPs following iTBS to S1, suggests that the possibility of indirect activation of M1 cannot be ruled out.

Experiment 4: Two Blocks of iTBS on SEPs

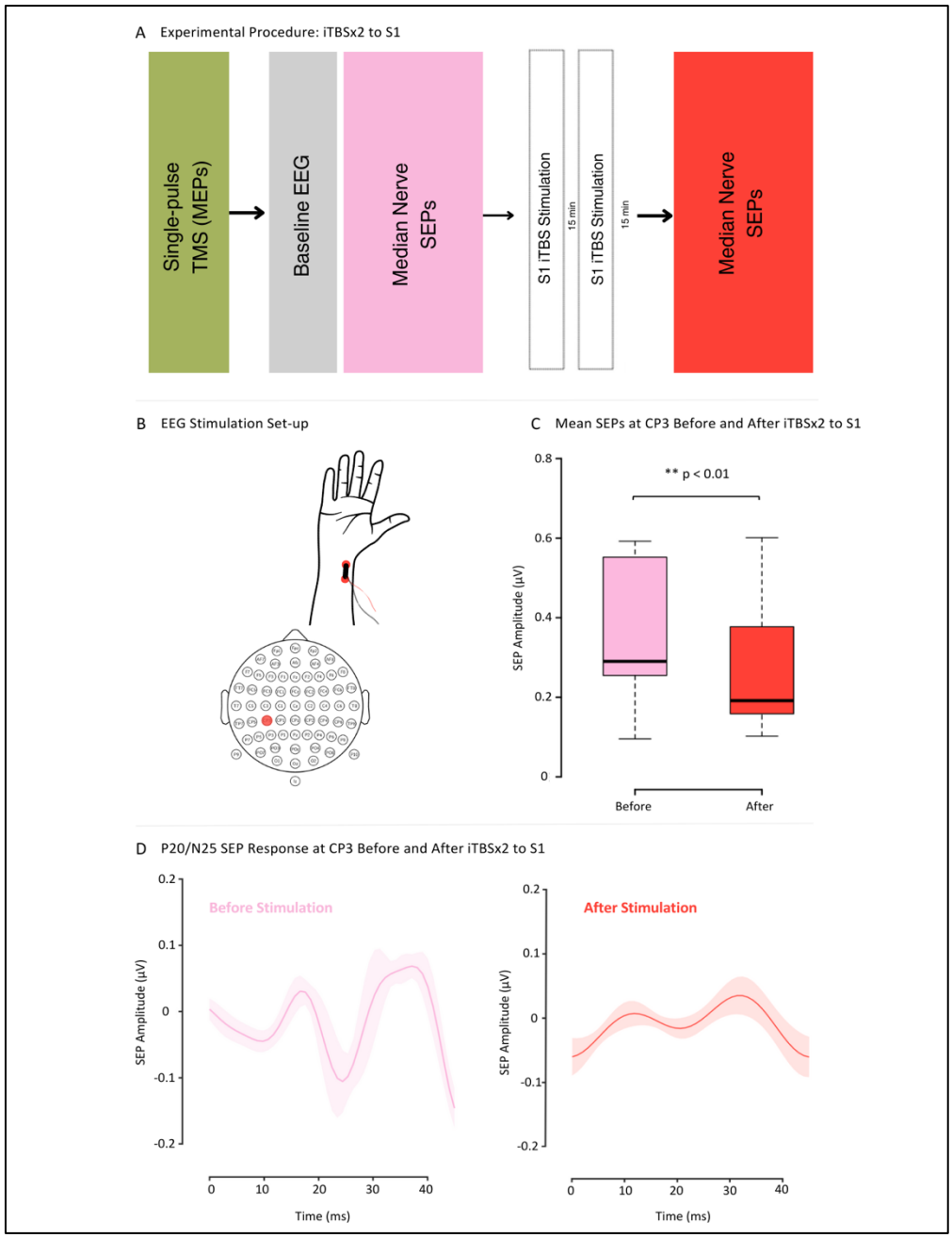


Figure 7.0 ***Upper Limb Motor Learning Study.*** **A** *Experimental Procedure: iTBSx2 to S1.* EEG was acquired alongside square-wave pulse stimulation to the right median nerve to obtain the mean of SEPs before and after two blocks of iTBS. **B** *EEG and Stimulation Set-up.* A surface bar electrode was positioned at the wrist to deliver trains of median nerve stimulation. Only the left hemisphere was acquired during EEG. The channel of interest is CP3 sitting over hand area S1. **C** *Mean SEPs at CP3 Before and After iTBSx2 to S1.* The EEG data were pre-processed and analyzed to obtain the group mean SEP before (pink) and after (red) two blocks of iTBS to S1 **D** *P20/N25 Response at CP3 Before and After iTBSx2 to S1* The cleaned EEG data was epoched by stimulation event. The mean of epochs demonstrates the P1/N1 component of median nerve stimulation before (pink) and after (red) stimulation.

Finally, Figure 7.0 highlights the experimental procedure of using EEG to obtain mean SEP responses before and after two blocks of iTBS to S1 (Fig. 7A). The P_1N_1 cortical S1 response at 20/25ms was analyzed at channel CP3 following electrical stimulation to the right median nerve (Fig.7B). Figure 7C uses a box and whisker plot to demonstrate differences in mean SEP amplitudes, and it is evident that despite response variability to iTBSx2 at either time point, group mean SEPs decreased after brain stimulation. In Figure 7D, a flattening of the SEP waveform occurs after stimulation at P20/N25, when compared to SEP amplitudes before stimulation. This decrease was found significant using a paired-samples t-test [$t(9) = 3.198$, $p = 0.011$, $d = 0.217$].

5 | Discussion

