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INVESTIGATING THE EFFECTS OF TRANSCRANIAL DIRECT CURRENT STIMULATION ON UPPER-LIMB SENSORIMOTOR ADAPTATION

by

MATTHEW CHRISTOPHER WEIGHTMAN

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Abstract

Due to its capacity to modulate neural excitability and induce plasticity in the motor system, transcranial direct current stimulation (TDCS) has become a popular research tool, with hope for clinical translation. As a result, over the last two decades there has been a rapid rise in studies utilising the technique, with many positive findings in basic research and rehabilitation settings. However, of late there have been a growing number of studies reporting null or conflicting findings, casting doubt over the potential use of TDCS for real-world therapeutic application. This thesis aimed to draw on mechanistic theories of TDCS action to investigate ways in which stimulation can be applied more effectively to modulate behaviour.

Results show that anodal TDCS targeted at the cerebellum or primary motor cortex (M1) can selectively improve motor adaptation of the proximal and distal upper limb respectively, which is dependent on the level of control exerted by the stimulated regions over fractionated hand and finger or whole arm reaching movements. This double-dissociated finding was extended using cathodal stimulation, where cerebellar stimulation inhibited adaptive performance of reach behaviour. Paradoxically, adaptation dexterous hand movements were also enhanced by cathodal cerebellar TDCS, highlighting how the connectivity of brain regions can affect stimulation results. Further results suggest that the timing of stimulation can also be important. When short epochs of TDCS were applied coincidentally with movements during an adaptation task, only movements performed during simultaneous stimulation were enhanced, with similar interleaved movements unaffected. Finally, and after a shift in focus due to circumstances relating to the COVID-19 pandemic, findings suggest that prolonged motor preparation periods are insufficient to reliably achieve complete compensation during motor adaptation tasks, with residual errors present at different magnitudes of cursor rotation.

Collectively, these results highlight how different stimulation protocols can affect

behavioural outcomes. They particularly underscore the importance of considering functional and anatomical factors associated with the stimulated regions when targeting different neural substrates, as well as canonical theories associated with the behaviour under investigation. Finally, the results presented here provide support for the continued development of TDCS research, with the hope it can help contribute to meaningful advances in the field and increase overall knowledge of the brain function.

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List of Abbreviations

AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid
AMPAR	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid Receptor
AUC	Area Under the Curve
BF	Bayes Factor
CBI	Cerebello-Brain Inhibition
CCW	Counter-Clockwise
CI	Confidence Interval
CM	Corticomotoneuronal
CNS	Central Nervous System
CW	Clockwise
DBS	Deep Brain Stimulation
DCS	Direct Current Stimulation
DLPFC	Dorsolateral Prefrontal Cortex
EEG	Electroencephalography
EMG	Electromyography
FC	Force Compensation
fMRI	Functional Magnetic Resonance Imaging
GABA	γ-aminobutyric acid
HD-TDCS	High-Definition Transcranial Direct Current Stimulation
JTHFT	Jebsen-Taylor Hand Function Test
LD	Lateral Deviation
LTD	Long-Term Depression
LTP	Long-Term Potentiation
M1	Primary Motor Cortex
MEP	Motor Evoked Potential
MRS	Magnetic Resonance Spectroscopy

NIBS	Non-Invasive Brain Stimulation
NMDA	N-Methyl-D-Aspartic Acid
NMDAR	N Methyl-D-Aspartate Receptor
PAS	Paired Associative Stimulation
PD	Parkinson's Disease
PPC	Posterior Parietal Cortex
SD	Standard Deviation
SE	Standard Error
TACS	Transcranial Alternating Current Stimulation
TDCS	Transcranial Direct Current Stimulation
TES	Transcranial Electrical Stimulation
TFUS	Transcranial Focused Ultrasound Stimulation
TMS	Transcranial Magnetic Stimulation
TRNS	Transcranial Random Noise Stimulation
VAS	Visual Analogue Scale
VGCC	Voltage-Gated Calcium Channel

Chapter 1

General Introduction

1.1 A brief history of electrical brain stimulation

Stimulating the brain with electrical currents predates our understanding of electricity. Dating back to the Roman Empire, there are records for the use of the electrical properties of the torpedo fish to treat headaches (Sarmiento, San-Juan, & Prasath, 2016). Centuries later, the invention of the 'Voltaic pile' (an initial version of the modern battery) gave way for the development of electrical brain stimulation devices and allowed for greater exploration of the role of electricity in human and animal physiology (Clarke & Jacyna, 1987). In fact, the earliest uses of electrical forms of stimulation brought about many important discoveries in basic physiology; such as the electrical properties of muscle and nerve function, led by the pioneering work of Luigi Gavlvani (Glickstein, 2014). In less controlled attempts during the mid 19th century, electrical brain stimulation techniques - known then as electrotherapy - were being used to treat a plethora of different psychiatric disorders, with many reported positive outcomes (Steinberg, 2013). However, the lack of measuring and disclosing of stimulation parameters and patient diagnoses made interpreting and reproducing results difficult, perhaps leading to stalled further development. Animal studies reignited interest in electrical brain stimulation, when polarising currents were shown to produce direct and longer-lasting alterations to neural excitability and chemistry (Morrell, 1961; Bindman, Lippold, & Redfearn, 1962; Creutzfeldt, Fromm, & Kapp, 1962; Bindman, Lippold, & Redfearn, 1964; Purpura & McMurtry, 1965; Hayashi, Hattori, Moriwaki, Asaki, & Hori, 1988; Moriwaki, 1991; Islam, Aftabuddin, Moriwaki, Hattori, & Hori, 1995). However, it wasn't until the turn of the 21st century that the canonical form of human direct current application used today was born. In a series of seminal studies, it was shown that weak direct electrical currents applied to the human motor cortex can cause polarity-dependent alterations in neural excitability (Priori, Berardelli, Rona, Accornero, & Manfredi, 1998; Nitsche & Paulus, 2000, 2001; Nitsche, Nitsche, et al., 2003). As a result, a number of reliable stimulation parameter guidelines became readily available and allowed for an exponential growth in research

activity.

As it stands today, the field of brain stimulation has developed and branched into many forms of invasive and non-invasive techniques, all with the ultimate goal of modulating the activity or function of the nervous system (Gebodh et al., 2019). Non-invasive techniques of brain stimulation (or NIBS), most commonly use electrodes or other apparatus placed externally (e.g., on the scalp/head) to pass electrical currents or magnetic pulses to the targeted regions of the central nervous system (CNS) beneath them. Whereas, invasive methods that are used for clinical brain stimulation require surgery to implant stimulating electrodes within certain parts of the brain. Prevailing techniques of NIBS include: Transcranial direct current stimulation (TDCS); transcranial alternating current stimulation (TACS); transcranial random noise stimulation (TRNS); transcranial magnetic stimulation (TMS) and the relatively new transcranial focused ultrasound stimulation (TFUS), with perhaps the most notable method for invasive stimulation being deep brain stimulation (DBS). The desired target of brain stimulation and thus the effect it has on CNS function varies greatly depending on which stimulation technique is used, the individual methodological parameters and the anatomy of the subject receiving stimulation.

1.2 Transcranial direct current stimulation (TDCS)

TDCS (along with TMS) is perhaps the most common form of NIBS used to alter brain activity in neuroscience research today. The amount of research papers using the technique has skyrocketed from just 2 in 2000 to 972 in 2020 (PubMed search: 'Transcranial direct current stimulation'). In its modern form, TDCS passes a weak direct electrical current through the scull from electrodes placed on the scalp and, via subthreshold alterations of neuronal membrane potentials, modulates neural excitability and spontaneous brain activity (Nitsche & Paulus, 2000). Depending on the placement of the electrodes, and thus the current flow, TDCS can cause both increases

and diminutions in neural excitability of the targeted brain region. In simplicity: anodal stimulation (increase), cathodal stimulation (decrease). Unlike TMS, which uses magnetic coils to generate electrical currents in the brain (directly generating action potentials), TDCS cannot directly induce resting neuronal discharge.

1.2.1 Waveform

TDCS differs from other forms of transcranial electrical stimulation (TES), e.g., TACS, TRNS etc. and neuromodulatory techniques by the type of waveform it delivers to the brain. As in the name, TDCS delivers a sustained, continual direct current to the brain, which is usually ramped up and down over set intervals (Figure 1.1). It is likely that the development and growth in TDCS use within neuroscience research is attributable to the simplicity of waveform delivered (Gebodh et al., 2019). By contrast, TACS, which passes oscillating electrical activity through the skull, typically uses a sinusoidal waveform (Antal & Paulus, 2013), with TRNS delivering current at random oscillating frequencies (Terney, Chaieb, Moliadze, Antal, & Paulus, 2008).

