

Investigating cerebellar modulation of premotor inhibitory control during motor adaptation

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Motor adaptation is marked by neurophysiological changes in the motor cortex; however, other regions of the motor network such as the cerebellum and premotor cortex also contribute to this process. Enhancing cerebellar activity has been shown to increase the rate of motor adaptation (Galea et al., 2011; Koch et al., 2020), though it is unclear which neurophysiological mechanisms contributing to adaptation are influenced by the cerebellum. Pre-movement beta event-related desynchronization (β -ERD), which reflects a release of synchronized inhibitory control in the premotor cortex during movement planning, is one mechanism which may be modulated by the cerebellum through cerebellar-premotor cortical connections (Tzvi et al., 2020). I hypothesized that enhancing cerebellar activity with intermittent theta burst stimulation (iTBS) would improve participants' adaptation rate, increase β -ERD during motor adaptation, and that there would be a relationship between the task performance and the β -ERD. Thirty-four participants were assigned to receive either active (A-iTBS) or sham cerebellar iTBS (S-iTBS). In the first study session participants completed a brief practice session on a visuomotor rotation task, with no rotation, to familiarize them with the task timing and joystick control of the cursor. Following practice, participants received active or sham iTBS. After ten minutes they completed training on the task, with a 45° rotation to the cursor movement. Participants returned to the lab 24 hours later for session 2, to perform the task again to get a measure for how much of the learned rotation had been retained. Angular error at peak velocity was the primary behavioural measure, which was the angular difference between the ideal trajectory of the cursor and the actual trajectory of the cursor at peak velocity in the movement. The primary neurophysiological measure was β -ERD, the change in power in the β band from rest to movement planning and was measured using electroencephalography (EEG).

Results show a greater adaptation rate following active cerebellar iTBS, and an increase in β -ERD compared to sham cerebellar iTBS. The divergence in β -ERD change between groups is indicative of a cerebellar modulation of the motor cortical inhibitory control network. Interestingly, the enhanced release of inhibitory activity was not just present during the initial adaptation phase of training as predicted, but overall persisted across training. This finding may suggest that the effects of iTBS and the cerebellar influence on the premotor cortex were not specific to the adaptation period but persist through the entire training session. There was no difference between groups in the amount of the skill which was acquired during training or the amount of the skill which was retained between session 1 and session 2. Results from this study further our understanding of the connections between the cerebellum and the motor cortex as they relate to acquiring motor skills, as well as inform future skill training and rehabilitation protocols.

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List of Abbreviations

AE	Angular error at peak velocity
A-iTBS	Active intermittent theta burst stimulation
AMPA	Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMT	Active motor threshold
BG	Basal ganglia
β -ERD	Beta event related desynchronization
Ca^{2+}	Calcium
cTBS	Continuous theta burst stimulation
CB	Cerebellum
CB-iTBS	Cerebellar intermittent theta burst stimulation
dIPFC	Dorsolateral prefrontal cortex
EEG	Electroencephalography
EMG	Electromyography
ERD	Event-related desynchronization
ERSP	Event-related spectral perturbation
ERP	Event-related potential
fMRI	Functional magnetic resonance imaging
FDI	First dorsal interosseous
GABA	Gamma-aminobutyric acid
ICA	Independent component analysis
iTBS	Intermittent theta burst stimulation
LTD	Long term depression
LTP	Long term potentiation
M1	Primary motor cortex
MRP	Movement-related cortical potential
Na^{2+}	Sodium
NMDA	N-methyl-D-aspartate
PMC	Premotor cortex
PMd	Dorsal premotor cortex
PMv	Ventral premotor cortex
PPC	Posterior parietal cortex
rTMS	Repetitive transcranial magnetic stimulation
RT	Response time
S1	Primary somatosensory cortex
SPE	Sensory prediction error
SMA	Supplementary motor area
S-iTBS	Sham intermittent theta burst stimulation
TMS	Transcranial magnetic stimulation
TOD	Time of day

1. Introduction

Every day we perform motor tasks by activating a complex and integrated system of motor control, requiring frequent communication between numerous cortical and subcortical regions in order to produce a desired movement. In many daily and leisure activities an action will be repeatedly performed, such as using a knife to chop carrots or hitting a tennis ball with a racquet. As we repeatedly perform actions, the involved brain regions undergo adaptive changes to make movements accurate and efficient.

Adaptation relies on detecting and correcting for movement errors caused by disruptions within our environment to regain or improve the expected level of performance. These disruptions could be internal, a result of injury or physical changes in the brain or body, or external changes to the environment or objects within the environment. Adaptation is measured by task performance, wherein a decrease in error on a motor task is indicative of increased adaptation to a perturbation. Such adaptation is underpinned by activity changes in the sensorimotor regions of the brain. Measuring physiological changes in sensorimotor regions may provide an index of early physiological changes that underlie subsequent behavioural changes and motor adaptation. However, there are knowledge gaps regarding the nature of the relationship between physiological and behavioural changes and how regions external to the sensorimotor cortex can contribute to these physiological adaptive processes. Specifically, in understanding how physiological changes in activity in the cerebellum which detects and communicates the error resulting from behaviour, and the dorsal premotor cortex which plans movement, are related to the behavioural improvements observed during motor adaptation. This study aimed to investigate how the cerebellum influences activity in the dorsal premotor area,

both regions which contribute to movement planning and coordination, promote motor adaptation.

Understanding the process of adaptation in the brain can contribute to developing training methods to enhance learning in sport or skilled occupational tasks. This understanding is also important for researchers and clinicians to identify causes of motor impairment to performing and adapting motor skills and to develop rehabilitation techniques and tools for persons with such impairments.

2. Literature Review

2.1 Motor Planning and Adaptation

2.1.1 Defining Adaptation and Learning

Motor learning refers to a process where a novel motor skill or adaptation is acquired through practice and reaches a point where the skill can be successfully, automatically performed and can be recalled at a later time. The term motor adaptation refers to a dominant process in the earliest stage of motor learning, in which sensory feedback is used to determine movement error and inform adjustments that should be made to subsequent movements. This error-driven process occurs gradually on a trial-to-trial basis, throughout a period of repetitive practice lasting minutes to several hours (Martin et al., 1996). During adaptation there is significant variability in error, rapid performance improvements and an overall increase of excitability within cortical regions contributing to the movement planning and execution (Wise et al., 1998). These movements are voluntary and driven by external environmental cues, and the sensory feedback cues are the primary driver of the neurophysiological activity and movement-related changes which result in improved performance.

Stages of learning beyond the adaptation stage, which will be referred to in this document as ‘later stages of learning’ occur once performance measures asymptote. Behaviourally, the changes observed during later stages of learning will be much less dramatic than changes which occur during the adaptation stage. The changes in later stages of learning aim to make performance more reliable and efficient in terms of time, energy expenditure, attentional allocation, and synaptic efficiency. This involves a shift from externally to internally driven movements where neural efficiency and internal motivation primarily activate different regions of the cortex which influence motor planning and execution (Karni et al., 1998). In later stages of

learning there is a greater weighting of contribution from neuroanatomical regions different from those primarily involved in adaptation (Della-Maggiore et al. 2004; Wise et al., 1998). These neuroanatomical regions and their roles in motor learning will be further discussed in section 2.2.

2.1.2 Fast and Slow Learning Processes

Adaptation and later stages of learning are terms which can be used to identify periods of time in which certain neurological processes and behavioural outcomes are observed, whereas the terms ‘fast learning’ and ‘slow learning’ categorize neural processes that are simultaneously occurring but contribute to different components of learning. The ability to discriminate adaptation from later stages of learning is determined in part by distinct neural mechanisms which contribute to these processes.

The fast-learning system is externally guided, dependent on error feedback, and is associated with general increases in excitability and functional connectivity between involved regions such as the cerebellum, posterior parietal cortex (PPC), primary somatosensory cortex (S1), and the premotor cortex (PMC). Fast learning processes are predominant during the adaptation phase of learning but continue to be active throughout the motor learning process. Fast learning involves error correction, decreased sensory gating, decreased inhibitory control, increased excitatory functioning and greater attention to task information.

The slow learning system is internally driven and more heavily relies on activity in the basal ganglia, aims to improve efficiency of neural resources and reflects excitability changes in the primary motor cortex (M1) (Coltman et al., 2019). Slow learning processes account for about 80% of the later stages of learning, but also contributes to about 10% of adaptation (Joiner & Smith, 2008). Slow learning processes produce slow reduction in error compared to fast learning, but develop greater retention (Coltman et al., 2019; Joiner & Smith, 2008).

2.1.3 Theories of Adaptive Learning

The theoretical framework for planning and adapting movement assumes that movement plans are based on previous experience and require integration of multimodal sensory feedback in order to adapt. The previous movement experience is expressed in the forward model (also referred to as the internal inverse model), which is a representation of the expected outcome of the movement, based on the motor output commands and current sensory state (Miall & Wolpert, 1996). This forward model is used to generate a sensory prediction error (SPE) by comparing the actual sensory results of a movement to the predicted sensory result. During task adaptation, the SPE is used to update the forward model leading to better motor plans and improved movement accuracy (Morehead & de Xivry, 2021; Wolpert & Flanagan, 2001).

Motor adaptation is more than simply an error correction, and likely includes other cost-benefit weighing processes to determine optimal movement (Bastian, 2008; Izawa et al., 2008). This theoretical model is called the optimal control model, which considers both the movement goal as well as the metabolic cost of reaching the goal and seeks to minimize the energy expenditure to perform the task.

It is important to note this model explains implicit adaptation, which refers to the subconscious aspects of learning, and relies on slow learning processes. The alternative is explicit adaptation which refers to the adaptive processes that occur when there is a conscious effort to modify the movement plan in order to reach the movement goal and relies on the fast-learning process (McDougle et al., 2015). Adaptation to motor tasks often requires both the explicit and implicit adaptation processes, where there is an awareness of the need to adjust movement, but the error signalling and adjustments to the forward model happen implicitly.

2.1.4 Neurophysiological Mechanisms Behind Adaptation

The error correction and model updating process, aimed at producing the most effective and efficient motor command affect changes in synaptic activity and in the strength of synaptic connections. Synaptic connections involved in producing successful task performance will be repeatedly used and therefore will have increased synaptic activity. As synaptic activity increases at the glutamatergic synaptic connections, the primary excitatory synaptic connections in the motor cortex, the post-synaptic neurons will be strengthened through a process called long term potentiation (LTP). Increases in glutamatergic synaptic activity triggers the Ca^{2+} dependent increase in AMPA receptor presence in the membrane, which increases the excitability of the neuron, or the likelihood and rate of firing, which signifies the early-phase of LTP (Lüscher & Malenka, 2012). These early stages serve to increase the excitability of the neurons which are involved in the new motor skill being performed. The increased density of AMPA receptor presence in the membrane is temporary and will begin to reverse as the synaptic connections are no longer required. This may happen if the motor task requiring such activity has not been performed for a period of time, or as a result of synaptic efficiency, in which the group neurons required for the task become more selective. If the increase in synaptic activity continues, the neuron will undergo structural changes to increase the number of synaptic connections between cells, including increased NMDA receptors in the membrane and dendritic growth. These structural changes in the cell are the late stages of LTP and are reflective of learning.

2.1.5 Retention

Retention is a measure of the degree to which the adapted motor task is retained when tested after a period of no training. In visuomotor adaptation tasks, short term retention is sometimes measured by the rate of de-adaptation from the task: how long the newly adapted task

performance persists when the perturbation is removed. The longer it takes to “lose” the adapted movement, the greater the retention of the movement adaptation. Long-term retention, measured 24+ hours following a session of practice can be quantified by the amount of performance error and error rates at the beginning of a subsequent test session, as compared to measures from the end of the previous test session.

The retention of a newly learned task is highly dependent on the slow learning process (Joiner & Smith, 2008) and the amount of time spent practicing the skill after an asymptote in performance error where later stages of learning are predominant. Retention is also associated with physiological changes during training, including excitability changes in the primary motor cortex where increased excitability leads to greater retention (Galea et al., 2011), as a result of LTP in the motor cortex.

2.2 Neuroanatomy and Regional Contributions to Motor Planning and Adaptation

Motor adaptation is contingent on the contributions from the motor, somatosensory, and visual cortices, and the cerebellum which are part of a large network that primarily functions to control movement.

2.2.1 Primary Motor Cortex

The motor cortex is comprised of 3 main divisions, the M1, PMC, and the supplementary motor area (SMA), all of which contribute to motor planning and movement execution. M1 is located in the precentral gyrus and is somatotopically organized. M1 receives inputs from the PMC, SMA, S1, and from other cortical and subcortical regions via the thalamus. These inputs arrive in layers II, III and IV of the primary motor cortex and synapse onto facilitatory and inhibitory intraneuronal populations within M1, influence the neuronal excitability/synaptic activity in M1 and therefore influence the generation of the motor command. The main outputs

from M1 are the pyramidal neurons in layer V which join, and primarily form the corticospinal (CS) tract. The CS tract carries voluntary motor commands to the spinal cord, where they continue to be influenced by other afferent and efferent signals before being transynaptically relayed to the effector muscles.

The superficial layers of M1 contain both facilitatory and inhibitory populations of interneurons. These interneurons synapse onto the dendrites of CS neurons. Although the exact structure and function of the synaptic connections between the surrounding cortical regions and the M1 interneurons is not completely understood, it is understood that converging inputs largely from non-primary motor regions such as the PMC and SMA, as well as the BG and other intracortical neurons which relay input from distant cortical regions selectively synapse onto these populations of neurons to influence the motor command. Ultimately, it is the proportion of inhibitory to facilitatory synaptic activity on a combination of CS neurons which determines the motor output command.