The study of neural facilitation through non-invasive brain stimulation techniques is integral to advancing our understanding of neural plasticity. While one block of iTBS has been shown to facilitate cortical activity as assessed using various measures of plastic change (for a review, see Chung et al., 2016), an optimal iTBS stimulation pattern for inducing consistent and powerful post-stimulation effects on neuronal excitability and behaviour is yet to be established (Corp et al., 2020). Thus, with the goal of identifying a more robust stimulation protocol, the differential effects of two blocks of iTBS on motor learning and cortical excitability were explored in a series of four experiments.

Intermittent theta burst stimulation was provided to either the primary motor cortex (M1), the primary somatosensory cortex (S1), or a control brain region before participants underwent training in an upper-limb force-field adaptation task. M1 stimulation was of interest due to the motor cortex contribution to effector-specific plasticity and task-related planning in motor learning (Muellbacher et al., 2001; Romei et al., 2009; Riek et al., 2012; Hamel et al., 2017), while stimulation to S1 sought to facilitate the perceptual learning and consolidation processes that contribute to motor learning and motor memory stabilization (Vahdat et al., 2014; Cuppone et al., 2018; Kumar et al., 2019; Mirdamadi & Block, 2020; Ebrahimi & Ostry, 2024). Furthermore, the control stimulation site differed between experiments. In experiment one, one block of iTBS was administered to the vertex of the skull, while two blocks of iTBS in experiment two were applied over the medial occipital lobe. In studies focusing on cognition and memory in the dlPFC, vertex control stimulation appears in the literature as a standard practice (for a review, see Lowe et al., 2018). However, when investigating facilitatory

sensorimotor learning processes through lateralized stimulation, this site may not be neutral due to potential current spread to the adjacent paracentral lobule and supplementary motor area (SMA) (Pizem et al., 2022). Consequently, with a change in the control stimulation site, behavioral data obtained from stimulation to the medial occipital lobe in experiment two may be more appropriate for comparing brain stimulation groups.