1.2.2 Electrodes

As mentioned previously, conventional TDCS is delivered via two electrodes placed on the scalp (an anode and cathode, Figure 1.1). The anode represents the positively charged terminal and the cathode a negatively charged one (Nitsche et al., 2008). To say that the anode increases excitability, whereas the cathode decreases it is an oversimplification; as all current that enters the brain must exit thereafter. Current passes from the anodal electrode, through intermediary neural substrates and exits at the location of the cathodal electrode (Bikson, Rahman, & Datta, 2012; Bikson, Paulus, Esmaeilpour, Kronberg, & Nitsche, 2019), creating surface-positive and surface-negative potentials. In addition, individual gross brain-morphology, tissue, fluid and other brain structures all affect the flow of current between the electrodes

(Miranda, Lomarev, & Hallett, 2006; Bikson, Datta, Rahman, & Scaturro, 2010). Traditionally, conductive rubber electrodes (size = 5 x 5cm^2 or 5 x 7cm^2) are positioned at different locations on the scalp/head in order to direct maximal current towards the desired neural target (Khadka, Woods, & Bikson, 2019). The size of these stimulating electrodes comes at a cost of focality, with studies showing that the induced electric fields are large and not always focussed onto the region of interest (Nathan, Sinha, Gordon, Lesser, & Thakor, 1993; Nitsche et al., 2007; Datta et al., 2009). Saline soaked sponges or conductive gels are used to maintain contact with the skin and allow transference of ions, whilst preventing direct contact between the electrode and subject (Palm et al., 2014; Solomons & Shanmugasundaram, 2020). Once electrodes are placed in the desired montage they must be affixed to the head by adhesive straps or electrode caps to ensure consistent current delivery and minimise movement (Woods et al., 2016).

High-definition TDCS (HD-TDCS)

Given the low focality of 'conventional' TDCS electrode parameters, new methods seeking to improve the spatial distribution of current, have been developed. High-definition TDCS (HD-TDCS) uses an array of smaller stimulating electrodes, with a 4x1-ring configuration being particularly popular (see Villamar et al., 2013). Research has shown that these high-definition electrode montages successfully modulate a narrower region of the brain (Datta et al., 2009; H.-I. Kuo et al., 2013).

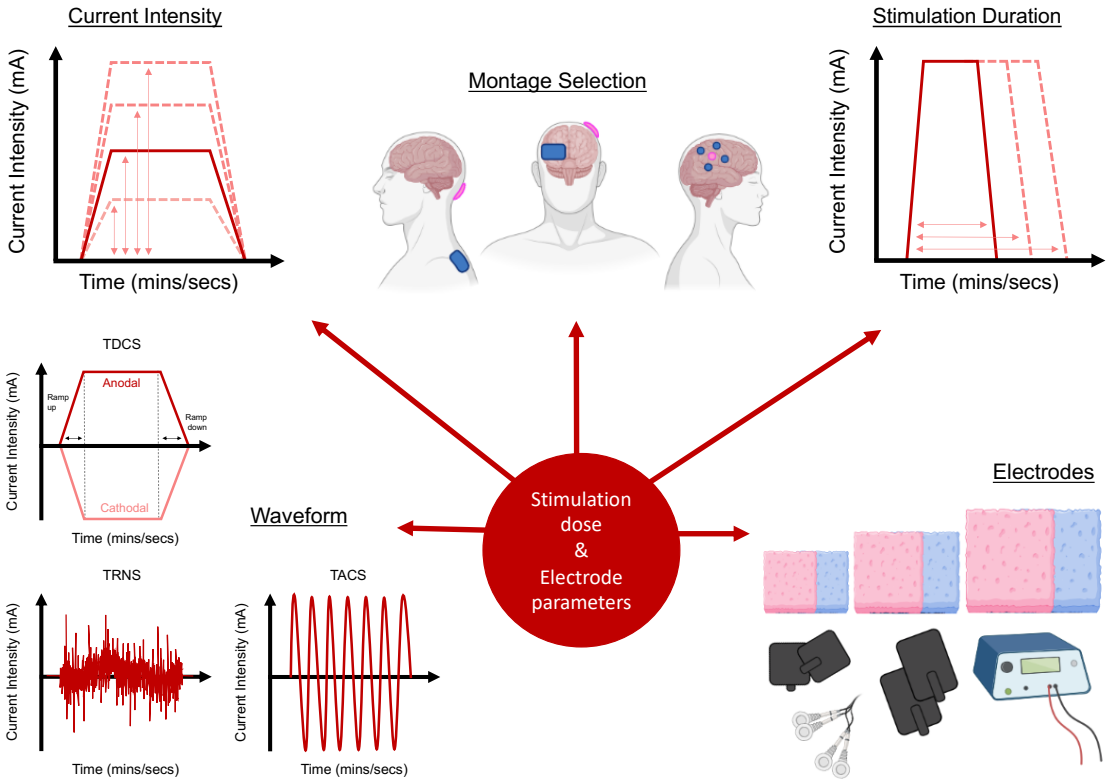


Figure 1.1: *An outline of the different TDCS parameters available, including: a comparison of the various TES waveforms; the variation of current intensities used; popular electrode montages used to modulate cortical excitability; considerations of the duration of direct current application and the different types of electrodes used for TDCS (adapted from Gebodh et al., 2019).*

1.2.3 Intensity and dose

A further consideration of TDCS application is the current intensity and duration of stimulation used (Figure 1.1). In terms of human studies, Nitsche and Paulus, (2000) displayed short term modulation of the primary motor cortex (M1) excitability after just 4 seconds of anodal TDCS. The application of TDCS ranging between 5-15 minutes has shown to alter neural excitability in a polarity specific manner and produce long lasting after effects for up to 1 hour post-stimulation (Nitsche & Paulus, 2000, 2001; Nitsche, Nitsche, et al., 2003). Increasing the stimulation duration is not necessarily related to

an increase in excitability or after effect (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013), as long stimulation protocols have been associated with a reversal of polarity effects (Hassanzahraee, Nitsche, Zoghi, & Jaberzadeh, 2020a).

With regards to stimulation intensity, it is widely accepted that increasing the applied direct current (milliampere (mA)) will increase the electric field/current density (volt per meter (V/m)) in the brain (Bikson et al., 2015), however, the brain's response to this increased electric field is less well understood. *In vitro* work from Bikson and colleagues (2004) using rat hippocampal slices, showed a generally linear relationship between electric field generation and membrane polarisation, which only uncoupled at very high intensities. Overall, the intensities used in this study were far higher than those appropriate for human research (above 10 mA) and thus difficult to relate to human TDCS intensity-dose relationships. Traditionally, an intensity of 1/2 mA is used in human TDCS research, which is believed to induce electric fields between ∼0.4-1.0 V/m. Although evidence is mixed, most studies report a non-linear relationship between current intensity and excitability/plastic effects (Jamil et al., 2017; Esmaeilpour et al., 2018; Agboada, Samani, Jamil, Kuo, & Nitsche, 2019; Hassanzahraee, Nitsche, Zoghi, & Jaberzadeh, 2020b), with some reporting reductions or a reversal of neural modulations. These studies investigating stimulation dose highlight the importance of an evidence-based approach to TDCS methodologies, when designing future research (Evans et al., 2020).

1.3 TDCS mechanisms of action

The mechanisms surrounding how direct currents induce short-term (acute) effects on resting membrane potential and neuronal firing rates/excitability are reasonably well documented and understood. Yet, a detailed understanding of how these alterations in neuronal excitability translate into reported long-lasting plastic effects (Bindman et al., 1962) is less clear, with theories surrounding how behavioural/cognitive changes are

induced even more lacking.

1.3.1 Acute effects

As discussed in the previous section, TDCS aims to modulate neuronal excitability via alterations of resting membrane potentials, thus shifting the probability of incoming activity generating a new action potential either closer or further from threshold (depending on the polarity of stimulation applied over the brain region of interest). These effects have been found in numerous human and animal studies (Creutzfeldt et al., 1962; Bindman et al., 1964; Nitsche & Paulus, 2000, 2001), even after very brief periods of stimulation. Neurochemical evidence supports a membrane potential mechanism for acute TDCS effects. Blocking calcium (Ca^{2+}) and sodium channels - key for membrane polarisation - resulted in an elimination of any neuronal excitability modulations induced by short-lasting anodal stimulation (Nitsche, Fricke, et al., 2003). In contrast, N-methyl-D-aspartate (NMDA) receptor antagonist, known to be involved in long-term potentiation (LTP) and depression (LTD)-type plasticity (Bennett, 2000; Malenka & Bear, 2004), had no effect on acute excitability changes post anodal TDCS, suggesting direct current alterations are not driven by changes in synaptic efficacy.