M1 is actively involved in generating and executing motor commands, however during the adaptation and learning process, structural or excitability changes in M1 do not occur until later in the adaptation and learning process, only following the early adaptive changes in S1 (Ohashi et al., 2019) and other motor preparatory areas. The adaptive changes which occur in M1 are part of the slow learning process and contribute to the consolidation and retention of the learned movement (Galea et al., 2011; Karni et al., 1998; Muellbacher et al., 2002; Obhi, 2002).

2.2.2 Premotor and Supplementary Motor Cortices

The two major non-primary motor regions, the SMA and PMC contribute to movement planning and execution each in distinct ways. The SMA, located rostral to M1 along the midline, is commonly known for its role in sequencing complex movements (Lee & Quessy, 2003;

Mushiake et al., 1990) and generating self-paced movements (Jahanshahi et al., 1995; Smith & Staines, 2012). There are few neurons in the SMA which contribute to the CS tract, however most SMA influence on the motor command occurs by influencing synaptic activity in M1 (Fried et al., 1991).

The PMC can be further subdivided into the dorsal PMC (PMd) and ventral PMC (PMv) which are located rostral to M1. Both regions are involved in planning and coordinating motor commands. The PMv is involved in plans for object manipulation by influencing the grasping components of a motor plan (Davare et al., 2015), and is more heavily involved in precision movements of the hands, feet, and mouth (Binkofski & Buccino, 2006).

The PMd is largely implicated in adaptation owing to its role in planning movement parameters, such as trajectory, speed, distance, maneuvers to avoid obstacles, as well as the grasping actions for movements of varying complexity (Cisek & Kalaska, 2005; Davare et al., 2015; Pilacinski & Lindner, 2019; Vesia et al., 2018). Several movement plans can be encoded simultaneously in the PMd. In addition to movement planning, the PMd is also implicated in selecting the appropriate movement plan to be executed and in generating that command (Ciesk & Kalaska 2005).

The PMd primarily influences M1 through excitatory interneurons which synapse onto separate facilitatory and inhibitory populations of interneurons within M1, which ultimately influence the pyramidal neurons of the corticospinal tract (Reis et al., 2008). At rest the PMd has a net inhibitory influence over the motor cortex (Vesia et al., 2018; Wolfe et al., 2021). During visuomotor adaptation, the PMd exhibits cortical excitability changes in the neuronal populations influencing both facilitatory and inhibitory motor cortical neurons (Wise et al., 1998). The timing

patterns of activity at the synapses of excitatory and inhibitory interneuronal populations in M1 is, in effect, the way in which the PMd influences the motor command (Kosche et al., 2015). There is some overlap between the neurons of the PMd and the M1, both in anatomical location and function, and consistent with the SMA and S1, the PMd has a small portion of direct contributions to the CS tract. However, most outputs from the PMd synapse onto the interneurons in layer II & III of M1 to influence the motor command.

In addition to the significant connectivity with M1, the PMd has functional connections to the parietal cortex (Wise et al., 1997), cerebellum (Tzvi et al., 2104; 2020), basal ganglia (Marsden, 1987), and other frontal regions (Schulz et al., 2019), which relay a variety of information to the PMd which is used to create and select movement plans. Evidence from human functional imaging studies suggests the PMd is topographically organized into five functional clusters or subregions (Genon et al., 2017), which provides some order to its multitude of functional connections and complex contribution to motor control.

2.2.3 Cerebellum

The cerebellum is a major contributor to the process of motor adaptation, owing to its role in motor coordination, movement error detection and correction. Though a small structure, the cerebellum is connected to cortical and subcortical regions in multiple ways, which enable the cerebellum to influence motivation and coordination of movement in various types and stages of learning (Bernard & Seidler 2013; Bostan et al., 2010; Tzvi et al., 2014; 2020).

The cerebellum is divided into three functional regions, the cerebrocerebellum, spinocerebellum, and vestibulocerebellum. The cerebrocerebellum occupies the lateral portions of the anterior and posterior lobes of the cerebellum and the spinocerebellum the medial region of the anterior and posterior lobes of the cerebellum. It is these two functional regions, largely

the cerebrocerebellum which is more often referred to in scientific literature as the lateral posterior region of the cerebellum. The lateral posterior region of the cerebellum is involved in voluntary control of movement and a major contributor to motor adaptation. Incoming afferent inputs carrying sensory information from the body and inputs from cortical and subcortical regions enter the cerebellum, sensory afferent inputs to the spinocerebellum and cortical inputs to the cerebrocerebellum. These inputs are further integrated to carry out functions relating to error correction and motor control.

Inputs to the cerebellum arrive via the climbing fibres and mossy fibres. Climbing fibres have a considerable influence on the activity in a small number of Purkinje neurons through numerous synaptic connections. The mossy fibres have a less significant impact on the activity in a large number of Purkinje neurons through few synapses on each neuron, via the parallel fibres of the granule cells. Concerning motor functions and error correction, the Purkinje neurons are the primary output neuron and synapse onto neurons in the dentate nucleus, one of the deep cerebellar nuclei. These outputs from the dentate nucleus form the cerebellar-thalamo-cortical network, projecting to the contralateral ventrolateral thalamus which relays to the motor cortex (Kelly & Strick, 2000; Kandel et al., 2000, p.964-965), BG (Hoover & Strick, 1999; Bostan et al., 2010; Hoshi et al., 2005), and modulates activity in other non-motor frontal regions, likely via the subthalamic nucleus (STN) (Bostan et al., 2010; Picazio et al., 2016).

Similar to M1, the major output signals from the dentate nucleus are a result of weighting the facilitatory inputs from the mossy and climbing fibres and the inhibitory inputs from the Purkinje fibres. Purkinje fibres are GABAergic inhibitory neurons, however the post synaptic terminals at the synapse with the climbing fibres have NMDA receptors which receive excitatory glutamatergic synaptic inputs (Piochon et al., 2010). The climbing fibres, which originate in the

inferior olivary nucleus (ION), play a key role in modulating the excitability of the Purkinje fibre response to other cerebellar cortical neurons, and therefore the output response from the Purkinje cells to the dentate nucleus (Kandel et al., 2000, p. 975-976). This dominant effect is a result of the highly specific and multitudinous synaptic connections between a climbing fibre and Purkinje neuron. Inducing LTD in the postsynaptic Purkinje neurons will increase dentate nuclei output therefore increasing the cerebellar influence over the motor cortical regions.

The cerebellum influences the motor cortex by 'direct' connections to the motor cortex via the cerebellar-thalamo-cortical loop as well as through connections to the striatum, referred to as the cerebellar-striato-cortical loop. The cerebellum-PMd (CB-PMd) connections are distinct from the cerebellar-M1 connections, and likely have functionally distinct purposes to promote adaptation. CB-PMd connections are implicated in error correction, force production and movement rate control (Tanaka et al., 2009). Furthermore, evidence from imaging studies suggests there is bidirectional modulation between the motor cortex and cerebellum (Tzvi et al., 2014; 2020). The cerebellar influence over the motor cortex is inhibitory and during movement planning, the cerebellar inhibitory control over the PMd (Tzvi et al., 2020) and M1 (Spampinato & Celnik 2017) is released. During adaptation, this pattern of inhibitory release from the CB-PMd connections is greatest at the beginning of adaptation, when error signalling is presumably greatest and reverts as the adapted task becomes learned. Conversely, the PMd-CB connections are excitatory and enhanced during adaptation. In connection, greater attenuation of the predominant CB-PMd inhibition is correlated with faster adaptation to a visuomotor mapping task (Tzvi et al., 2020).

The cerebellum is involved in both implicit and explicit strategies of visuomotor adaptation (Butcher et al., 2017). Much of the activity in the posterior cerebellum during

adaptation is related to error detection and processing, specifically using sensory-prediction errors to inform movement during adaptation (Spampinato & Celnik 2017; Tseng et al., 2007) and updating sensory perceptual models (Statton et al., 2018). As such, the cerebellum is a critical contributor to fast learning and damage to the cerebellum will greatly, if not completely, impair this process (Smith et al., 2006). Numerous studies which targeted the posterior cerebellum show that in later stages of learning and retention, the role of the cerebellum is not significant beyond its archetypal role in movement coordination and error correction (Galea et al 2011; Spampinato & Celnik 2017; Tseng et al., 2007; Tzvi et al., 2020).

In contrast to these findings the results from a meta-analysis of cerebellar activity during a variety of motor learning studies suggest the cerebellum, contributes to both the fast learning, adaptation mechanisms as well as slow, late stage of learning mechanisms (Bernard & Seidler, 2013). The lack of consensus is in part due to the tendency for researchers to refer to ‘the cerebellum’ as one homogenous structure, without explicitly identifying the targeted cerebellar region(s) in the discussion. Meta-analyses using data from various imaging studies (Bernard & Seidler, 2013; Lohse et al., 2014) have more clearly indicated the distinction between regions within the cerebellum and how they contribute to different aspects or stages of adaptation and learning.

2.2.4 Occipital and Parietal Cortex

In visuomotor adaptation tasks, the target position and other relevant visual cues from the environment are processed in the occipital cortex, the most posterior region of the cerebral cortex. The occipital cortex can be divided into the primary visual cortex (V1) which is the furthest posterior and processes the most raw, simple visual information coming from the optic tract via the lateral geniculate nucleus and optic radiation. As visual information is processed it

flows anteriorly through V2, V3, becoming increasingly integrated. Visual information regarding movement then flows dorsal and rostrally through the dorsal stream pathway, into the posterior parietal cortex (PPC) where the visual information is further integrated with other relevant sensory information regarding the impending movement.

The parietal cortex can be divided into two functionally distinct regions, the somatosensory cortex (S1) and the PPC. S1 is located directly caudal to the central sulcus and M1. The PPC is between S1 and the occipital visual cortex. S1 receives and processes predominantly tactile and proprioceptive information, which allows the brain to determine the current position of the body and features of the object(s) that are being manipulated. S1 has direct connections to the motor cortex through interneurons in the superficial layers of the cortex and thalamic relay neurons, both of which can indirectly influence the generation of the motor command, as well as a small number of neurons which join to the corticospinal tract to directly influence the motor output command (Toyoshima & Sakai, 1982).

In visuomotor tasks the PPC integrates visual information from the visual cortex and other sensory modalities to inform the movement plan, which is encoded simply as the target coordinates for a straight trajectory movement (Pilacinski & Lindner, 2019). This simple trajectory plan may be updated in the PMC to fit a more complex movement, as previously discussed (section 2.2.2 PMd). The PPC is also implicated in the adaptive changes which occur during motor learning (Della-Maggiore et al., 2004), however the contribution from the PPC is significantly reduced in motor task adaptation lacking adequate visual feedback (Chung et al., 2017). The PPC influences motor planning through corticocortical connections to the motor cortex (Babb et al., 1984) and some evidence suggests that the PPC also has a small number of

direct contributions to the CS tract, which originate from area 5 of the PPC, immediately caudal to S1 (Rathelot et al., 2017).

2.2.5 Basal Ganglia

The BG are a group of subcortical regions and nuclei which are involved in motor functions and integrating emotion and motivation with motor control (Báez-Mendoza & Schultz, 2013). Notable regions of the BG pertaining to motor learning are the striatum, which receives input from cortical regions and CB (Lanciego et al., 2012; Tzvi et al., 2020) and the substantia nigra and globus pallidus, which output to the thalamus and relay to the frontal lobe, notably the motor cortex for contributions to motor control (Lanciego et al., 2012). BG contributions are prominent in the later stages of learning, relating to internally guided movement planning and motivation for movement (Báez-Mendoza & Schultz, 2013) and by contributing to the precision details of a learned motor skill (Dhawale et al., 2021).

2.3 Research Methods to Induce and Modulate Motor Adaptation

2.3.1 Visuomotor Adaptation

Visuomotor adaptation has been studied using a variety of tasks, the most common of which are the visuomotor rotation task, prism adaptation, and forcefield adaptation. Visuomotor adaptation tasks involve an altered relationship between the movement and the visual feedback, and both proprioceptive and visual feedback are essential for task adaptation (Shabbott & Sainburg, 2010). However, depending on the type of perturbation applied the sensory contribution will be weighted slightly different between the tasks. Forcefield adaptation tasks use a robotic arm which exerts a lateral force during the movement. This type of perturbation manipulates the proprioceptive sensory information and therefore places a slightly greater reliance on proprioceptive system feedback, although visual feedback is also essential for task

success. Both visuomotor rotation tasks and prism adaptation use altered visual feedback and therefore requires a greater dependence on the visual system feedback. Prism adaptation tasks involve a participant in a study to wear glasses which shift vision through a prism so what the individual is viewing is 30° different from reality. Prism adaptations are often used in reaching movement or throwing tasks; however, dependent measures are limited to end of movement error and these tasks are not ideal for pairing with EEG or for obtaining real-time neurophysiological measurements. Visuomotor rotation tasks require participants to move a central cursor toward a target on a screen, however instead of the perturbation being applied to the tool used to move the cursor, the visual feedback is rotated so the cursor follows a rotated trajectory: often 30°, 45°, or 60°, from the expected trajectory path. In both the visuomotor rotation and forcefield adaptation tasks participants' vision of their hand is obscured, which forces a greater dependence on the SPE and therefore the implicit learning processes (Tzvi et al, 2021). As such, visuomotor rotation and forcefield adaptation tasks can be used to probe activity in the connections between the cerebellum and motor cortical regions, which play a vital role in the implicit learning process (Butcher et al., 2017; Tzvi et al., 2020).