In experiment one (iTBSx1), participants received one block of iTBS, and in experiment two (iTBSx2), participants received two blocks of iTBS spaced by 15 minutes. During the behavioural learning phase of the experiment, the force-field load was introduced gradually and all participants in both experiments learned to adapt to the force similarly by the end of the training period (Fig.1A & Fig.3A). Participants returned 24 hours later for tests of retention and relearning with abrupt force-field trials, and here, they were found to retain and relearn day one's adaptation task at comparable rates between conditions in both experiments.

In two additional explorations, experiments three and four, the mean amplitude of motor evoked (MEPs) or somatosensory evoked potentials (SEPs) was obtained before and after two rounds of iTBS in new participants. Cases of expected facilitatory responses occurred in three of ten M1-MEP participants (Fig.3B), however, group mean SEPs were suppressed after two rounds of iTBS. Altogether, two blocks of iTBS did not better facilitate, or reduce the response variability, of cortical activity nor motor learning than one block of stimulation. Consistent with elements of the existing literature, these findings provide additional insights on the time course and ROI-specific changes associated with iTBS. A detailed discussion of four specific outcomes follows.

iTBS Induces Transient Effects on Motor Learning

Non-invasive brain stimulation is traditionally characterized by its ability to temporarily modulate neural processes. Nevertheless, recent interests focus on its potential role in facilitating motor learning (Jaberzadeh & Zoghi et al., 2013) and motor recovery (Liew et al., 2014), aiming to elicit stimulation effects that have a lasting impact on behavior. In this study, transient effects of iTBS on initial learning were observed in both upper-limb motor learning experiments. *One block of iTBS* to S1 reduced learning during the initial task training in experiment one (Fig. 2B), and M1 participants receiving *two blocks of iTBS* in experiment two appeared to adapt to the incremental load at a faster rate during learning (Fig. 4B), though this effect was not statistically reliable. Therefore, the derived effects of iTBS on early stages of upper-limb motor adaptation may vary based on both the number of iTBS blocks administered and the specific brain region of interest. While these early changes did not lead to sustained differences in consolidated performance, these findings suggest the volatility of iTBS in its application to motor learning.

Research demonstrates that one block of iTBS can result in an initial increase in excitatory (cortical excitation) or a rise in gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter (Hoppenrath & Funke, 2013). In the same work, it was shown that a decrease in cortical excitability may subsequently occur around forty minutes after stimulation. A precaution for the possibility of patterned increases and decreases in post-stimulation cortical activity, as observed in changes in MEPs, was first described in the initial detailing of the iTBS protocol (Huang et al., 2005). Accordingly, the impaired performance observed in S1-iTBSx1 participants may extend from an interaction with induced early-phase inhibition. Limited

research explores the effects of S1 iTBS on motor learning and consolidation; however, the disruption of motor learning processes following one block of iTBS to other motor learning areas is evident in few studies (M1: Jelić et al., 2015; Stökel et al., 2015; dlPFC: Gann et al., 2022) among others that also show one block of iTBS to M1 can increase (Teo et al., 2011) or have no effect on performance (Vallence et al., 2013). The latter is consistent with the regression coefficient data in this thesis showing that one block of iTBS did not affect day one learning in M1 participants (Fig. 2C).

Across both upper-limb motor experiments, differences in day one learning subsided by day two, as retention and relearning were comparable among brain stimulation conditions (Fig.2C & 4C). These findings support recent research indicating that iTBS may not be effective for enhancing 24-hour motor consolidation processes (Gann et al., 2022). As a result, behavioral changes appear to be limited to the brief window of altered cortical activity that follows stimulation. López-Alonso (2015) further highlights this relationship between iTBS and motor learning processes by demonstrating that one block of iTBS to M1 was not correlated with achieved motor learning in a visuomotor adaptation task (VAT), a serial reaction time task (SRTT), or a sequential visual isometric pinch task (SVIPT). Instead, iTBS was associated with decreases in the trial-by-trial reaction times produced during execution of the SRTT, and this effect was exclusively found in participants who showed a facilitatory MEP response to stimulation. Therefore, the cortical changes that follow iTBS may temporarily affect motor planning and execution, but not the capacity for motor learning through long-term neuroplasticity and consolidation processes.