1.3.2 Long-lasting effects

The longer lasting after-effects induced by TDCS are thought to require prolonged stimulation periods - tens of minutes, as opposed to the few seconds required to cause acute effects (Nitsche & Paulus, 2000, 2001; Nitsche, Nitsche, et al., 2003). After-effects have been shown to last from minutes to days after TDCS application, depending of the specific stimulation protocol used (Nitsche & Paulus, 2000, 2001; Nitsche, Nitsche, et al., 2003; Jamil et al., 2017; Monte-Silva, Kuo, Liebetanz, Paulus, & Nitsche, 2010). Bindman and colleagues (1964) were one of the first to demonstrate these long-lasting effects in animals. They found polarity-dependent dependent effects

on evoked potentials and spontaneous activity in the rat sensorimotor cortex, which were still present 5 hours after direct current was applied. These effects have been widely speculated to be dependent on LTP/LTD-like synaptic changes, driven by protein synthesis (Gartside, 1968; Fritsch et al., 2010; Stagg, Antal, & Nitsche, 2018).

It is proposed that neuroplastic effects induced by TDCS are somewhat driven by activity at glutamatergic synapses (Figure 1.2). In contrast to acute effects, NMDA receptor antagonist dextromethorphane abolished long-lasting modulations in neural excitability after both anodal and cathodal stimulation (Nitsche, Fricke, et al., 2003). Further work from Nitsche et al. (2004) supported this view as D-Cyloserine, a partial NMDA agonist, potentiated the increases in motor cortical excitability associated with TDCS. Studies using magnetic resonance spectroscopy (MRS) have also reported some relatively reliable polarity-dependent changes in glutamate and γ-aminobutyric acid (GABA), and it is suggested that these alterations may regulate the plastic effects following TDCS application (Stagg et al., 2009; Clark, Coffman, Trumbo, & Gasparovic, 2011; Stagg et al., 2018). With current knowledge, the prevailing theory is that increased neuronal excitability activates NMDA receptors and leads to an influx of intacellular Ca^{2+}. The amount of Ca^{2+} influx mediates the modulatory effect (strengthening or weakening) via inserting or removing glutamatergic AMPA receptors (AMPAR) from the membrane. High levels of Ca^{2+}, likely induces LTP-like plasticity and low levels results in LTD (Stagg et al., 2018; Figure. 1.2). It is also suggested that there are Ca^{2+} concentrations where no plasticity is induced, which highlights the importance of the state of the system being modulated by TDCS and also may explain the non-linear dose-response of stimulation.

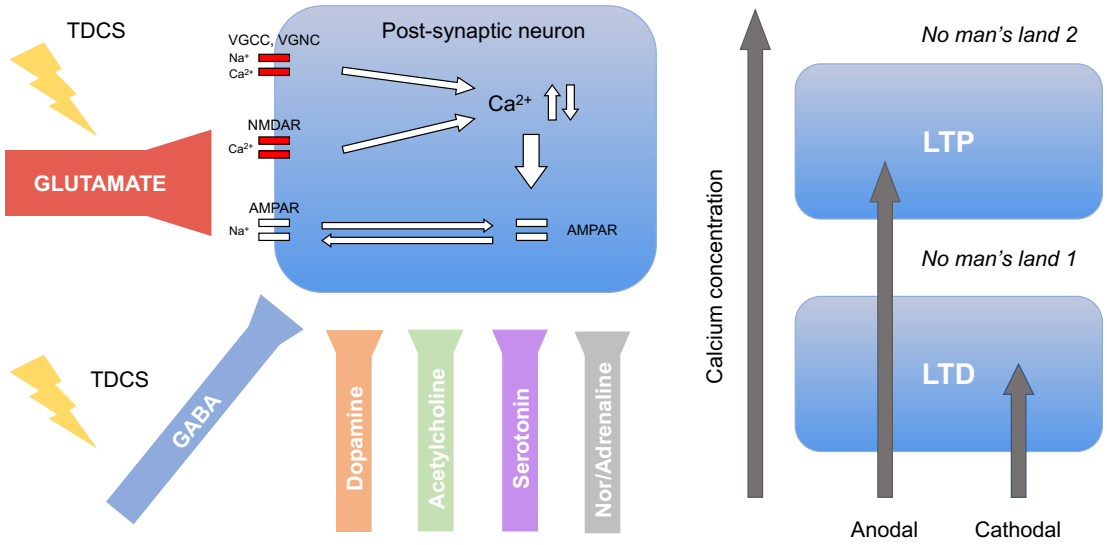


Figure 1.2: *The proposed mechanism of TDCS-based neuroplastic effects (modified from Stagg et al., 2018). (Left) It is presumed that TDCS induces plasticity at glutamatergic synapses via intracellular Ca^{2+} concentration, which is mediated by GABA reductions. TDCS acts to increase or decrease intracelluar Ca^{2+} flux via voltage-gated Ca^{2+} channels (VGCC) and NMDA receptors (NMDAR). The concentration of intraneuronal Ca^{2+} determines the insertion/removal of AMPA receptors (AMPAR) and regulates the extent of synaptic plasticity. Dopamine, acetylcholine, serotonin, nor/adrenaline etc. are also likely to impact on TDCS effects. (Right) The induced plastic effects of TDCS depend of the concentration of Ca^{2+} in the post-synaptic neuron. High Ca^{2+} influx as a result of anodal TDCS induces LTP and it is assumed that low Ca^{2+} concentration post cathodal TDCS results in LTD. There are also however, Ca^{2+} concentrations where no plasticity is induced.*

1.3.3 Cerebellar TDCS

The mechanisms discussed thus far have all been constrained to studies investigating the effects of direct currents on the cortex (primarily M1). Given the vastly different anatomy and function of the cerebellum it cannot simply be assumed that the application of direct currents will affect it in the same way as cortical structures. Early work in animal models, investigating the effects of direct currents on the cerebellum, demonstrated that the cerebellum is in fact highly susceptive to external polarisation (Mollica, Moruzzi, & Naquet, 1953a, 1953b, 1953c). Further research from Joynt (1958) displayed polarity-dependent effects on Purkinje cell firing rate (the sole output neurons of the cerebellum), whereby an anodal current increased spontaneous activity, which could be silenced by reversing the direction of current flow. Similar relationships were also identified by Brookhart and Blachly, (1952) and Granit and Phillips, (1957), with the reliability of effects dependent on electrode positioning due to the highly folded structure of the cerebellar cortex.

More recent work in humans revealed that the cerebellum is susceptible to modulations from both TDCS and TMS (Ugawa et al., 1991; Ugawa, Uesaka, Terao, Hanajima, & Kanazawa, 1995; Werhahn, Taylor, Ridding, Meyer, & Rothwell, 1996). Stimulation applied to the cerebellum has been assessed indirectly by means of its influence on M1. Purkinje cells project from the cerebellar cortex to the dentate nucleus (the largest deep cerebellar nuclei) via inhibitory connections, which then connect - via the thalamus - to M1 through disynaptic excitatory pathways. These connections form the cerebello-thalamo-cortical pathway (Allen & Tsukahara, 1974; Kelly & Strick, 2003; Daskalakis et al., 2004) and at rest it is suggested the cerebellum exerts an overall inhibitory tone over M1 (termed cerebello-brain inhibition (CBI)). Measuring motor evoked potentials (MEPs) after a conditioning TMS pulse over the cerebellum, followed by a test pulse over M1 will indicate the extent of CBI. Thus, modulations to cerebellar excitability via TDCS can be probed using cerebellar-M1 connectivity. In 2009, Galea et al. demonstrated that - in a similar way to the cortex -

the cerebellum can also be modulated in a polarity-specific manner. They showed that cerebellar anodal TDCS increased the inhibitory tone exerted over M1, whereas cathodal stimulation decreased it.

It is believed that the acute effects of cerebellar TDCS are induced via the polarisation of Purkinje cells and therefore modulating the activity of the deep cerebellar nuclei (Galea et al., 2009; Grimaldi et al., 2016; Zhang, Hancock, & Santaniello, 2021). As with cortical stimulation, the types of cells affected by TDCS is dependent on the electrode montage and orientation of the resultant electric field (Chan & Nicholson, 1986). Although there is little research investigating the effects of cerebellar TDCS on neurotransmitter levels, with what does exist displaying mixed results (Jalali, Chowdhury, Wilson, Miall, & Galea, 2018), it is plausible to suggest that changes in neurotransmitter levels e.g., glutamate or GABA may mediate longer lasting TDCS effects. Additionally, it has been suggested that mechanisms such as; alterations in ionic gradients, receptor transportation and the activation or inactivation of gene expression and protein synthesis could also contribute to cerebellar TDCS after-effects (Grimaldi et al., 2016).

1.3.4 Theories of behavioural effects

A pivotal question remaining in the field of TDCS mechanisms is: how does the application of weak direct currents, which only produce small electric fields in the brain, modulate complex aspects of motor and cognitive functions? Relatively recently, a number of models have been proposed to help explain how TDCS affects complex behaviour, with an integration of these theories likely the most optimal tool to understand observed effects.