2.3.2 Theta Burst stimulation

Theta burst stimulation (TBS) uses transcranial magnetic stimulation (TMS) to repeatedly stimulate a region of the brain, which temporarily modulates cortical activity in the targeted region. In TBS, bursts of 3 pulses are delivered at 50 Hz, repeated at 5Hz. These bursts are delivered in either a continuous bursting pattern (cTBS) until 600 total stimulations have been delivered (about 40 seconds total), or in an intermittent bursting pattern (iTBS) where bursts are delivered in sets of 10 bursts with a 5Hz interval for 2 second trains, repeated every ten seconds, until 600 total stimulations have been delivered (about 3 minutes total).

In the human motor cortex, cTBS reduces corticospinal output, likely through a long-term depression (LTD)-like mechanism in the excitatory interneurons within the superficial layers of the motor cortex. On the other hand, iTBS increases excitability in the motor cortex likely through inducing an LTP-like effect within the excitatory interneurons. The two methods of TBS likely affect different microcircuits affecting the corticospinal output (Di Lazzaro et al., 2005; Di Lazzaro et al., 2008; Huang et al., 2007). A similar bidirectional modulatory effect has been observed following TBS to the cerebellum, where cTBS has an LTD like effect and iTBS has an LTP like effect in the cerebellar cortex (Koch et al., 2008). However, since the effect of TBS on the cerebellar excitability is not directly measurable, these conclusions are speculative, based on observations of how the cerebellum is known to influence motor cortical network excitability and how TBS to the cerebellum affects those influences.

One proposed explanation for the effect of iTBS on cerebellar cortical excitability is that it occurs by enhancing the excitability of the Purkinje neurons, thereby inducing a similar effect to that of the climbing fibres, which modulates the Purkinje response to other synaptic input and the output to the dentate nucleus (see section 2.2.3 Cerebellum). Given the previously observed enhancement of adaptation following iTBS (Koch et al., 2020) and the understanding that TBS induces plasticity like changes in NMDA receptors (Huang et al., 2007) which are present in the climbing fibre-Purkinje cell synapse (Piochon et al., 2010), this is a likely mechanism to explain the effect of iTBS in the cerebellum. Increasing the Purkinje inhibitory output to the dentate, increases the dentate inhibitory influence over the contralateral ventrolateral thalamus which decreases the excitatory influence over the inhibitory PMC interneurons, overall having a disinhibiting effect in the PMC (Casula et al., 2016).

It is also important to note that not all people have the expected response to TBS. Numerous characteristics may contribute to an individual's response to TMS, including age, sex, pharmacological influences, circadian rhythm, genetic factors influencing neurotrophins, attention (Ridding & Ziemann, 2010), network connectivity within the beta band frequency in frontocentral-M1 circuits (Hordacre et al., 2021) and resting state functional connectivity within PMC-M1 circuits (Nettekoven et al., 2015). There is no direct way to determine if and how an individual will respond to a TBS protocol, however TBS has been successfully used as an experimental tool to investigate the behavioural and neurophysiological effects of up- or downregulating brain activity in cerebral and cerebellar cortical regions.

2.4 Neurophysiological Measures of Motor Planning and Adaptation

2.4.1 Beta Oscillatory Activity and Event Related Desynchronization

Oscillatory activity in the beta (β) frequency band (13-30 Hz) is reflective of inhibitory activity; where power increases, oscillatory spiking, and spiking synchronization exhibits greater inhibitory control. β oscillatory activity is particularly prevalent in neural circuits involved in motor functioning and the maintenance of control in rest state (Engel & Fries, 2010; Pfurtscheller & Da Silva, 1999). β spiking patterns are a mechanism to control the network activity state in the sensorimotor cortex and to prevent unprompted changes in the rest state activity. As such, decreases in β activity allow for changes in network activity to occur (Engel & Fries, 2010). The beta spiking patterns also play a role in facilitating short (intraregional) and long (interregional) range communication, where period of greater spiking activity can facilitate the timed arrival of long-range information (Little et al., 2019). Beta activity is largely present and believed to be generated primarily in the sensorimotor cortex and the BG (Little et al., 2019; Chandrasekaran et al., 2019) but also can be measured in the frontal and parietal regions (Chung

et al., 2017; Özdenici et al., 2017). Regarding motor planning and adaptation, beta activity is linked to inhibitory control and model updating in response to error detection (Little et al., 2019; Tan et al., 2014) and may also be linked to response selectivity and hierarchical processing (Little et al., 2019).

Beta event related desynchronization (β -ERD) refers to the spiking patterns in response to a particular event, which alters the baseline or maintenance oscillatory activity in a frequency band. ERD as a measure of neurological activity has an advantage over event related potentials (ERPs) because they can be measured in power changes and do not have to be perfectly time and phase locked to get an accurate measure. In periods of synchronization the power increases and in periods of desynchronization, the power decreases. A synchronization of spiking may reflect a cohesion of neural activity or a controlled inhibitory pattern of spiking to allow for specific signals to be passed. Desynchronization reflects a disinhibition, where the inhibitory spiking is more sporadic or not synced, to allow for greater spread of synaptic activity and more local communication (Little et al., 2019).

Pre-movement β -ERD in the motor cortical regions is reflective of the activity during the model updating, movement planning and action selection (Little et al., 2019; Nakayashiki et al., 2014). Given the knowledge that the PMd is largely implicated in movement planning and action selection, through inhibitory circuit activity, it is postulated that the pre-movement β -ERD is reflective, at least in part, of the modulations in PMd inhibitory activity. Additionally, decreases in β -ERD are correlated with shorter reaction times (Pollok et al., 2014) and greater uncertainty of movement planning (Tzagarakis et al., 2010). The general release of inhibition may be a natural mechanism which enables planning and execution to accommodate the undetermined movement parameters, following error feedback signalling an insufficient or inefficient motor

plan. Alternatively, some have argued the pre-movement β -ERD is not related to the generation of the motor command, but instead is involved in the sensory processing and model updating for the purpose of motor planning, but not the motor planning process itself (Alayrangues et al., 2019).

Uncertainty in the feedforward model is an important component of motor adaptation, as it initiates neurophysiological processes to improve the internal model and therefore generation of the optimal motor plan. Uncertainty leads to a greater reliance on sensory feedback to update the internal model used to determine the feedforward model (Tan et al., 2016) and causes changes in inhibitory control (Torrecillos et al., 2015; Tzagarakis et al., 2010) and corticospinal excitability (Bestmann et al., 2008), which facilitates modulation of future movement plans. An association between uncertainty in the movement outcome and β -ERD has been observed during the pre-movement, planning phase of motor task performance (Tzagarakis et al., 2010).

2.4.2 Behavioural Measures

Behavioural improvements are an obvious marker of adaptation and can be measured in movement success, efficiency, and speed. The simplest of the behavioral measures is the completion accuracy, measuring whether the participant reached the target. In a practical sense this behavioral measure is quite relevant since in many day-to-day motor tasks it doesn't matter how a movement goal is reached, as long as it can be done. However, simple measures of outcome don't provide much insight into the neurophysiological processes which aim to optimize movement and neural efficiency, or the movement planning and decision-making process. To address this, in ballistic movements which do not allow time for online feedback, the angular error at peak velocity is used to measure the amount of error in the execution of the

movement plan (Koch et al., 2020). Reaction time (RT) is an indicator of the certainty of the internal feedforward model and the movement plan.

3. Rationale, Objectives and Hypotheses

3.1 Rationale

The PMd is primarily responsible for generating and communicating the movement plan to M1 during task performance and is heavily influenced by cerebellar inputs informing error and updates to movement plans (Ciesk & Kalaska, 2004; Tzvi et al., 2020). β -ERD measured in the sensorimotor cortex reflects these error and movement planning processes, and thus the activity in the PMd-M1 interactions. Specifically, changes in β -ERD have been linked to the confidence of the motor plan and error in performance over individual trials during task performance (Tan et al., 2014; Tzagarakis et al., 2010). It is unclear how activity in these β generating circuits systematically change over a period of motor training, and how those changes promote adaptation. Further, despite well-established functional connections between the PMd and cerebellum related to motor planning, it is still unknown if the cerebellum exerts influence through modulation of the activity in β generating circuits to enhance the motor learning process.

This study sought to understand how the premotor inhibitory activity relates to changes in performance during motor learning, as well as to understand how the cerebellum modulates premotor activity to enhance learning. This was investigated by measuring pre-movement β -ERD, which is reflective of the planning activity, in relation to the behavioural changes during learning.

3.2 Objectives and hypotheses

The objectives for this study were:

1. Confirm findings from previous studies that found CB-iTBS improves the rate of adaptation (Koch et al., 2020, Galea et al., 2011).

Hypothesis: The rate of adaptation will be greater in the active iTBS group (A-iTBS) than in the sham iTBS group (S-iTBS).

2. To understand how the changes in activity in the PMC inhibitory circuits relate to error reduction during adaptation to a motor task.

Hypothesis: The release of PMC inhibitory activity, as seen in the pre-movement β -ERD, will be greatest following greater movement errors. Previous findings have shown that greater changes in pre-movement β -ERD between the beginning and end of a period of motor training is related to greater overall decreases in error rates (Little et al., 2019). Greater errors are likely to occur at the beginning of training, and will also demand a more robust model update, when compared to the end of training where the errors are smaller and the motor plan may need minor adjustments to update the model.

3. To identify potential influences the CB has on the PMC activity to influence motor adaptation.

Hypothesis: Change from β -ERD at the end of practice to the beginning of adaptation will be greater in A-iTBS compared to S-iTBS but will return to practice magnitude by the end of training. The cerebellum has functional connections to the PMd in order to influence motor planning during adaptation (Tzvi et al., 2020), therefore I expect the enhanced activity in the cerebellar cortex will cause an enhanced disinhibition of the CB-PMd interactions in the early stage of training.

4. To determine whether enhancing cerebellar activity will improve the amount of error reduction or retention of the acquired motor task.

Hypothesis 1: A-iTBS will have a greater amount of learning (decrease in error) than the S-iTBS when comparing the participants baseline error to the error at the end of training.

Hypothesis 2: A-iTBS will have greater retention of the task, due to the expected increased rate of adaptation (Koch et al., 2020) which will enable participants to transition quicker into the later stage of learning. The dominant processes in the later stages of learning contribute to greater retention, therefore increasing the total time spent in late learning, compared to S-iTBS. Therefore, although the cerebellum is not directly involved in processes contributing to retention (Galea et al., 2011; Spampinato & Celnik 2017), the enhanced cerebellar activity will facilitate the potential for improved retention within the given training period.

Alternatively, it is possible the amount of retention will not differ significantly between groups. Based on the understanding of the fast and slow learning processes simultaneously and independently occurring (Coltman et al., 2019; Joiner & Smith, 2008), enhancing the fast-learning process by modulating cerebellar activity may have no effect on the slow learning process, which contributes to retention (Joiner & Smith, 2008; Smith et al., 2006).

4. Methods

4.1 Participants

Thirty-four participants (15 male, 19 female) were recruited from the University of Waterloo community. Participants were between the ages of 18-40, free of neurological pathologies, not taking psychotropic medications, did not have a history of severe head injury where loss of consciousness had occurred, had 20/20 or corrected to 20/20 vision, were fluent in English, and had no allergies to the adhesive gels or electrode pads. Participants were pseudo-randomly placed into either A-iTBS or S-iTBS. Participants who had experienced TMS in the past were placed in A-iTBS. Both groups were under the impression they were receiving A-iTBS, so as not to differentially influence behaviour between groups. A-iTBS had 8 females, 9 males, an average age of 22.5 +/- 2.1 years old, 2 left-handed. S-iTBS had 11 females, 6 males, an average age of 21.6 +/- 2.7 years old, 4 were left-handed, and all S-iTBS participants were naïve to TMS.

4.2 Active and Sham iTBS

Using the MagPro R30 stimulator (MagVenture, GA, USA), iTBS targeted the posterior lobule in the cerebellum, the stimulation site for which is 1 cm inferior and 3 cm lateral from the inion on the ipsilateral dominant hand side. For A-iTBS, the coil was set at 80% of the participant's active motor threshold (AMT), the stimulus intensity which evokes 200 μ V twitch during a 10% contraction 50% of the time and was positioned with current directed toward the head. For S-iTBS, the stimulus intensity of the coil was set at 20% of the participant's AMT and placed perpendicular to the skull so the current is directed away from, parallel to, the head (Koch et al., 2008; Koch et al., 2020).

4.3 Motor Task

The motor task for this study is a visuomotor rotation task (Fig. 2). Participants were seated 70 cm away from a computer and used their dominant hand to manipulate a joystick to control the cursor on the computer screen (Fig. 1).

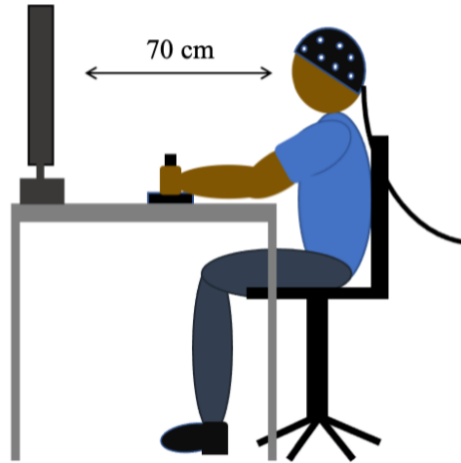


Figure 1. Study set up. Participant position for motor task practice and training.