Two Blocks of iTBS does not Enhance Achieved Motor Learning

Findings from experiment two present that administering a second block of iTBS to M1 or S1 did not enhance motor learning beyond that of control stimulation in a force-field adaptation task (Fig. 4C). Small differences between one and two blocks of iTBS were evident in force-based measures of learning where channel trial analyses highlighted that iTBSx2 participants performed with more lateral force at the end of learning (Table 1.0 & 2.0). However, given that such differences do not appear between iTBSx2's M1, S1 and Control (at the medial occipital lobe) conditions (Fig. 4C), it can be inferred that two rounds of iTBS had no effect on learned force compensation. Instead, it is possible that the primary effects of iTBS are the impaired behaviour observed in iTBSx1 S1 participants (Fig. 2C), along with minimally hindered maximum performance in experiment one's M1 and vertex Control conditions.

These differences observed between one and two blocks of iTBS may coincide with evidence showing that the effects of iTBS on cortical activity are particularly time sensitive. In a study following the changes of MEPs in response to differently spaced iTBS protocols, two blocks of iTBS separated by 15 minutes facilitated MEP amplitudes up to one hour in various participants (Tse et al., 2018). When spaced by five minutes, MEPs were significantly suppressed, and with one block of iTBS, MEPs had no change. In light of this work, participants in experiment two received two blocks of iTBS that were each followed by a 15-minute post-stimulation period to examine the effects of a double-block iTBS procedure on motor performance. Nonetheless, differences in learning, retention and relearning were not observed. It is possible that changes in MEPs induced by iTBS, as seen in the double-stimulation protocol by Tse et al (2018), weakly correlate with mechanisms of motor learning (Agostino et al., 2008;

Vallence et al., 2013; Lopez-Alonso et al., 2018). Accordingly, while two blocks of iTBS increased the MEP amplitude of three distinct participants in experiment three of this work (Fig. 5B), a different stimulation protocol – one using repeated stimulation blocks over multiple sessions (Platz et al., 2018; Hanlon et al., 2023) or alternative between-block intervals—may be required to induce lasting behavioural changes on motor performance, if these are indeed possible.

Lastly, the use of a second iTBS block adds complexity to the infinitesimal neural operations that follow brain stimulation. Gamboa et al (2010) describe that the second of the two iTBS blocks can reverse changes induced by the first through mechanisms of homeostatic plasticity. This "reversal" of activity may lead to a complete negative effect of two rounds of iTBS on cortical excitability (Chen et al., 2022) or a return to baseline where pre and post stimulation measures do not differ (Bakulin et al., 2022). In experiments three and four, iTBSx2 to M1 (Fig. 5B) and S1 (Fig. 5E) produced varied changes in MEPs, as some participants demonstrated suppressed cortical activity, some demonstrated no change and others showed distinct iTBS facilitation (Fig. 5C & 5F). This variability more corresponds with the literature classifying participants as either responders or non-responders to iTBS (Hamada et al., 2013; López-Alonso et al., 2015; Nettekoven et al., 2015; Spitz et al., 2022). In the current data, however, it is unclear whether the same kind of classification is appropriate, as a second block of iTBS may also endure concerns for test-retest reliability and intraindividual variability (Tse et al., 2018, Bakulin et al., 2022).

iTBS Neural Facilitation Response is Dependent on ROI

The M1 and S1 cortices, among other cortical and subcortical motor areas, assume different roles in motor adaptation learning as each ROI differs in its cortical makeup and functional contribution to the learning process. Accordingly, it is possible that the resulting cortical activity elicited from a specific iTBS protocol may be dependent on the stimulated brain region of interest. Current literature supports the notion that cerebellar iTBS can enhance the learning and consolidation of motor adaptation tasks (Bonnì et al., 2020; Koch et al., 2020; Liao et al., 2024). Yet, between-study conclusions from measures of motor learning and cortical excitability following M1 or S1 stimulation remain varied (López-Alonso et al., 2015; Jones et al., 2016; Liao et al., 2023). In the current work, S1 suppression (Fig. 2B & Fig. 7C) and occurrences of M1 excitation (Fig. 3B & 6B) after one and two blocks of iTBS are recurring observations throughout the described experiments. As such, it is necessary to delineate how patterns of inhibition and excitation correlate with achieved motor learning in these cortical areas for a more complete understanding of neuroplasticity.