One of the simpler theories, born from the influential work of Nitsche and colleagues (2000, 2001; 2003), suggests that behavioural changes induced by TDCS are directly related to membrane polarisation. In other words, depolarisation and the resultant increases in neural excitability resulting from anodal TDCS, will facilitate

behaviour. Whereas, cathodal TDCS induced hyperpolarisation and reduced excitability, will cause behavioural detriments. This model has been termed the 'Stimulation dependent' (Fertonani & Miniussi, 2017) or the 'Sliding-scale' model (Bikson & Rahman, 2013) and is dependent on which brain region is targeted by stimulation. This model (anodal-excitation/cathodal-inhibition) can be further extended to the neurotransmitter level, where it is proposed that polarity-dependent shifts in excitatory and inhibitory neurotransmitter concentrations (glutamate and GABA respectively) can affect the degree or direction of behavioural changes observed during tasks (Stagg et al., 2009; Clark et al., 2011; Stagg, Bachtiar, & Johansen-Berg, 2011; B. Krause, Márquez-Ruiz, & Cohen Kadosh, 2013). Notwithstanding these studies, it has been suggested that MEPs (and thus neural excitability) are poor indicators of behaviour change (McDonnell & Ridding, 2006; Ridding & Rothwell, 2007; Bestmann & Krakauer, 2015) and as stated above the relationship between TDCS-dose and excitability modulations is non-linear (Batsikadze et al., 2013). In addition, there are examples where stimulation polarity has caused an 'opposite' behavioural result (Pirulli, Fertonani, & Miniussi, 2014) and mixed evidence with regards to the relationship between neurotransmitter levels and learning extent (Jalali et al., 2018). Despite being a positive starting point, this model is likely inadequate to explain the complex behavioural results obtained to date.

The 'activity-selectivity' or 'activity-dependent' model is an improvement of the previous theory, as it takes into account the state of the brain region/circuit during the period of stimulation. This model suggests that TDCS acts to preferentially modulate neural circuits that are active or activated by task performance, whilst leaving other networks unaffected (Bikson & Rahman, 2013; Fertonani & Miniussi, 2017). Although electric fields generated by TDCS are insufficient to trigger action potentials and instead increase the probability of their occurrence (Purpura & McMurtry, 1965), active neural circuits may have heightened sensitivity to modulation as more of their neurons will be closer to discharge thresholds (Bikson & Rahman, 2013). It has been

suggested that TDCS alone cannot alter synaptic efficacy, however if paired with a behavioural task, it may act upon engaged 'task-related' synapses in order to boost Hebbian-like plasticity (Hebb, 1949; Kronberg, Bridi, Abel, Bikson, & Parra, 2017; Kronberg, Rahman, Sharma, Bikson, & Parra, 2020). In contrast, if TDCS is applied during rest, it is more likely to modulate resting-state networks, such as the default mode network (Li et al., 2019). This model inherently incorporates functional specificity as it suggests that the stimulated region and associated circuitry will only be potentiated if activated by endogenous task related activity. Conversely, inactive neighbouring regions - still within range of the electric field - will not be modulated (Bikson & Rahman, 2013). In support of this model, several studies have demonstrated modulated behaviour using TDCS depending of the neural activity generated by engagement in the task (Bortoletto, Pellicciari, Rodella, & Miniussi, 2015; Pisoni et al., 2018; Boroda, Sponheim, Fiecas, & Lim, 2020). However, further research combining TES and neuroimaging techniques are required to fully explore the circuit/network effects of stimulation on behaviour.

Additional models include 'input-selectivity' and 'stochastic resonance' (Bikson & Rahman, 2013; Fertonani & Miniussi, 2017). Input-selectivity describes a process whereby TDCS can switch a circuit or network from one state to another - enhancing one process at the cost of another. This model emphasises that the enhancement of one process may inhibit another, without suggesting that stimulation results in a zero-sum effect (Luber, 2014). There is some behavioural evidence for this model, which highlights that processing resources may be limited and thus must be redistributed to modulate performance (Iuculano & Kadosh, 2013). In this study, the authors applied TDCS to either the posterior parietal cortex (PPC) or dorsolateral prefrontal cortex (DLPFC) over 6 days during numerical learning tasks. They observed a double dissociation of stimulation effects: stimulation applied to the PPC enhanced numerical learning but impaired automaticity of the learned material, whereas TDCS over DLPFC compromised learning but facilitated automaticity of the learned material. These

results suggest that the facilitation of certain cognitive functions may come at a cost of others during TDCS application. The stochastic resonance model posits that as direct currents are not focal and thus affect many different neurons, the produced electric field will be considered as noise by the brain (Fertonani & Miniussi, 2017). This model references work suggesting that noise added to a nonlinear system can modulate the performance of that system by altering the signal-to-noise ratio (McDonnell & Ward, 2011). It is suggested that the addition of noise can facilitate or inhibit performance dependent on the level of noise inserted and the ongoing activity of the networks affected (similar to activity-selectivity). The stochastic resonance model may shed some light on the inconsistent results observed using TDCS, as too much or too little noise may be detrimental or have negligible effects on behaviour (De Berker, Bikson, & Bestmann, 2013; Miniussi, Harris, & Ruzzoli, 2013; Fertonani & Miniussi, 2017).

Each of the models presented here have merit and sound rationale regarding the effects of TDCS on motor/cognitive modulations. Given the complexity of brain function, the enhancement or inhibition of behaviour elicited by TDCS is probably best described by a combination of these theories. The stimulation protocol, parameters used and task being performed will all likely influence the interpretation of results. That being said, there are still missing links between physiology, computation and behaviour, which require further investigation in order to untangle the multifaceted reported effects (Bestmann, de Berker, & Bonaiuto, 2015).

1.4 Current applications of TDCS

Given that it is well tolerated, cheap, easy to apply, portable and capable of altering neural excitability and plasticity, TDCS has become a prominent tool in both experimental and rehabilitative research.

1.4.1 Psychiatry

Psychiatric disorders such as major depressive disorder, bipolar disorder, schizophrenia and obsessive compulsive disorder represent a leading cause of disability worldwide (Whiteford et al., 2013). Different structural and functional abnormalities have been identified as possible biomarkers of these disorders, including: cortical thinning, dopamine dysfunction, hippocampal dysfunction, disrupted connectivity, hyper/hypoactivity, as well as a reduced capacity for neural plasticity (Grimm et al., 2008; Howes et al., 2012; M.-F. Kuo, Paulus, & Nitsche, 2014; M.-F. Kuo, Chen, & Nitsche, 2017; Schmaal et al., 2017; Schobel et al., 2009). Given a large percentage of patients are resistant to traditional treatments, there has been a growing interest in the utilisation of TDCS as a potential therapy. Overall, TDCS has shown promise in the improvement of clinical symptoms of numerous psychiatric disorders (Brunelin et al., 2012; Brunoni & Palm, 2019; D'Urso et al., 2016; Loo et al., 2012), with stimulation parameters and protocol length cited as key determiners of efficacy (M.-F. Kuo et al., 2017).

1.4.2 Ageing

The world population is ageing; the life expectancy of a person born in 2019 is projected to be approximately seven years longer than a one born in 2000 (World Health Organization, 2021). With advancing age comes declines in sensorimotor and cognitive functions, which can affect the ability of older adults to carry out activities of daily living and thus impact on their independence (Seidler et al., 2010; Pascual-Leone et al., 2011). Typically, older adults suffer deficits in balance, gait and many other aspects of motor control (e.g., coordination, speed, variability etc.), in addition to cognitive declines such as working memory, attention and dual-tasking (Hasselkus & Shambes, 1975; Laughton et al., 2003; Ketcham & Stelmach, 2004; Gazzaley, Cooney, Rissman, & D'esposito, 2005; Hollman, Kovash, Kubik, & Linbo, 2007). Reductions in

gray and white matter underpin a lot of these age-related deficits, along with impaired Ca^{2+} mediated LTP/LTD induction (Burke & Barnes, 2006; Seidler et al., 2010). Given the excitability and plasticity modulating capacities of TDCS, it has gained traction as a potential adjunct therapy to ameliorate the declines in motor and cognitive control in older populations. Despite highlighting several caveats to the use of TDCS in ageing research, in a recent meta-analysis Summers and colleagues (2016) reported an overall beneficial effect of anodal TDCS on motor and cognitive functions in older adults. Previous research has displayed positive effects of TDCS in ageing populations on motor adaptation (Hardwick & Celnik, 2014; Panouillères, Joundi, Brittain, & Jenkinson, 2015; Weightman, Brittain, Punt, Miall, & Jenkinson, 2020), motor function (Hummel et al., 2010), working memory (Arciniega, Gözenman, Jones, Stephens, & Berryhill, 2018; Nissim et al., 2019) and attention (Brosnan et al., 2018). In spite of the promising results displayed thus far, there are still several considerations regarding how the structural, functional and connectivity related changes associated with increasing age influence TDCS-mediated effects e.g., current flow differences (Woods et al., 2019).