An 'x' was visible in the centre of the computer screen, which represented the starting position for the cursor. Each trial started with the centre x and the red target (6 mm) presented on the screen in one of eight positions, equidistant from the centre cross 45° apart (Fig. 2B). Targets appeared pseudo randomly at each position every 8 trials. The green cursor (6 mm) appeared 750ms following the target appearance, which was the cue to move. Participants were instructed to move the cursor as quickly and accurately as possible from the centre of the screen and pass through the target. The cursor and target disappeared when the cursor has passed the outer boundary of the target or when the time limit of 750ms was exceeded, which concluded the trial. Between each trial there was a 2 second pause where only the centre x was visible on the screen (Fig. 2A). The cursor moved in real time, updating as fast as the computer processed the loop, which was about 11ms.

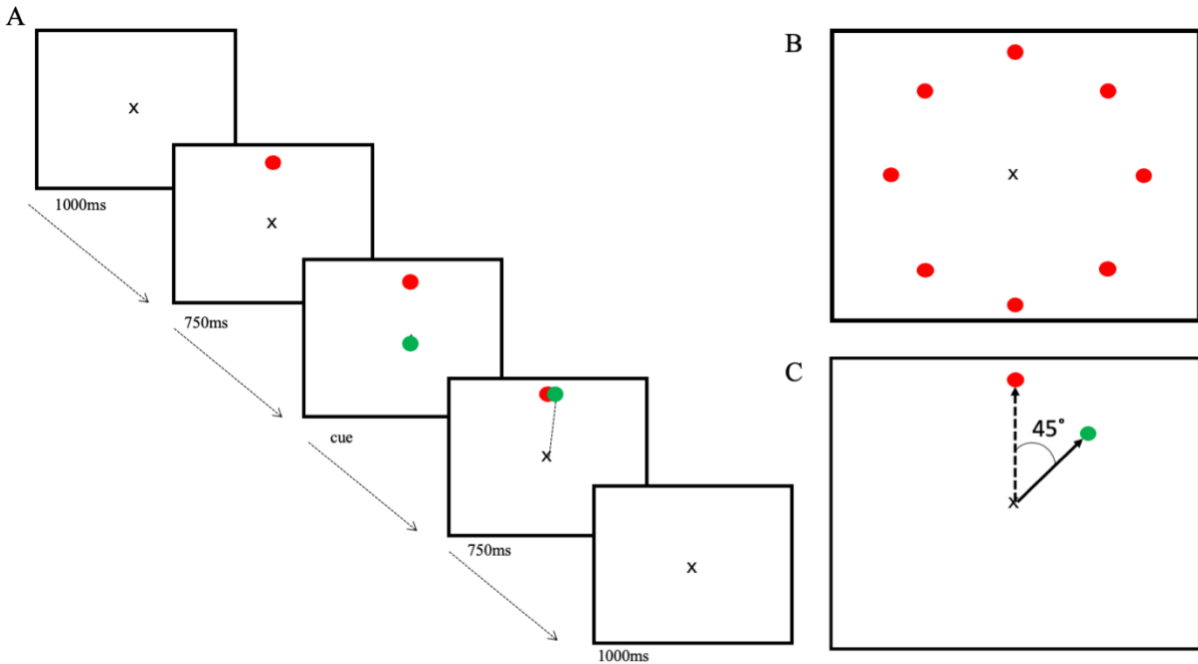


Figure 2. Trial sequence and timing of events. A. The events and timing of an individual trial: 2000ms of rest, followed by a target appearance for 750ms to prepare for movement, then the cursor appearance as the cue to move with 750ms to allow for execution. B. All possible target locations. C. Cursor movement rotation presented in the motor adaptation task.

4.4 Experimental Design & Procedures

This study followed a mixed measures design and consisted of two experimental sessions. The first session was approximately 1.5 hours in duration, the second session which was scheduled approximately 24 hours after the first session, was about 15 minutes long.

Following consent and screening, the dominant-hand index finger and ulnar styloid point on the wrist was prepped by using an abrasive gel to remove dead skin and dirt and cleaned with alcohol. Surface electromyographic (EMG) recording electrodes were placed on the prepped areas, two over the first dorsal interossei (FDI) and one on the ulnar styloid. Next, the participant's AMT was found by applying TMS (MagVenture, GA, USA) over the motor hotspot for the FDI muscle ($M1_{\text{FDI}}$), the location within the motor cortex which elicits the greatest,

reliable twitch in the FDI. The motor threshold was determined by eliciting a twitch in the FDI muscle of at least 200 μ V, five times out of ten consecutive trials during a ~10% muscle contraction.

After the motor threshold procedure, the electroencephalography (EEG) cap was prepped. To optimize the contact between the electrode and the scalp, the hair under each electrode site was moved out of the way, and the skin was lightly abraded. This was done using a blunt syringe. Conductive gel was then inserted into each electrode with the syringe. Once each electrode had an impedance < 5 Kohm, preparation was complete.

Prior to administering iTBS and the initiation of data collection, each participant completed 2 practice blocks of the motor task. For the practice blocks, individuals were seated about 70 cm away from computer screen and instructed they would be using the joystick to move a cursor through targets on the screen. Participants were instructed to watch for the appearance of the target at one of 8 locations near the perimeter of the grey box. Less than a second later, the cursor, a green circle, would appear on top of the centre x on the screen and that was their cue to use the joystick to move the cursor through the target, in a straight line, as quickly and accurately as possible. Participants were told they had less than a second to make the movement so it should be made in a quick striking motion. It was also emphasized to participants to wait until the cursor appearance before moving the joystick. Each practice block was 40 trials in length, each of the 8 targets appeared in a pseudorandom order every 8 trials the participant. The practice blocks allowed the participant to understand the timing of the task, the relationship between the joystick and cursor movement, and provided a reference measure for each participant's unperturbed pre-movement β -ERD and joystick control error.

Once the practice blocks were completed, the participant received either active iTBS or sham iTBS. To administer iTBS, the participant was seated, facedown with their head resting on a foam head support on the table. The TMS coil arm was positioned to hold the coil in place for the duration of the stimulation. The intensity of the stimulator output for the intermittent theta burst stimulation (iTBS) or sham iTBS was set at 80% of the AMT. Cerebellar iTBS (CB-iTBS) was delivered 1 cm inferior and 3 cm to the right of the inion for a total duration of 3 minutes. Sham iTBS procedure followed the same protocol, however the coil intensity was decreased to 20% of motor threshold and placed perpendicular to the skull, so the iTBS current would be directed away from the participant's head.

The experimental task, which built on the practice, commenced 10 minutes after iTBS was complete (Koch et al., 2020). Individuals performed the same task, however the trajectory of the cursor deviated 45° clockwise from the expected path (Fig. 1C). Participants were told they would notice a difference in the relationship between the joystick movement and the cursor movement on the screen, but the goal was still to move the cursor through the target in a straight line, as quickly and accurately as possible. Participants completed 40 trials per block, and 10 blocks (400 trials total). This is to ensure the task becomes adapted to and some level of automaticity will be reached (Koch et al., 2020). Each block was separated by a short (approximately 30 second) break and participants were given the option for a longer break if needed. EEG was recorded for the duration of the training and experimental task to obtain measures of cortical activity. The timing of events, and joystick movements were recorded and later used to measure error. The entire experimental session lasted approximately one and a half to two hours.

Subjects returned to the lab for a retention test about 24 hours after the first session. Since sleep can affect consolidation, all participants filled out the St Mary's Hospital Sleep Questionnaire upon their return to the lab on day 2. Participants completed two blocks of 40 trials (80 trials total) of the experimental task, which allowed for comparison between the movement error at the end of the experimental task in session 1 and in the beginning of session 2 as a measure of the amount of retention of the learned motor task.

4.5 Data Acquisition

EEG was recorded from a 32-channel cap using the International 10-20 system, using ten recording electrodes located over the sensorimotor regions. The electrodes used were located over the sensorimotor cortex: FCZ, FC3, FC4, CPZ, CP3, CP4, C3, CZ, C4, and FP1 which was used to identify blinks and facial movement. Reference electrodes were placed on the right and left mastoids. Data was amplified, filtered (DC- 200Hz, 6dB octave roll-off) and digitized at 1000Hz (SynAmps2, Scan 4.5, Compumedics Neuroscan, Charlotte NC, USA) before being stored off-line for analysis.

Behavioural data was measured in voltage changes from the joystick movement and recorded in the LabVIEW program used to run the motor training task. The movement data was collected at a rate as quickly as the loop updating the cursor position could be completed, which was approximately 1 sample every 11ms or 90Hz.

4.6 Data Analysis

The motor task program run in LabVIEW sent event codes to the running EEG file denoting the target position and appearance, the appearance of the cursor, and the initial movement of the cursor. Event code files for each block were extracted from the continuous EEG file. Event codes identified the location specific appearance of the target, the appearance of

the cursor on the centre 'x', and the onset of movement which was triggered by the cursor passing through the bounds of the start position. Mistrials where the participant either moved before cued to do so or did not move at all within the 750ms movement time window were identified by missing the event code for the onset of movement were removed from both the behavioral and EEG analysis.

4.6.1 EEG Collection and Cleaning

EEG data was collected with Neuroscan (Compumedics Neuroscan, NC, USA) software. Separate continuous EEG files were created for each block of trials. EEG data was imported to EEGLAB run on MatLab Simulink, was band pass filtered between 1 and 50 Hz. Independent component analysis (ICA) was run on each participant's data and the component containing blinks was removed from the datasets. After filtering and ICA blink removal, all datasets were scrolled through and portions of the data which were obviously corrupted by noise from muscle activity or other sporadic bursts of line noise were removed from the data.

4.6.2 EEG Epoching

Trials were epoched every 3500ms with the cue to move at time 0 including the 1750ms prior and 1750ms following. Each epoch captured the premovement rest period for the first 1000ms (-1750ms – -750ms), the appearance of the target location and planning to move for 750ms (-750 – 0ms) , the cue to move at time 0 with 750ms for the movement execution which ended when the cursor passed the target bounds or the 750ms time limit expired, (0ms – ~750ms) followed by the 1000ms post movement rest period (750ms – 1750ms). Epochs corresponding to mistrials were removed from analysis. Some epochs were also eliminated (or not created) by not having enough data or missing event codes after noise contaminated segments were removed.

4.6.3 β -ERD calculation

Pre-movement β -ERD was quantified by performing a time-frequency analysis at the FC3 (or FC4 in left-handed participants) electrode and measuring the difference in power in the beta band (13-30Hz) during the movement planning period from the baseline power. The change in power from baseline, which in β -ERD is a decrease in power, was computed by using the divisive baseline removal method in EEGLAB. This method removes the baseline by dividing the power at all timepoints by the mean baseline power across the defined baseline time period, for each frequency. The planning period was defined as -500ms, which is 150ms after the target appearance to allow for recognition and relay of the visual stimulus to motor planning areas, to 50ms after the cue to move, which will not be confounded by the arrival of the visual stimulus but comes close to the final generation of the motor command, limiting conflicting (or potentially unrelated) contents or type of neural activity in the signal. The baseline period was from the beginning of the epoch, -1750ms to the target appearance at -750ms.

After the data was epoched, individual trials were saved separately for β -ERD-error relationship regression analysis, as well as concatenated into bins of 8 trials to represent each the pre-adaptation (PRE), early adaptation (EARLY) and late adaptation (LATE) timepoints. The PRE bin consisted of the last 8 viable trials in the practice period when no perturbation was present, the EARLY bin consisted of the first 8 viable trials in the training period when the perturbation was introduced, and the LATE bin consisted of the last 8 viable trials in the training period (Fig 3). For the individually saved trials, β -ERD was computed for each trial. For the pre, early, and late bins the baseline was removed from each individual trial, then the mean β -ERD of the bin was computed by averaging each timepoint at each frequency across all 8 trials, and then

by computing the mean power across the time range in the entire 13-30Hz frequency range. This process was completed separately for each individual participant.

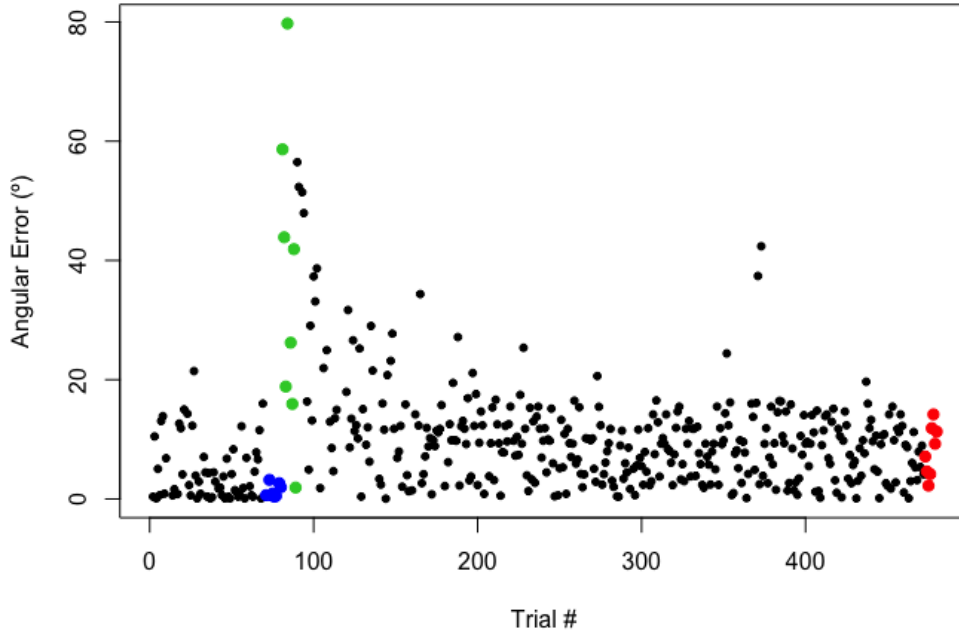


Figure 3. Angular error across training example plot. Plot of an individual's behavioural data to display trials corresponding to the epochs included in the bin for pre (coloured in blue), for early (coloured in green), and late (coloured in red).