As previously described, research indicates that M1 primarily reflects activity specific to the muscle activation and use-dependent demands of a task during motor performance, rather than activity related to the preservation of acquired skills (Muellbacher et al., 2001; Romei et al., 2009; Riek et al., 2012; Hamel et al., 2017). While one block of iTBS did not produce differences in M1 learning in experiment one, the evidence for the role of M1 in early motor learning pairs well with the current data showing that M1-iTBSx2 participants showed brief improvements in day one adaptation with no differences incurred by asymptote near the end of the training block (Fig. 4B). In motor learning experiments using the Purdue pegboard task, a

comparable M1 response trajectory was observed (Filipovic et al., 2013; Jelić et al., 2015). Here, motor performance relative to placebo stimulation was marginally greater immediately after one block of iTBS. Yet, thirty minutes later, participants' performance declined significantly, falling below that of control. This suggests that the facilitatory effect of iTBS on M1 may be limited to the early stages of motor learning, particularly influenced by the inherent time course of M1 processes.

When considering S1, it has been well-documented that S1 plays a critical role in the error correction and consolidation processes of motor skill learning (Vahdat et al., 2014; Cuppone et al., 2018; Kumar et al., 2019), and NIBS tools are instrumental to investigating the cortical changes associated with these sensorimotor mechanisms. In a review by Sasaki et al (2022), facilitatory NIBS techniques were found to enhance somatosensory task performance in 41% of studies and increased SEPs in 22%. Findings from experiments one and four in this thesis, respectively, would fall in the categories of the remaining 59% and 78% of datasets in Sasaki et al's review: S1-iTBSx1 participants showed impaired motor performance during day one learning (Fig. 2C), and SEPs were found to significantly decrease after two blocks of iTBS to S1 (Fig. 7C). This suggests that the iTBS protocols used in the current work were capable of eliciting inhibitory changes on S1 activity.

It is understood that the S1 cortex uses both excitatory and inhibitory circuits to propagate cortical changes in learning and memory (Lee et al., 2013). However, there has been no research to date which examines the specific ways in which varied blocks of iTBS affect the underlying mechanisms of this region. In light of the findings on S1 performance and cortical excitability in this thesis, it is conceivable that iTBS may influence the firing of inhibitory

neuromodulator interneurons, such as somatostatin, that play a crucial role in the regulation of theta-gamma coupling and neuroplasticity in S1 (Kuki et al., 2015; Antonoudiou et al., 2020). Poreisz et al (2008) propose from analyses of pain stimulation laser-evoked potentials (LEPs) that theta-burst techniques in general induce an inhibitory effect on S1 activity. Further research is required to examine the specific factors involved in determining the direction of iTBS-induced changes in S1.

iTBS Induces Response Variability

The inter and intraindividual response variability observed following one block of iTBS has been a growing topic of concern (Hinder et al., 2014; Nettekoven et al., 2015; Schilberg et al., 2017; Corp et al., 2020; Katagiri et al., 2020; Leodori et al., 2021). Despite administering two blocks of iTBS before participants learned a task or engaged in an ERP study, findings from the experiments conducted in this thesis show that between-participant response variability did not improve with increased exposure to iTBS. In measures of perpendicular deviation at maximum velocity, participants in experiments one (Fig. 3C) and two (Fig. 5C) performed variably throughout day one learning and day two relearning, making differences between conditions difficult to distinguish. Moreover, it was particularly found that iTBSx2 significantly increased ($p < 0.001$) the post-stimulation variability of MEPs following both M1 and S1 stimulation (Fig. 6B & 6E).