1.4.3 Stroke and other motor disorders

For some time now, there has been interest in the use of TDCS as a potential adjuvant neuromodulatory technique to enhance rehabilitation in a number of different neurological disorders/conditions. Stroke is the leading cause of long-term disability worldwide, with spontaneous recovery rates tending to plateau around 3-6 months. However, further functional improvements are still possible - even in chronic stroke - with specific rehabilitation. Therefore, TDCS has been indicated as a potential tool to enhance outcomes of existing rehabilitation protocols in both acute and chronic stroke sufferers. A large percentage of stroke research has focussed on countering the proposed interhemispheric imbalance model of stroke recovery (Murase, Duque, Mazzocchio, & Cohen, 2004), by attempting to increase the excitability of the inhibited

lesioned hemisphere and/or decrease that of the contralesional hemisphere. Stimulation combined with occupational/physical therapy has been shown to significantly increase functional motor outcomes compared to sham conditions (Lindenberg, Renga, Zhu, Nair, & Schlaug, 2010; Nair, Renga, Lindenberg, Zhu, & Schlaug, 2011). Recent research however, has called into question the validity of this model, suggesting that interhemispheric imbalance may actually underscore recovery in chronic stroke and found no evidence of abnormal interhemispheric inhibition in acute sufferers (Xu et al., 2019).

Many additional studies have found positive results of ipsilesional TDCS on motor outcomes post-stroke. Results suggest that anodal TDCS can be beneficial to performance in the Jebsen-Taylor hand function test (JTHFT) and other motor learning/functional tasks (Hummel et al., 2005; Boggio et al., 2007; D. Y. Kim, Ohn, Yang, Park, & Jung, 2009; Stagg et al., 2012; Allman et al., 2016; Pavlova, Semenov, & Guekht, 2020). Notwithstanding these results, there have been mixed results following meta-analyses on whether TDCS facilitates motor performance post-stroke. In their systematic review and meta-analysis Kang, Summers, and Cauraugh (2016) reported long-term beneficial effects of TDCS on motor training in both subacute and chronic stages of stroke, with a relatively large effect size. Whereas a separate analysis found very poor evidence to support the effectiveness of TDCS in improving motor outcomes and activities of daily living (Elsner, Kugler, Pohl, & Mehrholz, 2020). Therefore, despite some positive results, more larger scale randomised control trials are required to determine the efficacy of TDCS in stroke rehabilitation moving forward.

TDCS has also shown some promise as an adjunct therapy for various symptoms of Parkinson's Disease and cerebellar ataxias (Fregni et al., 2006; Valentino et al., 2014; Salimpour, Mari, & Shadmehr, 2015; Benussi et al., 2017, 2018; Maas, Helmich, & van de Warrenburg, 2019), however calls for higher powered, double-blinded studies have been made in order to establish overall effectiveness.

1.5 TDCS controversy

Although TDCS has been regarded as having great promise in both research and applied rehabilitation settings, the technique has attracted some recent criticism and thus scepticism regarding its efficacy and potential future applications (see review Filmer, Mattingley, and Dux, 2020). One of the major criticisms of TDCS is that the electric fields generated in the brain are insufficient to modulate neuronal function. In a series of experiments using both rodents and human cadavers, Vöröslakos et al. (2018) determined that the current intensities used in traditional TDCS studies (1-2mA) may not be high enough to produce electric fields capable of affecting neuronal circuits (> 1.0 V/m). The authors therefore suggested that indirect mechanisms may be responsible for the cognitive and behavioural effects described in previous TDCS studies. However, there a number of non-human primate studies, which refute these claims and have displayed both neurophysiological and behavioural effects with current densities around 0.4 V/m (Reato, Rahman, Bikson, & Parra, 2010; Kar, Duijnhouwer, & Krekelberg, 2017; M. R. Krause et al., 2017), suggesting that the intensities of TES used in human research are likely sufficient to induce the reported behavioural effects. These conflicting suggestions may also be reconciled by considering the numerous biochemical changes that occur after death (Opitz, Falchier, Linn, Milham, & Schroeder, 2017). Temperature differences between in vivo vs cadaver studies appears to be a critical variable. Cadavers are generally stored in colder environments which will significantly reduce the conductivity of tissues and the degree of this temperature change is non-uniform due to a lack of blood flow, further confounding results.

A further concern regarding TDCS use, is that some of the reported effects are small, inconsistent and are not always reliably modulated by stimulation. A lack of reproducible effects is certainly not a new phenomenon in neuroscience/psychology research and not one solely isolated to the field of TDCS. However, this does not preclude it from further scrutiny, in order to understand potential reasons and outline

technical improvements. A large degree of the 'replication crisis' in TDCS research may be attributed to underpowered studies (and thus exaggerated effect sizes), highly heterogeneous methodologies and anatomical differences among participants (J.-H. Kim et al., 2014; Minarik et al., 2016; Polania, Nitsche, & Ruff, 2018). In fact, the vast disparity in study methodology and purpose makes meta-analytic approaches to determine TDCS efficacy difficult (Nitsche, Bikson, & Bestmann, 2015). Despite this, attempted analyses have found strong support, mixed and negligible evidence for various TDCS effects (Horvath, Forte, & Carter, 2015b; Hill, Fitzgerald, & Hoy, 2016; Summers et al., 2016). Inter/intra-individual variability, within and between experiments, has also been a cause of contention regarding the reliability of TDCS effects (Ridding & Ziemann, 2010; Chew, Ho, & Loo, 2015; Li, Uehara, & Hanakawa, 2015; Filmer et al., 2020). Study design and individual differences in head and brain anatomy have been cited as potential confounds, with calls for more care to be taken when designing TDCS-based studies. Other participant-specific qualities e.g., ceiling and floor effects, relating to task performance, can also impact the replicability of TDCS results (Woods et al., 2016).

The lack of mechanistic understanding as to how TDCS exerts its effects on neural tissue and complex behaviours, has been deemed limiting to understanding present results and further development of the technique (Bestmann et al., 2015). However, as highlighted in a previous section, there are several emerging mechanistic theories which aim to shed light on TDCS-based effects. Rather than invalidating previous results, the current gaps in knowledge regarding TDCS mechanisms highlights an area for renewed investigation.

1.6 Sensorimotor adaptation

The ability of our sensorimotor system to recalibrate and adjust planned movements in response to changes in one's body or environment is essential for accurate and

successful motor performance. This phenomenon - termed sensorimotor adaptation - occurs frequently during our everyday lives, when for example, we experience injury or fatigue, or walk on an uneven or slippery surface. Sensorimotor adaptation is also evident when individuals switch between using and manipulating tools or objects of different shapes weights and sizes. In all of these instances, prior motor commands that would have resulted in successful performance now fall short and must be adapted in order to restore accuracy (for reviews, see Shadmehr, Smith, and Krakauer, 2010; Krakauer, Hadjiosif, Xu, Wong, and Haith, 2011).

In a laboratory setting, sensorimotor adaptation can be elicited using a number of different approaches, for example: prism glasses (Martin, Keating, Goodkin, Bastian, & Thach, 1996), visuomotor rotation tasks (Krakauer, Pine, Ghilardi, & Ghez, 2000), novel force-fields (Shadmehr & Mussa-Ivaldi, 1994) and split-belt treadmills (Reisman, Block, & Bastian, 2005). In these tasks - after an initial period of familiarisation - a visual displacement or dynamic (e.g., force) perturbation is imposed to movement/movement feedback, which induces errors in performance. Adapting movements in these perturbed environments involves the incremental updating of an internal (forward) model (Miall & Wolpert, 1996; Wolpert, Miall, & Kawato, 1998). This forward model predicts the consequences of ongoing motor commands and generates sensory prediction errors when there is a discrepancy between the predicted and actual state (Figure 1.3). Sensory prediction errors are then used to gradually re-calibrate the forward model so that it more closely represents the new dynamical environment and updated motor commands become increasingly accurate (Tseng, Diedrichsen, Krakauer, Shadmehr, & Bastian, 2007; Huang, Haith, Mazzoni, & Krakauer, 2011). There is broad evidence to suggest that forward models exist within the cerebellum (Miall & Wolpert, 1996; Martin et al., 1996; Wolpert et al., 1998; Miall, Weir, Wolpert, & Stein, 1993; Tseng et al., 2007). Additionally, this form of adaptation is believed to be highly cerebellar-dependent, as patients with cerebellar dysfunction often perform poorly in these tasks (Martin et al., 1996; Maschke, Gomez, Ebner, &

Konczak, 2004; Smith & Shadmehr, 2005; Bastian, 2006; Tseng et al., 2007; Wong, Marvel, Taylor, & Krakauer, 2019).