To account for individual and group differences in β -ERD during the practice period, the measures of β -ERD in early adaptation (β -ERD_{early}) and at the end of training (β -ERD_{late}) were measured as the change in β -ERD from the end of the practice session with no perturbation (β -ERD_{pre}). The β -ERD_{early} change was determined by measuring the change from β -ERD_{pre} to β -ERD_{early} (β -ERD Δ _{early}) within each individual participant (i), as shown by the equation:

$$\beta ERD_{early} i - \beta ERD_{pre} i = \beta ERD\Delta_{early} i$$

The process to measure the change in β -ERD_{late} from β -ERD_{pre} (β -ERD Δ _{late}) follows the same process as outlined for β -ERD Δ _{early}, shown by the equation:

$$\beta ERD_{late} i - \beta ERD_{pre} i = \beta ERD\Delta_{late} i$$

If there was no desynchronization in β -ERD_{pre} then the participant's data was not included in the β -ERD calculations and analysis, since they weren't exhibiting the neurophysiological process being measured.

From qualitative observation of the ERSP plots, it appeared as though there was a split in the β band activity between the higher frequencies and the lower frequencies (Fig. 4). To further explore this observation, the β -ERD change for each timepoint as described above was calculated 3 times, once for each the entire β band range (13-30Hz), for the low β band frequency range (13-20Hz) and for the high β frequency range (22-30Hz).

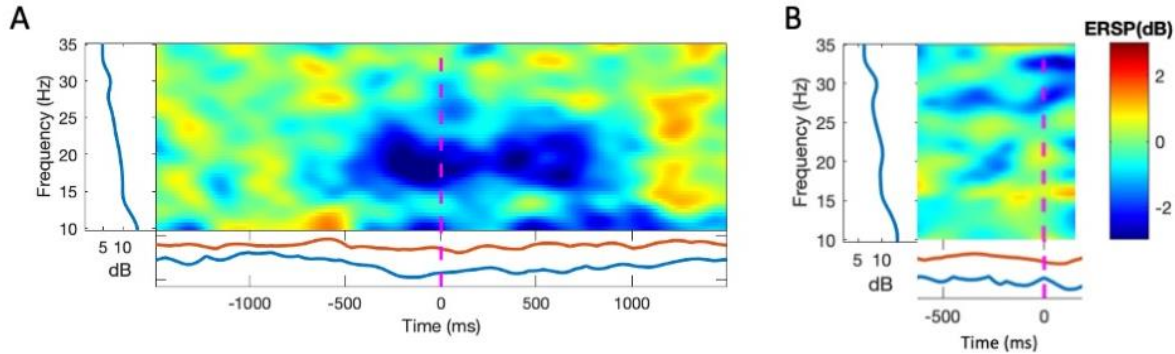


Figure 4. Example ERSP plot. A. Example ERSP plot from an individual participant's average β -ERD from practice. The frequency is shown on the y-axis, time in (ms) on the x-axis. The target appears at -750ms and time 0ms is the cue to move. The index for the colour map is shown on the right of the graph. Lower power (dB) indicates greater ERD. B. Example plot from an individual participant's β -ERD_{pre} in the movement planning time window, showing the distinction between high and low β activity.

For the regression analyses, datasets were created pairing the AE and subsequent β -ERD. All mistrials and trials for which the epochs were eliminated due to noise corruption were excluded from the dataset. Data from some participants was excluded from analysis because the AE values and β -ERD could not be reliably paired. This resulted from the EEG cleaning and epoching which altered the time frame and some event codes from noisy epochs were removed,

so the excluded datasets were altered in a way which was beyond my technical capability to resolve.

4.6.4 Behavioural

Behavioral measures of response time (RT) and angular error (AE) were collected from joystick data. The AE was measured at the peak velocity of the movement, when the cursor had travelled the maximum distance between 2 timepoints, as angular difference between the cursor location and the ideal trajectory for the cursor to have followed. RT was calculated as the difference in time between the appearance of the cue to move and the onset of movement, the time at which the cursor left the initial starting point.

An average of 15% of trials were flagged as mistrials and were omitted for each participant and an average of 3% of trials were omitted as outliers (greater than 2 standard deviations from the mean of each bin of 8 trials).

Adaptation rate was determined by an asymptotic regression function.

$$y(x) \sim y_f + (y_0 - y_f)e^{-\exp(\log \alpha)x}$$

This analysis was done in R using the self-starting asymptotic non-linear least squares (nls) function: $\text{nls}(y \sim \text{SSasymp}(x, y_f, y_0, \log \alpha))$, where y is the input, x is the time or trial number, y_f is the asymptote, y_0 is the starting point, and $\log \alpha$ is the rate constant. A rate constant closer to 0 indicates a faster rate of adaptation, or a more rapid change in error as it approaches the asymptote.

The process for binning trials for behavioural analysis follows the same pattern as stated in section 4.6.3, where the averaged final 8 trials in the practice period are represented in the PRE timepoint, the final 8 trials in the training period represent the LATE timepoint, and AE to represent the amount of retention (ret) was the first 8 trials of the retention test on the 2nd day.

The amount of learning was determined by the residual error when comparing late to the pre timepoints (learned). Lower residual error, or a smaller difference between the late and pre timepoint indicates that more learning had occurred, as the participant was able to recover a greater amount of their pre-perturbation accuracy. Retention was measured as the residual error, when comparing the ret to the late timepoint (Fig. 5).

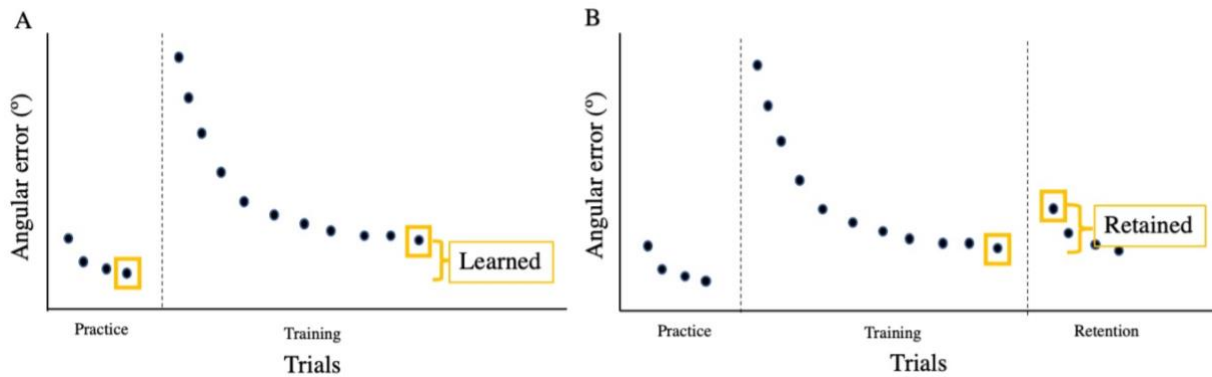


Figure 5. Calculation of amount learned and retained. A. Learned calculation. Angular error plotted over time for a hypothetical and condensed behavioural dataset. Yellow boxes indicate the error values being compared to calculate the residual error. B. Retained calculation.

4.7 Statistical Analysis

Levene’s test and Shapiro-wilk test were run prior to statistical testing to confirm all datasets met the assumption of normality and heteroscedasticity, respectively. Non-normally distributed data were addressed with non-parametric statistical tests.

1. Confirm findings from previous studies that found CB-iTBS improves the rate of adaptation (Koch et al., 2020, Galea et al., 2011).

For objective 1, a one-tailed independent samples t-test was run to determine whether the A-iTBS group was able to adapt to the rotation faster than S-iTBS. Group was treated as the independent variable and adaptation rate was the dependent variable.

2. To understand how the changes in activity in the PMC inhibitory circuits relate to error reduction during adaptation to a motor task.

For objective 2, a linear mixed model was run to determine whether a relationship exists between β -ERD and AE and in preceding trials in the adaptation period of training (blocks 1 and 2). β -ERD was the dependent variable. AE was treated as a continuous variable, and group, treated as a categorical variable with 2 levels (S-iTBS/A-iTBS), were included as fixed factors. Individual subject was treated as a random factor. Data from 4 participants was excluded from analysis because the AE values and β -ERD could not be reliably paired. The linear mixed model was also run using binned data to control for any noise that may contribute to individual trial variability in the β -ERD and 3 participants' data was removed because bins could not be reliably paired.

3. To identify potential influences the CB has on the PMC activity to influence motor adaptation.

For objective 3, a 2-way mixed model ANOVA was run to determine whether CB-iTBS influenced the β -ERD Δ measures at the beginning and end of the training session. Time was treated as the within-subjects factor with 2 levels (early/late) and group was treated as the between-subjects factor with 2 levels (A-iTBS/S-iTBS).

4. To determine whether enhancing cerebellar activity will improve the amount of error reduction or retention of the acquired motor task.

For objective 4, to determine whether the amount of the skill learned and retained was greater in the A-iTBS group than the S-iTBS group. The aligned rank transform was applied to the data and a non-parametric 2 way mixed-measures ANOVA was run to determine whether there was a difference between groups or a difference between group in the amount of the skill

learned or retained. Time treated as the within-subjects factor (Learned/Retained) and group (A-iTBS/S-iTBS) as the between-subjects factor. The LATE training value from the last bin was representative of the final average error, i.e., there was no substantial increase or decrease in error in the 8 trials included in the LATE bin.

5. Results

5.1 Adaptation Rate

The t-test revealed a significantly greater rate of learning in the A-iTBS group compared to the S-iTBS group [$t = 2.04$, $df = 32$, $p = 0.025$, A-iTBS = -2.58 ± 0.26 , S-iTBS = -3.22 ± 0.34 , Cohen's $D = 0.7$] (Fig. 6 & 7).

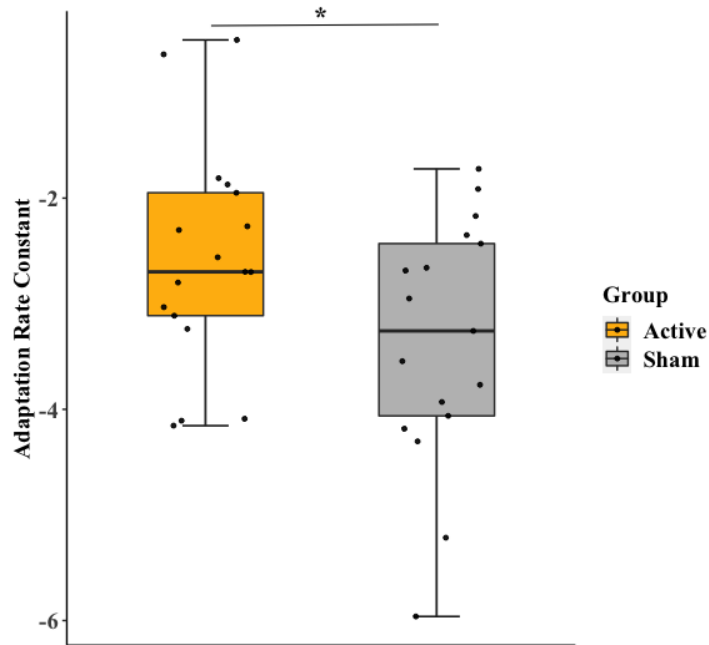


Figure 6. Adaptation rate between groups. Boxplot of error decay rate, used as the measure of adaptation rate, in each group. Datapoints on the boxplots each represent an individual participant's adaptation rate constant. * indicates significant difference $p < 0.05$

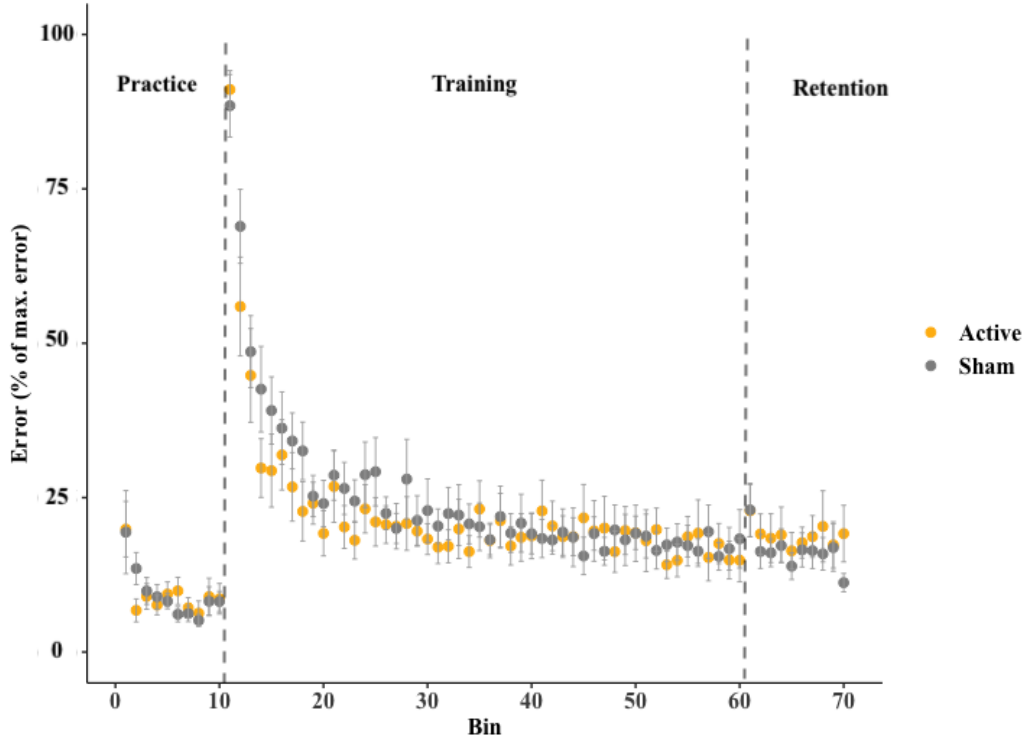


Figure 7. Error across practice, training, and retention. Group error rates plotted over time. Each data point represents the group average median error in each bin. Error values are normalized to the maximum median error within each participant for ease of viewing the comparison between groups. Error bars show the standard error of the mean. Bins 1 through 10 represent the Pre perturbation/Practice period, bins 11 through 60 show the training period, and bins 61 through 70 show the test on day two to measure the retention of the skill.