Research shows that two blocks of continuous theta burst stimulation (cTBS), the counterpart rTMS technique of iTBS that induces cortical suppression, more consistently interferes with neuronal activity across findings from experiments on motor learning and

cortical excitability (Goldsworthy et al., 2012; Kumar et al., 2019; Darainy et al., 2023; Ebrahimi & Ostry, 2024). This observation may extend from the nature of suppressive stimulation, where the efficacy of synaptic transmission is typically reduced (Cirillo et al., 2017). During facilitation, however, both an increase and decrease in synaptic transmission are plausible through various increases in excitatory or inhibitory post-synaptic potentials (Jackman & Regehr, 2017), thus making behavioural post-stimulation effects susceptible to the specific conditions and timing of neural activity.

Furthermore, stimulation effects may be dependent on individual pre-dispositions for resulting directional changes in cortical activity. Cheeran et al (2008) propose that participant responses to NIBS techniques may differ based on the variation of the brain-derived neurotrophic factor (BDNF) gene they possess, as each genetic allele corresponds to differences in the series of operations involved in synaptic plasticity. Other research provides that beyond potential responder-non-responder classifications, metaplasticity, the pre-condition of cortical activity that affects the direction of subsequent neural changes, is crucial to determining the course of plasticity after brain stimulation (Müller-Dahlhaus & Ziemann, 2014). Thus, pre-stimulation measures of cortical connectivity may be useful for determining the effects of iTBS on cortical activity. One solution for standardizing the effects of iTBS provides that the priming of cortical regions of interest with suppressive NIBS techniques may enhance the results of iTBS by reducing the variability of pre-stimulation metaplasticity (Hassanzahraee et al., 2017).

Limitations

The primary finding of this thesis lies in the conclusion that the addition of a second block of stimulation spaced by 15 minutes did not improve the efficacy of iTBS. The data reflects that while transient increases in neural facilitation may be observed during motor learning, the definitive effects of iTBS are dependent on the timing of the stimulation pattern, the targeted brain region of interest and interindividual biases for the direction of cortical change. Of note, however, the findings in this thesis are not without limitations.

Firstly, in the behavioural task, day one learning introduced force-field loads gradually to engage implicit processes of motor learning, while day two's abrupt force-field loads favoured explicit mechanisms of motor performance. Here, the perturbation was more noticeable than participants had previously experienced on day one, and the potential use of explicit motor strategies on day two may have partially occluded the retrieval of implicitly learned motor transformations acquired during skill learning. However, abrupt loads, instead of gradual loads, were used on day two to ensure that participants' retention wouldn't be masked by gradual increases in performance that would occur alongside incremental changes in load. Secondly, the control stimulation point differed between upper-limb motor learning experiments with experiment one's control conditions receiving stimulation to the vertex of skull and experiment two's control conditions receiving stimulation over the medial occipital lobe. The difference in control stimulation sites makes between-experiment (i.e. iTBSx1 vs. iTBSx2) comparisons challenging. This necessitates careful consideration in the interpretation of results, as the baseline comparison for M1 and S1 stimulation effects may endure non-neutral stimulation confounds. Finally, given the breadth of literature on the effects of a single block of iTBS on

MEPs and SEP, this thesis does not include a single-block ERP experiment, thereby restricting analyses of the two rounds of iTBS stimulation employed in experiments three and four to comparisons with previous single-block iTBS conclusions.

6 | Conclusion

The study of intermittent theta burst stimulation (iTBS) encompasses a multifaceted exploration into its effects on neural facilitation, synaptic plasticity, and learning processes across diverse contexts and experimental paradigms. Developed to enhance cortical excitability and facilitate neuroplasticity through non-invasive stimulation to cortical brain regions of interest, the technique offers valuable insights to the study of neuromodulation, increasing our understanding of mechanisms of brain function and human behaviour.