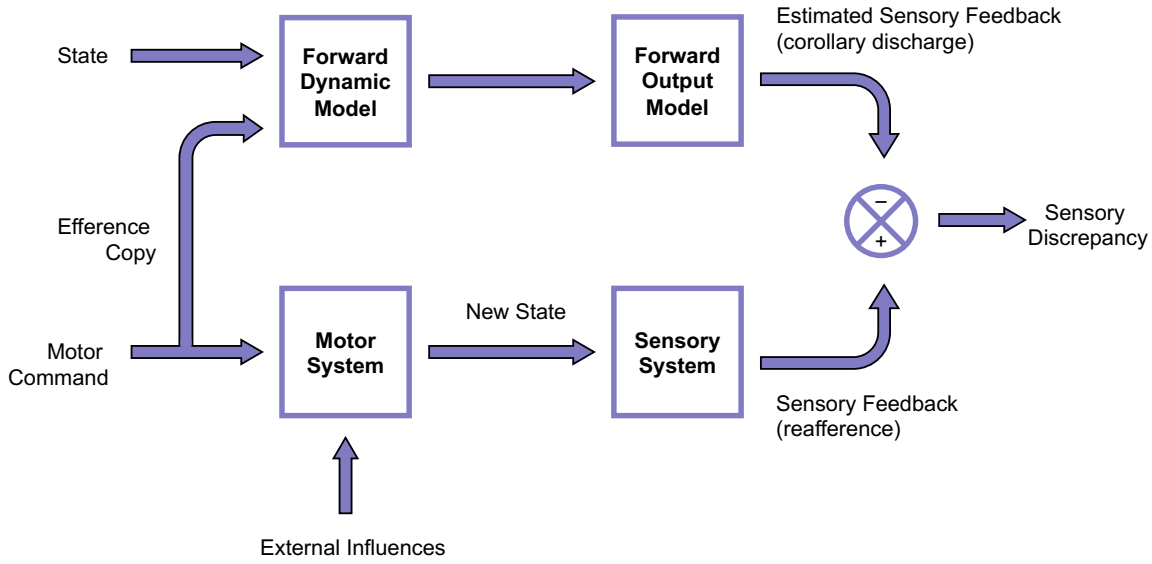


Figure 1.3: *Schematic diagram of how the forward model predicts the sensory outcomes of a motor command (top row). These predictions are compared to the actual sensory consequences of the command (bottom row). When there is a mismatch between the predicted and actual state, sensory prediction errors update the internal representation of the environment and are used to modify subsequent movements in order to restore accuracy (adapted from Miall and Wolpert, 1996).*

There is also appreciable evidence to suggest that other, more explicit strategic process can contribute to successful adaptation (Heuer & Hegele, 2008; Taylor & Ivry, 2011; Taylor, Krakauer, & Ivry, 2014; McDougle, Bond, & Taylor, 2015; McDougle & Taylor, 2019). These processes involve conscious actions to counter the experienced perturbations and are likely under greater cortical control (Taylor & Ivry, 2014; McDougle et al., 2015; Wolpe et al., 2020). Much work has been done to understand the various contributions of subconscious (cerebellar driven - implicit) and strategic (explicit) processes to successful adaptation, however, it remains unclear whether these processes work in combination or opposition during different types of adaptive learning (Mazzoni & Krakauer, 2006; Bond & Taylor, 2015; Miyamoto, Wang, & Smith, 2020; Avraham, Morehead, Kim, & Ivry, 2021). Furthermore, recent work has highlighted that the methodology used to measure 'implicit' and 'explicit' processes likely affect their relative contribution, which can be problematic when interpreting results (Hadjiosif & Krakauer, 2021; Maresch, Werner, & Donchin, 2021).

1.6.1 TDCS and motor adaptation

Sensorimotor adaptation is known to play an important role in maintaining motor accuracy throughout life. Consequently, over the last decade or so, much research has been dedicated to investigating the effect of TDCS on motor adaptation. Stimulation has been shown to improve adaptation in various different tasks; from visuomotor and force-field adaptation tasks, to gait and saccadic adaptation (Galea, Vazquez, Pasricha, Orban de Xivry, & Celnik, 2010; Jayaram et al., 2012; Kaski, Quadir, Patel, Yousif, & Bronstein, 2012; Block & Celnik, 2013; Hardwick & Celnik, 2014; Herzfeld et al., 2014; Panouillères et al., 2015; Fernandez et al., 2017; Leow, Marinovic, Riek, & Carroll, 2017; Kumari et al., 2020). Given the cerebellum is critical to successful adaptation, the majority of these studies applied TDCS to the cerebellum and speculate that improved performance is a result of enhanced forward model realignment. However, targeting M1 with TDCS has also shown to modulate aspects of motor

adaptation. Galea, Vazquez, et al. (2010) found that stimulating M1 during a visuomotor adaptation did not enhance online learning, but rather improved retention of the adapted state, highlighting the importance of M1 in motor memory. As introduced in an earlier section, there has been a problem with replicating results from TDCS studies, which also evident when combined with motor adaptation. Some recent studies have either failed to replicate or found null results when applying TDCS with different motor adaptation protocols (Hulst et al., 2017; Jalali, Miall, & Galea, 2017; Mamlins, Hulst, Donchin, Timmann, & Claassen, 2019). These studies emphasise a need for renewed efforts to understand the mechanistic interplay between stimulation and processes involved in motor adaptation - specifically what may be driving improved performance in studies with positive results and how can stimulation protocols be improved to more specifically target behaviour.

1.7 Concluding remarks

With this background in mind, we turn to the focus of the present work. The evidence presented thus far, suggests that TDCS shows some promise as a potential adjunct neuromodulatory therapy, but also highlights some of the problems and caveats to its use. In this thesis we aimed to investigate how stimulation may be more effectively applied in order to more reliably modulate behaviour. As TDCS has previously been shown to modulate sensorimotor adaptation, we aimed to apply stimulation during a series of motor adaptation tasks - with specific focus on the neural substrates targeted by stimulation protocols and the specific timing of stimulation administration.

In Chapter 2, evidence regarding the structure/function of the motor hierarchy was used to target stimulation at neural substrates which may exert preferential control over specific movements during a visuomotor adaptation task. This study aimed to help explain conflicting behavioural evidence (Hardwick and Celnik, 2014 vs Panouillères et al., 2015) and was built from historical work conducted by Lawrence

and Kuypers, (1968a, 1968b). As the brain undergoes age-related changes (Seidler et al., 2010), the influence of increasing age on targeted stimulation during the tasks was also examined. For Chapter 3, these findings were extended to assess whether reversing the stimulation polarity, reversed the behavioural results observed in Chapter 2, whilst maintaining the overall relationship between stimulation target and task. In Chapter 4 the focus shifts to improving the temporal specificity of TDCS. Based on canonical theories of motor learning (Hebb, 1949; Shatz, 1992), stimulation was delivered in very short bouts and coincidentally with movements during a motor adaptation task. Finally, due to restrictions on in-person research preventing the continuation of our planned work, Chapter 5 takes a minor detour and investigates why, during adaptation tasks, participants fail to achieve full compensation. This behaviour is especially evident in both Chapters 2 and 3. In order to investigate this, a visuomotor task was adapted to be run virtually and completed by participants at home.

Chapter 2

Targeted TDCS selectively improves motor adaptation with the proximal versus distal upper limb

2.1 Introduction

Good control of the upper limb is vital to carrying out even the most basic activities of daily living: eating, bathing, dressing etc. The subtle, but gradual decline in motor performance associated with increasing age can restrict the ability of older adults from safely carrying out these activities, having considerable consequences on their independence and well-being (Seidler, Alberts, & Stelmach, 2002; Seidler et al., 2010). In addition, upper limb motor deficits linked to age-related diseases such as stroke and Parkinson's Disease (PD) place further burdens on the quality of life of these older adults.

Normally, we smoothly integrate control of the arm and hand. However, the proximal and distal portions of the upper limb appear to be subserved by somewhat distinct neural substrates. The primary motor cortex (M1) seems to have a particularly important role in hand and finger movements. In primates, including humans, direct corticomotoneuronal (CM) projections from M1 to spinal motor neurons are thought to be key (Kuypers, 1981; Bortoff & Strick, 1993; Porter & Lemon, 1993; Lemon, 2008). Additionally, the large neural representations in M1 that code for hand and finger movements support its role in distal upper limb control (Penfield & Boldrey, 1937). M1, however, is only one of several nodes in the brain that contribute to accurate and coordinated movements of the upper limbs, such as the basal ganglia, cerebellum and spinal cord. Of these, the cerebellum has a particularly strong influence over movements of the proximal upper limb. The human cerebellar cortex contains motor representations of all four limbs, with prominent representations of the arms and hands (Mottolese et al., 2012) while cells in the monkey cerebellar cortex and nuclei fire with proximal arm movements (Fortier, Kalaska, & Smith, 1989). Additionally, the cerebellum has major connections to nuclei in the brainstem that are the origin of descending pathways controlling the proximal musculature and vast connections to important parietal reach-related areas (Clower, West, Lynch, & Strick, 2001; Prevosto, Graf, & Ugolini, 2009).