5.2 AE and β -ERD

For the individual trial analysis, the equation for the fitted LMM was:

$$\beta = -2.77 + x_{AE}(0.006) + x_{groupActive}(-0.13) + x_{AE*groupActive}(-0.009)$$

β -ERD was not significantly affected by AE [b=0.006, p= 0.096] or the interaction of group and AE [b= -0.009, p= 0.078] (Fig 8.).

For the binned trials analysis, the equation for the fitted LMM was:

$$\beta = -2.56 + x_{AE}(0.0005) + x_{groupActive}(-0.28) + x_{AE*groupActive}(-0.006)$$

AE [p= 0.65], AE and group interaction [p= 0.55] was not a good predictor of average β -ERD (Fig. 8).

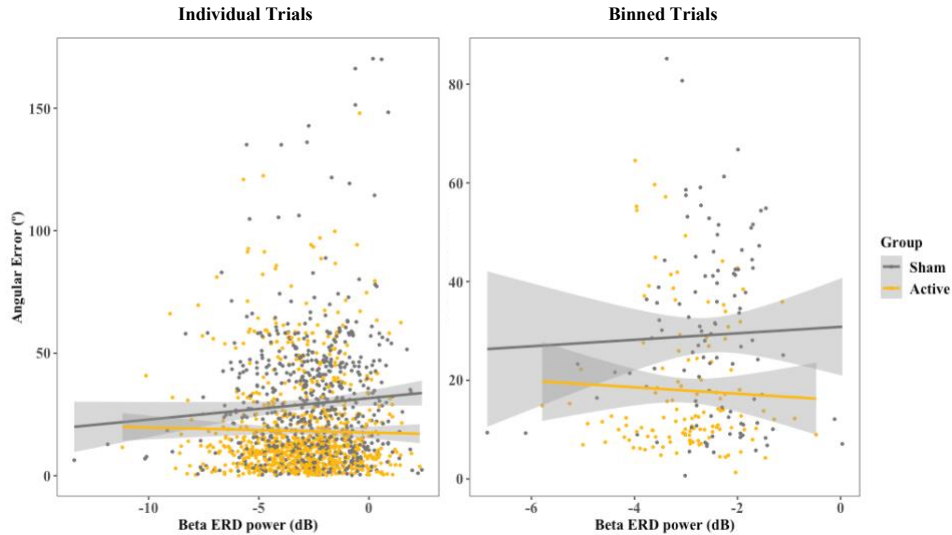


Figure 8. Angular Error and Beta ERD. Top row of plots show the individual trial AE and β -ERD plot, the left plot from the first two blocks of training, the right plot shows the last two blocks of training. Bottom row of plots shows the AE and β -ERD from bins of 8 trials from the first two blocks of training (left) and the last two blocks of training (right). Y axis is the AE in degrees, X-axis shows the β -ERD power. The grey area around the trend lines shows the 95% confidence interval for the fit of the linear regression model.

5.3 Beta ERD changes

Entire β band range (13-30Hz)

One subject's data from the S-iTBS group was removed from this analysis because they did not show any desynchronization in the β -ERD_{pre} measure. An additional participant's data was removed because their β -ERD_{late} was greater than 2 SD of the group mean.

Removal/inclusion of the individual participants data did not change the significance of the results. The interaction was not significant [$F_{1,30}=0.028$, $p=0.87$, $\eta^2=0.0004$]. There was a significant main effect of group [$F_{1,30}= 4.66$, $p=0.039$, $\eta^2= 0.067$]. There was no main effect of time [$F_{1,30}=0.22$, $p=0.64$, $\eta^2=0.004$] (Fig. 9).

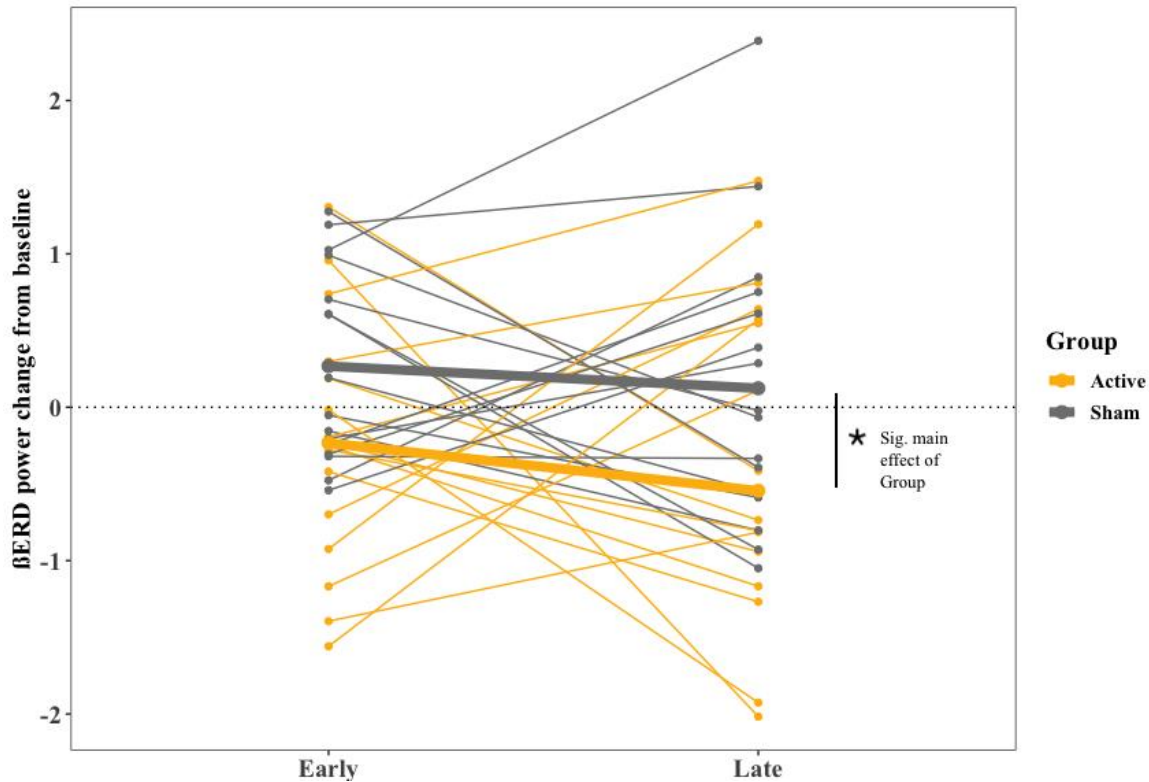


Figure 9. Beta ERD change early and late training. Change in β -ERD from Pre to Early (Early) and Pre to Late (Late) in each participant. 0 represents the β -ERD power in the Pre measure. Negative values indicate a greater power decrease or desynchronization and positive values represent an increase in power or less desynchronization. Thick bolded lines represent the group average. * Indicates a significant main effect of group, $p < 0.05$.

High β range (22-30Hz)

A 2 way mixed model ANOVA was run to determine whether CB-iTBS influenced the β -ERD Δ measures, specifically in the high β frequency band, at the beginning and end of the training session. Time was treated as the within-subjects factor with 2 levels (early/late) and group was treated as the between-subjects factor with 2 levels (A-iTBS/S-iTBS). The group by time interaction was not significant [$F_{1,30}=1.16$, $p=0.29$, $\eta^2=0.018$]. There was a main effect of group [$F_{1,30}=6.31$, $p=0.018$, $\eta^2=0.098$], but no significant main effect of time [$F_{1,30}=0.96$, $p=0.36$, $\eta^2=0.015$] (Fig. 10). One A-iTBS and two S-iTBS participants did not exhibit desynchronization in the pre measure and therefore were excluded from the high β range

analysis. Removal/inclusion of the individual participants data did not change the significance of the results.

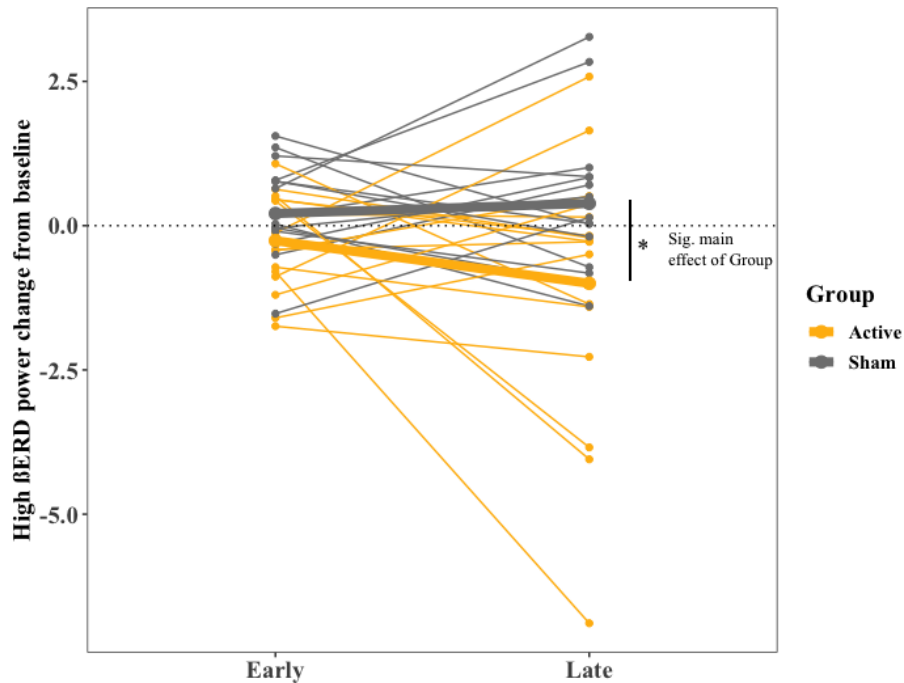


Figure 10. Beta ERD change early and late training- high beta frequency band. Change in β -ERD from Pre to Early (Early) and Pre to Late (Late) in each participant in the 22-30 Hz beta band range. 0 represents the β -ERD power in the Pre measure. Negative values indicate a greater power decrease or desynchronization and positive values represent an increase in power or less desynchronization. Thick bolded lines represent the group average. * indicates a significant main effect of group, $p < 0.05$.

Low β range (13-20Hz)

A 2-way mixed model ANOVA was run to determine whether CB-iTBS influenced the β -ERD Δ measures, specifically in the high β frequency band, at the beginning and end of the training session. Time was treated as the within-subjects factor with 2 levels (early/late) and group was treated as the between-subjects factor with 2 levels (A-iTBS/S-iTBS). There was no significant group by time interaction [$F_{1,24}=1.16$, $p=0.29$, $\eta^2=0.018$], and no significant main effect of group [$F_{1,24}=6.31$, $p=0.018$, $\eta^2=0.098$], time [$F_{1,24}=0.96$, $p=0.36$, $\eta^2=0.015$] (Fig. 11).

Five S-iTBS participants and three A-iTBS participants did not exhibit desynchronization in the Pre measure and therefore were excluded from the low β range analysis.

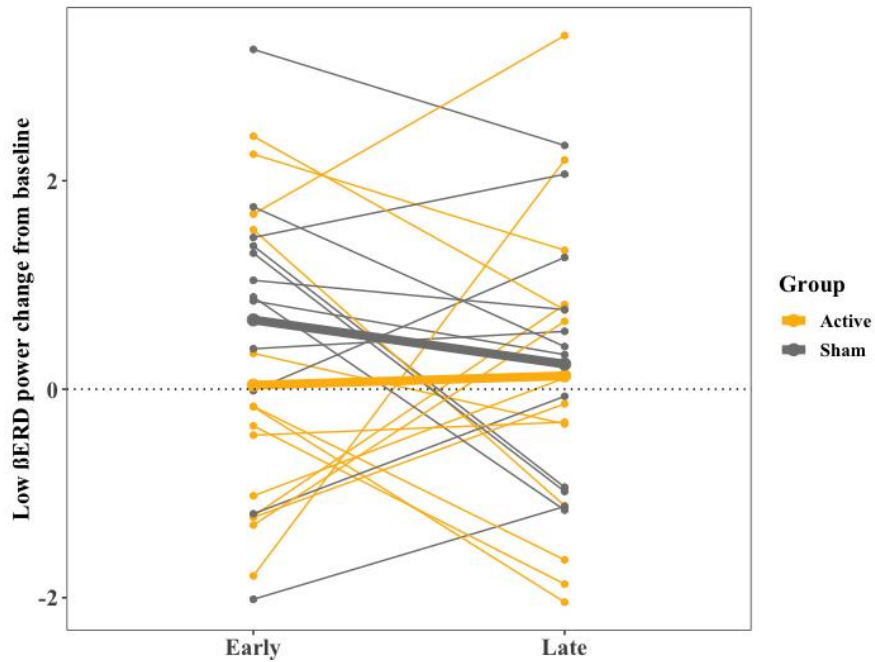


Figure 11. Beta ERD change early and late training- low beta frequency band. Change in β -ERD from Pre to Early (Early) and Pre to Late (Late) in each participant in the 13-20Hz beta band range. 0 represents the β -ERD power in the Pre measure. Negative values indicate a greater power decrease or desynchronization and positive values represent an increase in power or less desynchronization. Thick bolded lines represent the group average.