A standard application of iTBS involves administering one block of stimulation to a ROI. Using this protocol, research has shown that iTBS can increase cortical activity under various conditions, such as in individuals with specific genetic predispositions that determine the course of neuroplasticity or in individuals with varied states of pre-stimulation cortical metaplasticity. Differences in post-stimulation intervals have also been found to have an effect on the direction of iTBS-induced activity, as findings in the literature demonstrate increased, decreased, and unchanged measures of cortical excitability after differing post-stimulation periods. Accordingly, the observed differences in conclusions across studies challenge the efficacy of iTBS, underscoring the need for a more robust facilitatory transcranial magnetic stimulation (TMS) methodology.

Recent findings suggest that two blocks of iTBS, separated by a 15-minute post-stimulation delay, enhanced MEPs for up to 60 minutes (Tse et al., 2018). Additionally, advancements in the use of continuous theta burst stimulation (cTBS) advocating for the use of two rounds of brain stimulation provided prolonged and more reliable stimulation effects than

the use of one cTBS block (Goldsworthy et al., 2012a). In light of these works, this thesis proposed that the application of two blocks of iTBS may more effectively promote cortical excitability and neuroplasticity than a single round of stimulation. Two studies, each comprising two experiments, were conducted to assess this hypothesis, and overall, it was concluded that increased exposure to iTBS with the use of a second block of stimulation does not increase the efficacy of iTBS mechanisms.

Study one involved the investigation of iTBS on a two-day upper-limb motor learning task, and participants implicitly learned to adapt to a load perturbation. Dependent variables analyzed from movement trials occurring over day one and day two conveyed measures of exerted lateral force, an adaptation coefficient demonstrating the relationship between actual and expected force exertion, and perpendicular deviation at maximum velocity. Specifically, in experiment one, participants received one block of iTBS to either the primary motor cortex (M1), primary somatosensory cortex (S1), or the vertex of the skull (Control) before day one training, and measures of task retention and relearning were obtained 24 hours later. One block of iTBS to S1 resulted in significantly impaired force compensation, that is, adaptation to the load, on day one in comparison to the M1 and Control conditions – which did not differ – and no significant differences between retention or relearning were observed on day two.

Experiment two employed a behavioural task identical to that of experiment one. However, here, two blocks of iTBS were applied to M1, S1, and the medial occipital lobe (Control). No differences in learning, retention, or relearning were produced following a second block of stimulation. Yet, when each measure of learning and relearning were compared between experiments one and two, it was particularly found that one round of iTBS significantly

impaired the amount of lateral force exerted by participants in all conditions during day one learning, demonstrating that iTBS is capable of producing inhibitory effects on implicit skill acquisition. The findings from both motor learning experiments supported existing literature showing that observed effects of iTBS may be short-lived, thereby inducing minimal transient effects on cortical excitability. In addition to describing how iTBS may differently affect cortical ROIs, continued research may seek to explore how mechanisms of long-term plasticity can better correspond with those of iTBS.

Furthermore, in experiments three and four, motor (MEP) and somatosensory evoked potentials (SEPs) were assessed after two blocks of iTBS for a continued analysis of the effects of double iTBS on cortical excitability. In the MEP experiment, participants received brain stimulation to either M1 or S1. Few M1 stimulation participants responded to the iTBS procedure with significantly increased MEPs. Largely, significant increases in between-subject M1-MEP and S1-MEP variability following iTBS stimulation illustrated that the capacity for iTBS to induce both increases and decreases in cortical excitability may contribute to the complex and dynamic nature of its impact on interindividual cortical circuits. Lastly, in an analysis of SEPs after double-iTBS to S1, a significant inhibitory effect was observed. Further examinations may turn to a multi-methodological approach for iTBS study, including the use of neuroimaging in multiple ROIs and analyses of genetic markers to better tailor the effects of iTBS to individual needs.

Altogether, this thesis provides a thorough analysis of the effects of two rounds of iTBS on cortical excitability and motor learning, thereby laying a foundation for the refinement of the iTBS protocol and optimization of its application to diverse interventions.

7 | References

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