The differential control of the proximal versus the distal upper limb was highlighted by Don Lawrence and Hans Kuypers in the late 1960s (Lawrence & Kuypers, 1968a, 1968b). Their studies culminated in an experiment that lesioned the corticospinal tract in monkeys at the level of the pyramids. This procedure left the motor cortex intact, but removed its direct influence on the spinal cord. Although initially severe motor impairments were observed, the animals recovered rapidly and after a short period of time were able to walk, run, climb, and importantly use their arms to reach and grasp for food. However, they never recovered the ability to independently move their digits, always using all their fingers in concert. The dissociated recovery of the proximal and distal upper limb has also been displayed in humans post-stroke (Schambra et al., 2019) and following surgical extirpation of the motor cortex that was used as an early surgical intervention for epilepsy (Horsley, 1909; Foerster, 1936; Bucy, 1948). These findings show that recovery of hand muscles is more dependent on corticospinal tract integrity compared to arm muscles. Finally, there are age-related changes in the density and composition of the corticospinal tract (Terao, Sobue, Hashizume, Shimada, & Mitsuma, 1994; Hasan et al., 2010) and suggestions of differential changes in cortical grey matter (Walhovd et al., 2011; Fjell et al., 2013) that imply the relative contribution of M1 and the cerebellum might shift with advancing age.

With this background in mind, we turn to the recent literature on transcranial direct current stimulation (TDCS). Due to its capacity to modulate the excitability of different parts of the brain (Nitsche & Paulus, 2000, 2001; Galea et al., 2009), TDCS had become a popular research tool, with potential clinical translation. Behavioural studies have shown that the application of TDCS can improve various aspects of upper limb motor function and learning in healthy young adults (Nitsche, Schauenburg, et al., 2003; Galea, Vazquez, et al., 2010), older adults (Hardwick & Celnik, 2014; Panouillères et al., 2015) and patient populations (Hummel et al., 2005; Fregni et al., 2006). However, studies using TDCS have shown inconsistent effect sizes, both in the normal brain and in rehabilitation (Rossi, Sallustio, Di Legge, Stanzione, & Koch,

2013; Jalali et al., 2017). One possible reason for this inconsistency is the lack of spatial/functional specificity of TDCS. Unlike transcranial magnetic stimulation (TMS), there is little evidence that TDCS can be used to accurately modulate specific brain areas. It is also not clear that the behavioural tasks used have been chosen to highlight the contribution of the brain areas targeted. We therefore sought to combine targeted stimulation of the cerebellum and M1 with tasks that share similar motor control characteristics but isolate whole arm movements from hand/finger movements. Given the differing levels of control exerted by the cerebellum and M1 over proximal and distal muscles, we hypothesised that cerebellar but not M1 stimulation would improve performance in the arm movement task in healthy young adults. Conversely, M1 but not cerebellar stimulation would improve performance in the task requiring hand and finger movements. As there is of evidence for age-related change in these two motor regions, we also examined if this possible double dissociation was seen in older adults.

2.2 Methods and Materials

2.2.1 Participants

Ninety healthy younger adults (46 females; aged 18-29 years, mean 19.5 $\pm$ 1.4 (SD) years) and seventy-two healthy older adults (41 females; aged 66-84 years, mean 74.9 $\pm$ 4.1 years) gave written consent to take part in this study (approved by the Science, Technology, Engineering and Mathematics Ethical Review Committee at The University of Birmingham). Older adults were offered travel expenses for taking part and younger adults (all undergraduate students at the University of Birmingham) received research credits that counted towards their degree mark. Participants were all right-handed (self-report) and completed safety screening for the use of TMS and TDCS.

All participants were pseudo randomly assigned to either the joystick or vBOT task and then again into one of three stimulation groups (M1, Cerebellar or Sham):

- vBOT Task
  - M1 Stimulation: 15 young (7 females) and 12 older adults (6 females).
  - Cerebellar Stimulation: 15 young (8 females) and 12 older adults (7 females).
  - Sham Stimulation: 15 young (9 females) and 12 older adults (7 females).
- Joystick Task
  - M1 Stimulation: 15 young (8 females) and 12 older adults (7 females).
  - Cerebellar Stimulation: 15 young (7 females) and 12 older adults (7 females).
  - Sham Stimulation: 15 young (7 females) and 12 older adults (7 females).

2.2.2 Experimental Design

vBOT Task

Participants sat comfortably in an armless chair and used their right hand to grasp the handle of a custom-built two-dimensional planar robotic manipulandum (Howard, Ingram, & Wolpert, 2009) which allows movement in the horizontal plane (Figure 2.1a). The vBOT measured and stored the position of the handle at 1000Hz. The task display was reflected onto a horizontal 'semi silver' screen (60cm x 76cm) in front of the participants from a computer monitor (Mac Cinema HD Display) located directly above. The screen displayed a white outlined circle (diameter: 12cm) and a red cursor (diameter: 0.5cm), which was controlled by movement of the vBOT handle. At rest the cursor would be located in the centre of the of the circle. During the task a green target (diameter: 0.5cm) would alternate between the centre position and one of eight equidistant target locations around the circle perimeter, with a dwell time of 1 second in each position. Participants were instructed to make straight, fast movements with the vBOT handle towards and through the target and then return to the centre

position, without making corrective adjustments. The point where participants' movement crossed the perimeter circle (i.e. their final angle), would be displayed by an open red circle, remaining on screen until the target returned to the centre. The room was darkened prior to the start of the task to block vision of the hand/arm underneath the screen. In addition, a 'curtain' was attached to the vBOT frame and prevented participants viewing their upper arm. The vBOT handle was grasped with a power grip, and the 10-15 cm motion of the vBOT was achieved mainly with shoulder and elbow motion, and with only limited wrist flexion/extension.

Joystick Task

Participants were seated at a comfortable distance away from a vertical computer screen (22.5cm x 30.5cm), so that they could reach and manipulate a small, sprung joystick (APEM 9000 Series, 75 Hz sampling rate) with their right hand (Figure 2.1b). The joystick was 6.5cm in height, 2cm in width and fixed to the desk next to the computer screen with a clamp. The task display, paradigm and timings were exactly the same as for the vBOT task to allow between group comparisons. Participants were asked to make single, rapid and uncorrected movements with the joystick towards and through the target, then back to the centre. Vision of the hand was blocked during the task using an opaque box and participants were asked to refrain from moving their arm/shoulder. 2-3cm motion of the joystick was typically achieved by index finger and thumb movement and wrist abduction/adduction.