5.4 Learned and Retained

The ANOVA revealed a significant Group by Time interaction [$F_{1,64} = 5.62, p=0.021$].

Post-hoc analysis revealed the interaction was driven by the difference between the Learned and Retained residual error in the A-iTBS group [t-ratio= 2.49, $p=0.07$] (Fig. 12). Tukey method was used for the P-value adjustment.

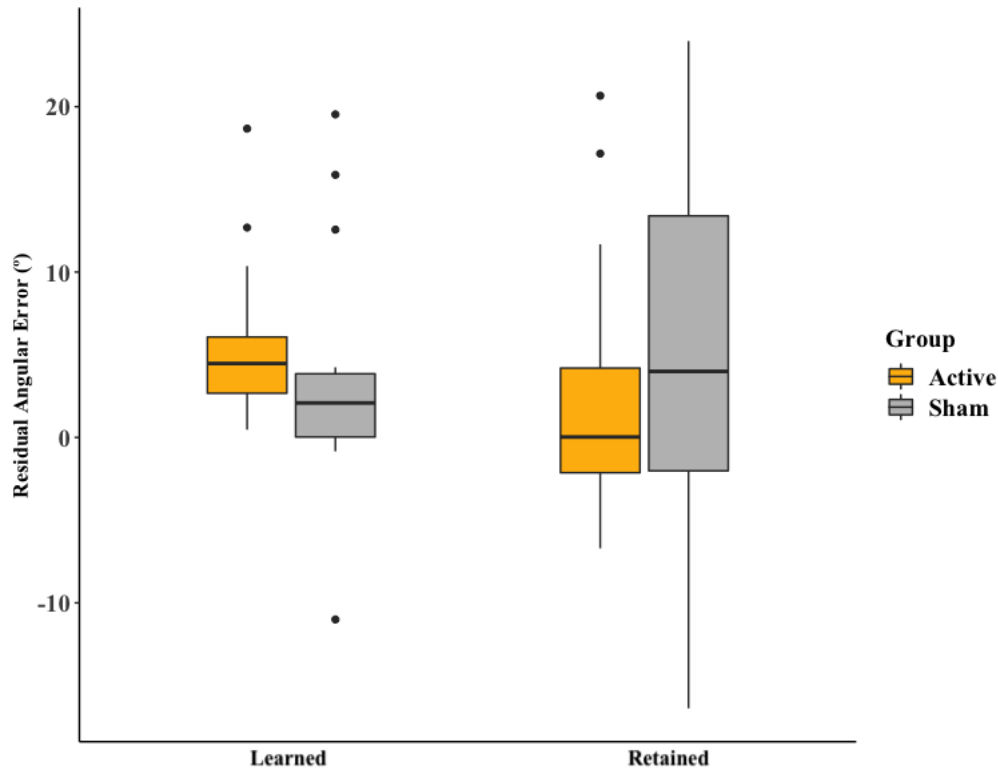


Figure 12. Amount learned and retained. Boxplot of the residual error indicating the amount of learning that had occurred (Learned) and the amount of the skill that was retained between sessions (Retained). A lower residual error indicates greater learning and greater retention, a negative residual error indicates a lower error than the error at the comparison timepoint.

5.5 Supplementary Data

Response Time

A 2-way mixed measures ANOVA was run to assess the effect of group and block on response times. Group was treated as the between-subjects factor, block as the within-subjects factor with 3 levels: Pre, Early, and Late. The Greenhouse-Geisser epsilon correction was applied to correct for violations of sphericity between blocks. The ANOVA revealed the interaction between group and block [$F_{1,86,59.43}=0.50$, $p=0.59$, $\eta^2=0.007$] was not significant. The main effect of group was not significant [$F_{1,32}=1.85$, $p=0.18$, $\eta^2=0.03$], but there was a significant main effect of block [$F_{1,86,59.43}=6.8$, $p=0.003$, $\eta^2=0.08$]. Tukey's HSD revealed a

significant difference between the response time at early training and late training [$p=0.02$, early = 373 ± 18.6 , late = 308 ± 15.8] (Fig. 13).

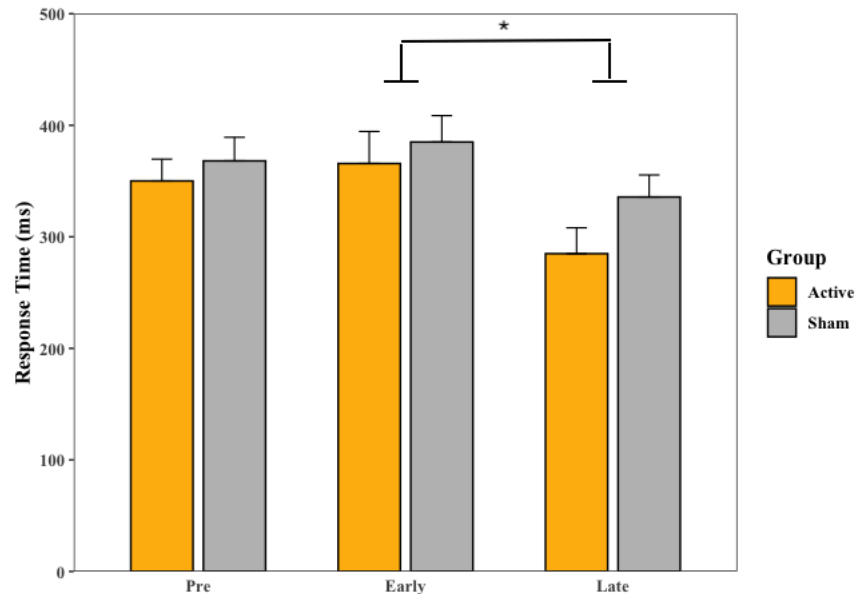


Figure 13. Response Times. Average response times at the Pre (last 8 trials of practice), Early (first 8 trials of training) and Late (last 8 trials of training) timepoints for each group. Error bars show the standard error of the mean. * indicates significant difference $p<0.05$.

Sleep questionnaire results

There was no difference between groups in any of the following measures of reported amount of sleep and sleep quality: total time slept overnight reported in hours [$t_{32} = -0.54$, $p=0.59$, A-iTBS = 7.53 ± 0.2 , S-iTBS = 7.74 ± 0.34] or how well participants slept on a scale of 1 (very badly) - 6 (very well) [$t_{32} = -0.4$ $p=0.7$, A-iTBS = 4.65 ± 0.24 , S-iTBS = 4.76 ± 0.18].

Behavioural Trials Eliminated

On average, 11% of all trials, including the practice, training, and retention trials, were flagged as mistrials and 2% of all trials were flagged as outliers for a total of 13% of all trials which were flagged and eliminated from the behavioural analysis. There was no difference between groups for either the number of mistrials [$t_{32} = -0.81$, $df=32$, $p=0.43$, A-iTBS = 55.8 ± 9.77 ,

S-iTBS=67.1±10.1] or the number of outlier trials [$t_{32}=1.0$, $df=32$, $p=0.33$, A-iTBS=13.6 ± 1.28, S-iTBS= 11.8 ± 1.22]. (Table 2 in appendix.)

6. Discussion

The general results from this study are consistent with previous literature identifying the role of the cerebellum in motor adaptation (Galea et al., 2011) and showing that enhancing cerebellar activity with iTBS improves the rate of adaptation on a visuomotor rotation task (Koch, 2020). This study adds to the literature by contributing to our understanding of how upregulating activity in the CB (directly or indirectly) affects changes in activity in the motor planning areas, namely the PMC, during motor planning.

The main objective of the study was to understand the relationship between the changes in PMC inhibitory activity and changes in error in the adaptation stage of motor skill learning. The absence of a significant relationship between AE and β -ERD do not support the main hypothesis that pre-movement β -ERD in the premotor cortex is modulated by movement error. The second objective was to gain insight into the mechanisms underlying the CB influence over the premotor cortex and motor adaptation. The results generally did support the hypothesis that CB-iTBS would increase β -ERD, however the hypothesis that β -ERD would return to pre-perturbation measures at the end of the training session was not supported by the data. The third and fourth objectives were to examine the effects of CB-iTBS on the behavioural measures of acquisition and retention of the motor skill. The results from this study support previous findings that CB-iTBS increases the rate of motor adaptation but did not affect the overall retention of the skill or the response times.

6.1 Adaptation rate

The first objective of the current study was to show that CB-iTBS increases the rate of adaptation on a visuomotor rotation task. Results confirmed that CB-iTBS does in fact improve the rate of adaptation since the rate of adaptation was statistically quicker in A-iTBS than in S-

iTBS. We expected to see this based on results from previous studies which have shown that CB-iTBS increases the adaptation rate in visuomotor rotation tasks (Galea et al., 2011; Koch et al., 2020).

Although there was a significant difference in adaptation rate between groups, the rate in both groups was notably quicker than the adaptation rate observed in the study by Koch et al. (2020). The difference between A-iTBS and S-iTBS of adaptation rate was less pronounced than the study by Koch et al. as well. This may be due to a number study parameters.

The first inconsistent parameter was that Koch et al. used a finger-controlled joystick as opposed to a handheld one used in the current study. The handheld joystick used for the current study was selected to increase the real-world relevance of the task and because most studies measuring β -ERD or other motor planning and preparation activity measures used tasks requiring wrist and forearm flexion/extension, not just finger flexion/extension. However, the finger-controlled joystick may have been more challenging to control by requiring more precise movements, therefore more challenging to adapt to the visuomotor rotation.

Second, Koch et al. had a 30° rotation and had targets positioned 60° apart instead of the 45° and 45° target separation used in the current study. The 45° rotation with targets placed 45° apart may have helped participants to visualize the rotation and how to correct for it, since they could imagine where the neighbouring target would be located and move as though they were aiming for that location. Instead of generating a completely new motor program to aim for the target, participants could adapt to using a familiar motor program for a new target. If the rotation had been seemingly more arbitrary, that strategy would not have been possible and may have increased the difficulty of the task, which may have resulted in a greater between group difference in learning rate.

Third, the bins consisted of 6 trials (one of each of the 6 target locations) in Koch et al., whereas our study binned 8 trials (one of each of the 8 target locations). Averaging fewer trials in each bin would spread error reduction over a greater number of points which visually stretches the adaptation curve, making it appear less steep.

The task in the current study may have been easy enough that the CB-iTBS was not as beneficial as it would have been in a more challenging task, where the learning rate would have been shallower and therefore a greater difference between groups may have been observable.

6.2 AE and β -ERD

The second objective of this study was to gain insight into the relationship between error and β -ERD. I hypothesized there would be a greater magnitude of β -ERD following trials with a greater AE, reflective of integration of feedback from previous movement error to adjust for upcoming movements. The results did not support this hypothesis and showed that AE was not a good predictor of β -ERD. Although sensory processing is affected by the magnitude of error (Torrecillos et al., 2015), it may be that model updating and planning of the subsequent movement results in an alteration in the pattern of inhibitory control in the preparatory network, but not a change in the overall magnitude of inhibitory control or release of inhibitory control. In other words, the microcircuits activity may change, and the inhibitory activity may migrate, but the overall amount of inhibitory control stays the same. It has been proposed the sensory integration and model updating/planning circuits function separately from one another so the sensory processing may be affected by the changes in error during adaptation, but the changes in one circuit may not be linearly reflected by changes in the other.

There are many other factors which could be contributing to both the β -ERD and the rate of adaptation. There are distinct neural networks and patterns of activity specific to implicit and

explicit learning processes, which rely on differing contributions notably from the cerebellum, dlPFC and distinct regions of the basal ganglia (Destrebecqz et al., 2005; Liew et al., 2018). Although the study was designed to target primarily implicit learning, participants presumably employed both processes, but with varying reliance on one or the other. The strategy and resulting distinct patterns of activity in these other brain regions may differently affect the inhibitory activity in the PMC or contribute to adaptation in alternate ways. Additionally, there may be other unknown neurophysiological processes which generate β band activity or other external electrical activity picked up by the electrode and not filtered out, which contribute to the power reading in the β band frequency and therefore add noise to the true β -ERD power change in the premotor areas. Alternatively, error reduction in upcoming movements may be determined by networks other than the premotor inhibitory control network which produces the β band activity.

β -ERD across the entire movement planning window may be too broad of a time window to identify a relationship between AE and subsequent β -ERD. The hypothesis that AE would influence the planning activity in the subsequent trial assumes that planning for the parameters of the upcoming movement occurs across the entire window of time, from the visual integration of the target until the cue to move. However, it is possible that changes in β -ERD related to the movement parameters which may be influenced by AE in the previous trial, occur while generating the motor command. In this case, β -ERD should be measured in the movement preparation window, between the cue to move and the onset of movement.

6.3 Beta ERD changes

The third objective of the study was to explore the relationship between the CB and PMC inhibitory control during movement planning. I hypothesized that A-iTBS would show an

increase in β -ERD in early training, reflective of an enhancement of the pre-movement CB excitatory influence over the PMC during adaptation, but that β -ERD would return to the baseline and similar to β -ERD in S-iTBS at the end of training. This was based on the understanding that the cerebellum is primarily involved in the adaptation phase of learning and less involved in later stages of learning (Galea et al., 2011). On average there was a β -ERD increase which persisted throughout training; however, qualitatively there appears to be two patterns of β -ERD change. In some the β -ERD increased further and others it decreased.

These patterns of change, β -ERD increasing over time and β -ERD decreasing over time, have several potential neurophysiological and behavioural explanations. The decrease in late β -ERD measures may reflect an increase in motor cortical excitability which can occur through LTP-like effects from 20 minutes of motor training (Classen et al., 1998, Ohashi et al., 2019). Decreased synchronized inhibitory activity in the PMC could also be a result from an overall enhancement of network excitability in the CB-PMd network. This explanation suggests the enhancement of the CB-PMd network activity is not specific to adaptation but movement planning in general, so the enhanced CB activity may have just enhanced PMC activity for the duration of the effects of the iTBS. iTBS has shown to increase excitability in the motor cortex for 60 minutes following stimulation (Wischnewski & Schutter, 2015). There may have been differences between individuals in motivation or attention at the end of training affecting the motor planning activity.

Across the entire β frequency range and the high and low frequency bands, the trend is a no change in β -ERD in the sham group compared to baseline. This is seemingly inconsistent with a previous report which showed greater β -ERD during adaptation phase (Torrecillos et al., 2015) compared to the end of a training period, in participants who did not receive any brain

stimulation. It was in part based on this study that I hypothesized there would be a greater β -ERD in the adaptation phase compared to baseline/practice and the end of training. However, the study by Torrecillos et al. (2015) did not measure the change in β -ERD from a baseline/unperturbed task to the adaptation task, so it is possible that we would see similar trends overall if we had just used absolute β -ERD measures. These differences could also be impacted by the differences in the parameters of their rotation task and because they measured from C3 the 4 surrounding electrodes, as opposed to the current study which just used FC3 (or FC4).

Although the previous research informing this study measured β band activity across the entire frequency range, 13-30Hz, the β band can be subdivided into the low β band range (~13-20Hz) and the high β band range (~22-30Hz). From a qualitative observation of results from this study, there appeared to be a clear divide in clusters of activity between the high frequency and low frequency β bands in some of the data, so I decided to further examine the separation of the 2 bands to further understand the activity in the β band as it related to CB-iTBS and motor adaptation. We found that the increase in β -ERD in A-iTBS observed in the entire frequency range was largely driven by the activity in the high frequency beta band. The A-iTBS high frequency β band showed an overall increase in β -ERD in both the early and late training measures. The low β frequency band did not show any between group differences or any differences between early and late training.

High β is thought to be involved in attentional processes, top-down control of visuomotor processing, and anticipation of task related cues. Greater power in the high β frequencies is associated with maintenance of 'ready' posture and faster reaction times (Saleh et al., 2010; Chandrasekaran et al., 2019, Zheng et al., 2008). This supports the theory that the substantial

divergence at late training in the high β band could be due to individual differences in attention, motivation, or strategy. This also is supported by the presence of anticipatory neurons in PMd (Crammond and Kalaska, 1996; Hoshi and Tanji 2006), a region which generates high β band activity and substantially contributes to the β band measures at the FC3 electrode. These results do not help us to understand the role of β band activity in the model updating, movement planning regard, but provides some insight into other processes. Low β is more prevalent in the deeper laminar structures and is notably present in the BG (Brown, 2003; Chandrasekaran et al., 2019). Greater power in low β , in the BG-cortical loop, is thought to be “anti-kinetic” (Brown, 2006) in keeping with the theory that β band activity maintains a steady state (Engel & Fries, 2010).

It is not surprising that the low β band did not show any changes, in early training, since low β hasn't been associated with motor adaptation processes. In fact, about 25% of participants did not even exhibit β -ERD in the low β -ERD_{pre} measure at all. This may be because the low β band activity is not a prominent contributor to the movement planning period and would only be involved in the release of inhibitory control during the generation of the motor command and movement execution. It is possible the CB-iTBS would have impacted activity in the BG through CB-BG-Cortical connections that were not detected in the EEG recordings because the surface electrode recordings are not sensitive enough to detect the changes in activity occurring in the BG. If there was a change in low β it likely would have been in late training since the BG is more involved in the processes which are prominent in late learning stages (Dhawale et al., 2021).

Although both an increase in adaptation rate and an increase in β -ERD were observed in A-iTBS, the results from the AE and β -ERD analysis do not support the hypothesis that β -ERD in the planning period directly relates to error reduction. Therefore, our assumption that the CB

affects error reduction, observed in adaptation, by influencing the magnitude of β -ERD in the PMC during the movement planning, is also not supported. It is not clear how the CB affects the rate of adaptation or whether there is a behavioural significance of the changes in β -ERD magnitude.

6.4 Amount learned and retained

The fourth objective was to determine whether CB-iTBS would influence either the amount of the skill acquired or the amount of the skill that would be retained when tested again the following day. I hypothesized A-iTBS would show both a greater amount of learning and retention of the motor task compared to S-iTBS. Contrary to this hypothesis, there was no difference between groups in the amount of the skill learned or retained. The significant group by time interaction was driven by a difference in residual error between the learned and retained timepoints in A-iTBS; however, this effect occurring exclusively in the active group is primarily due to a wide amount of variability in S-iTBS at the retained timepoint. It is unclear why the variability in S-iTBS was so large and is challenging to draw any conclusions about the practical meaning behind the interaction.

The lack of difference between groups in the amount retained is likely because the length of training time was too long to discern whether the CB-iTBS would have affected the retention of the learned rotation. In the current study design, about 75-80% of the training time was spent training after a plateau in AE had been reached, so the difference between groups in the amount of time spent training after plateau was not substantial enough to influence the amount of skill that could be retained, if a difference would have existed. This may have been assessed by reducing the amount of time spent training, which would have benefitted those who adapted quicker and plateaued earlier, therefore spending more time in the later stages of learning which

primarily contributes to consolidation of the skill. Given that both groups plateaued at a similar AE, we likely would not have seen a difference between A- and S-iTBS in amount of the skill acquired unless training had concluded prior to all groups reaching a plateau.

6.5 Supplementary data

There was no difference between groups in sleep quality or total sleep time, the TOD tested, participants' sex, handedness, or age. We can conclude that none of these factors would have been the driver of any difference or lack of difference, between groups on the adaptation rate, amount of learning, or consolidation of the learned rotation.

Response time was a supplemental measure of behavioural performance. There was a significant difference in response time between the early and late timepoint in both groups. The lack of difference between groups suggests that CB-iTBS did not impact the response times. However, it is likely that the early time point was not the most indicative of any potential differences in RT between groups, related to the confidence of the motor plan. RT may have differed when there was a divergence in the magnitude of AE, during adaptation.

7. Limitations

The 750ms planning window allowed us to measure motor planning separate from the generation of the motor command and movement, however it also provided opportunity for participants to employ extrinsic or explicit movement strategies. The goal was for the task to evoke implicit adaptation, and to measure activity in the CB-PMd connections that are involved in implicit adaptation. We did not include any analyses to distinguish between the implicit and explicit learning processes and therefore are unable to attribute the cortical activity measures to one process or the other.

Missing trials means we missed some data that was involved in the adaptation process, especially because a majority of mistrials happened during the first block. The mistrials from participant error happened because participants did not move in the 750ms time window or moved before they were cued to do so. This could be fixed in the future by enabling the event code for the onset of movement to occur prior to the cue to move, by altering the task so the cursor does not always start in the same location, or by having the target and cursor appear at the same time.

There are changes in β activity over the course of training that were not captured in the analysis. The β -ERD analysis only used the initial and final 8 trials in training the adaptation and late learning β -ERD measures respectively. There may be other changes in β -ERD happening during adaptation window or in later stages of learning that might provide insight into the relationship between β band activity and motor learning which were not included in the analysis. This could be examined in the future, using the current dataset.

8. Future Directions and Conclusions

Further analyses using data from this study should examine other measures of the movement preparation and sensorimotor integration and seek to understand how each of these measures is affected by CB-iTBS. One measure is β activity in the immediate pre-movement period, which would reflect the cortical activity related to the generation of the motor command. Another measure to explore is the amplitude of the movement related potential (MRP), a slow negative potential reflective of excitability in the motor cortex during movement planning and preparation leading up to movement execution. The MRP amplitude is another way to measure learning (Smith & Staines, 2006) and in externally cued movements is largely generated by activity in the PMC (Smith & Staines, 2012). The MRP would be another way to measure activity in the PMC during movement planning and preparation. The post-movement β event related synchronization which is a measure of error feedback and sensory integration (Tan et al., 2014; 2016; Torrecillos et al., 2015) would contribute to the understanding of how error informs movement planning and adaptation. Finally, alpha band activity prior to and following the movement, during adaptation and in later stages of learning, would provide insight into the sensory gating and cognitive control (Pollok et al., 2014). Alpha activity is also another process to explore to better understand how the CB affects sensorimotor cortical activity during adaptation.

In the future, it would be useful to discern the relationship between the CB influence over the inhibitory activity in the PMC and if and how it relates to error reduction. This could be done by using different combinations of tasks which require different strategies or have different parameters and using measures like paired pulse TMS or neuroimaging techniques. Gaining a better understanding into how these regions communicate to promote motor adaptation and

learning would help to be able to assess where deficits are occurring in individuals with neurological disease or damage and to provide targeted rehabilitation.

The main findings from this study are that CB-iTBS improved the rate of adaptation and increased pre-movement β -ERD in the PMC. These findings may be useful for neurorehabilitation and sport or technical training applications because they show that enhancing activity in the posterolateral CB can enhance the rate of skill acquisition and increase excitability through a release of inhibition in the motor cortex.

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Appendix

Table 1: Participant characteristics

Participant number	Group	Age	Sex	Handedness	Visit #1 Time of Day
1	Active	24	F	R	AM
2	Active	25	M	R	AFT
3	Sham	27	F	R	AM
4	Active	22	F	R	AFT
5	Active	24	F	R	AM
6	Sham	23	F	R	AFT
7	Sham	24	M	R	AM
8	Active	25	M	R	AFT
9	Sham	21	F	R	AM
10	Sham	23	F	R	PM
11	Active	21	F	R	PM
12	Active	18	M	L	PM
13	Sham	20	M	R	PM
14	Sham	23	F	R	AFT
15	Active	22	M	R	AM
16	Active	25	M	R	AFT
17	Sham	20	F	R	AFT
18	Active	22	M	R	AFT
19	Sham	22	M	L	AFT
20	Active	23	F	R	AFT
21	Sham	21	M	L	AM
22	Active	23	M	R	AFT
23	Sham	27	M	L	AFT
24	Active	19	F	R	AFT
25	Sham	20	F	R	AFT
26	Active	20	M	R	AFT
27	Sham	18	F	L	AFT
28	Active	24	M	R	AM
29	Sham	18	M	R	PM
30	Sham	21	F	R	PM
31	Sham	21	F	R	AFT
32	Active	23	F	R	AFT
33	Sham	18	F	R	AFT
34	Active	22	F	L	AM

Table 2: Trials eliminated

Participant number	Group	Mis-trials	% of total trials	Outliers	% of total trials	Total Eliminated	% of total trials
1	Active	49	9%	25	4%	74	13%
2	Active	33	6%	18	3%	51	9%
3	Sham	20	4%	17	3%	37	7%
4	Active	22	4%	19	3%	41	7%
5	Active	10	2%	17	3%	27	5%
6	Sham	93	17%	6	1%	99	18%
7	Sham	13	2%	16	3%	29	5%
8	Active	100	18%	4	1%	104	19%
9	Sham	136	24%	9	2%	145	26%
10	Sham	91	16%	14	3%	105	19%
11	Active	137	24%	9	2%	146	26%
12	Active	73	13%	16	3%	89	16%
13	Sham	71	13%	10	2%	81	14%
14	Sham	11	2%	10	2%	21	4%
15	Active	97	17%	8	1%	105	19%
16	Active	57	10%	15	3%	72	13%
17	Sham	26	5%	14	3%	40	7%
18	Active	49	9%	10	2%	59	11%
19	Sham	104	19%	9	2%	113	20%
20	Active	39	7%	11	2%	50	9%
21	Sham	47	8%	14	3%	61	11%
22	Active	29	5%	13	2%	42	8%
23	Sham	146	26%	6	1%	152	27%
24	Active	56	10%	13	2%	69	12%
25	Sham	39	7%	15	3%	54	10%
26	Active	131	23%	6	1%	137	24%
27	Sham	98	18%	8	1%	106	19%
28	Active	53	9%	16	3%	69	12%
29	Sham	31	6%	25	4%	56	10%
30	Sham	56	10%	14	3%	70	13%
31	Sham	92	16%	5	1%	97	17%
32	Active	11	2%	18	3%	29	5%
33	Sham	67	12%	9	2%	76	14%
34	Active	2	0%	13	2%	15	3%
Average		61	11%	13	2%	74	13%