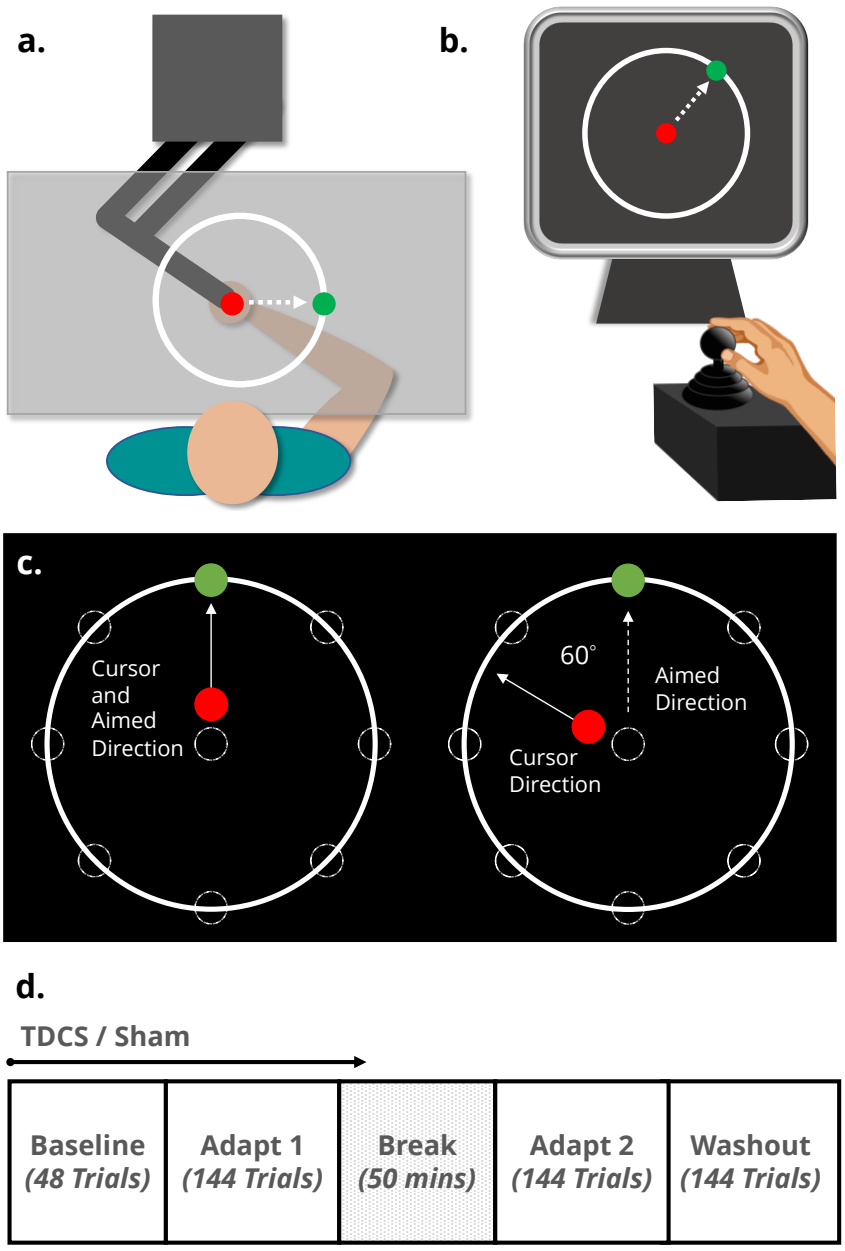


Figure 2.1: *Schematic diagrams of the vBOT (**a**) and joystick (**b**) experimental set up. **c:** An example of the display for both tasks during baseline/washout trials (left), where the aimed and cursor direction are matched and rotational perturbation trials (right), where a 60° counter-clockwise rotation is added to the vBOT handle/joystick. **d**: A time course of the study protocol. Each trial was to one of 8 targets, in pseudorandom order. In Adapt 1 and Adapt 2, a 60° rotation between movement of the vBOT/joystick and the displayed cursor was imposed. TDCS started at baseline (1.75 minutes), continued throughout Adapt 1 (5.25 minutes) and then was turned off 10 minutes into the break. After the break period, participants performed Adapt 2 and Washout blocks (5.25 minutes each).*

Visuomotor Rotation Paradigm

The behavioural task was split up into a baseline phase, two visuomotor adaptation phases (Adapt 1 and Adapt 2) separated by a break period, and a washout phase (Figure 2.1d). During baseline trials the on-screen cursor movement would match the movement of the joystick/vBOT handle. Throughout the two rotational phases, a 60° counter-clockwise (CCW) rotation was applied to the cursor with respect to the joystick/vBOT handle (Figure 2.1c). The Adapt 1 and 2 phases were separated by a 50-minute break period, where the participants sat at rest. The washout phase immediately followed Adapt 2 and returned the cursor rotation to 0°, so that it again matched the movement of the joystick/vBOT handle. There was no on-screen cue of this condition; prior to the experiment participants were told that a perturbation would be applied to the cursor at some point but were not informed about its nature. They were asked not to use any explicit strategies in order to overcome it, but to try their best to hit or get as close to the target as they could in each trial.

2.2.3 TDCS

TDCS was administered at 2mA via two saline soaked sponge electrodes measuring 5 x 7 cm, using a DC-Stimulator (neuroConn, Ilmenau, Germany). For M1 stimulation the anodal electrode was positioned over the hand area' of the left motor cortex, identified for each participant using single pulse TMS (Magstim 200 mono pulse stimulator/Magstim Radpid2 stimulator; Magstim Ltd, UK) and the cathode electrode was placed over the contralateral supraorbital ridge (Nitsche & Paulus, 2000). For cerebellar stimulation the anode was centred over the right cerebellar cortex, 3 cm lateral to the inion (Galea et al., 2009) and the cathode was placed on the superior aspect of the right trapezius muscle. This extra-cephalic reference has been found to maximally stimulate the cerebellar hemispheres and avoid unwanted current spread (Ferrucci et al., 2013; Ferrucci & Priori, 2014). In both stimulation conditions the

current was ramped up over 10 seconds and then held at 2mA for 17 minutes, before being ramped back down over a further 10 second period. For the sham condition, the electrode montage was pseudorandomly assigned to either the M1 or cerebellum arrangement for each participant. The stimulation was ramped up over 30 seconds, held for 30 seconds before ramping down over 30 seconds and then switched off. Longer ramping durations were chosen during the sham condition as they have been found to achieve high levels of blinding (Russo, Wallace, Fitzgerald, & Cooper, 2013). Ten-point visual analogue scale (VAS) questionnaires for perceived comfort and in their confidence in receiving active stimulation were used to determine whether sufficient blinding was achieved.

2.2.4 Data Analysis

The position of the joystick and vBOT handle were tracked trial-by-trial and recorded using custom analysis in MATLAB (version R2018b, Mathworks). Our primary outcome measure was rotational error defined as the angular displacement between the direction of participants' movement at peak velocity and the target location. Data from each participant during Baseline, Adapt 1, Adapt 2 and Washout phases was averaged across bins of 4 trials to be used in further analysis. Area under the curve calculations were performed in MATLAB for each participant in each adaptation phase and subsequently averaged across stimulation groups to quantify total rotational error during the tasks and indicate adaptive performance.

Frequentist statistical analyses were carried out in SPSS Statistics (IBM, version 25). ANOVAs were run in general linear model format, with significant main effects and interactions followed up with Bonferroni-adjusted post-hoc tests. Statistical significance was set at $p < 0.05$ and we report F values alongside partial eta squared (η_p^2) effect sizes.

Bayesian ANOVAs were carried out using JASP 0.10.1 (JASP Team, 2019; (Wagenmakers, Love, et al., 2018). Comparisons were made using Bayes Factors (BF), which were assigned descriptive classifications following Lee and Wagenmakers' (Lee

& Wagenmakers, 2013) modification of Jeffereys' (Jeffreys, 1961) scheme; BF of 1 provides no evidence, 1-3 anecdotal evidence, 3-10 moderate evidence, 10-30 strong evidence, 30-100 very strong evidence, and BF > 100 provides extreme evidence. All Bayesian ANOVAs considered 19 models; these were models admitting combinations of Age Group, Task and Stimulation Group, as-well their second and third-order interactions (Table. 2.1). The null model contains the grand mean only. We report posterior model odds (the change from prior to posterior model odds; BF_M), the Bayes Factor between models (BF), and the Bayes Factor (BF) to provide evidence for inclusion of terms in the chosen model. This latter measurement is the change from prior inclusions odds to posterior inclusion odds for each component, averaged by all models that includes the component (Wagenmakers, Marsman, et al., 2018).

Bayesian ANOVA models
> Null Model
> Age Group
> Task
> Stimulation Group
> Age Group + Task
> Age Group + Task + Age Group x Task
> Age Group + Stimulation Group
> Age Group + Stimulation Group + Age Group x Stimulation Group
> Age Group + Task + Stimulation Group
> Age Group + Task + Stimulation Group + Age Group x Task
> Age Group + Task + Stimulation Group + Age Group x Stimulation Group
> Age Group + Task + Stimulation Group + Task x Stimulation Group
> Age Group + Task + Stimulation Group + Age Group x Task + Age Group x Stimulation Group
> Age Group + Task + Stimulation Group + Age Group x Task + Task x Stimulation Group
> Age Group + Task + Stimulation Group + Age Group x Stimulation Group + Task x Stimulation Group
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> Age Group + Task + Stimulation Group + Age Group x Task + Age Group x Stimulation Group + Task x Stimulation Group + Age Group x Task x Stimulation Group
> Task + Stimulation Group
> Task + Stimulation Group + Task x Stimulation Group

Table 2.1: *The 19 models considered in all Bayesian ANOVAs. Models included combinations of the main effects; Age Group, Task and Stimulation Group and their associated second or third-order interactions (interactions could only be included in the model if the corresponding main effects were also present). Note that the dependent variable changed with each separate analysis.*

2.3 Results

2.3.1 Baseline performance did not differ between stimulation groups

Differences in baseline performance during the task were assessed using a three-way ANOVA (Age Group x Task x Stimulation Group), which revealed no significant main effect of Age Group or Stimulation Group ($F(1,150) = 1.57, p = 0.21, \eta_p^2 = 0.01$ and $F(2,150) = 1.56, p = 0.21, \eta_p^2 = 0.02$ respectively). There was however, a main effect of Task ($F(1,150) = 68.83, p < 0.001, \eta_p^2 = 0.32$) and an Age Group x Task interaction ($F(1,150) = 13.17, p < 0.001, \eta_p^2 = 0.081$). Post-hoc tests revealed significant differences in performance between age groups and tasks. There were similar differences between performance in the vBOT and joystick tasks for both age groups (Young Adults: $p = 0.01$, Older Adults: $p < 0.001$). However, with respect to task, older and younger adults performed similarly during baseline trials in the vBOT task ($p = 0.095$), whereas older adults made more errors than younger adults in the joystick task ($p < 0.001$). These differences between tasks likely stem from a slight negative (anti-clockwise) reaching bias in the vBOT task and a slight positive (clockwise) bias in the joystick task across both age groups at the beginning of baseline trials (Figure 2.2). As we found no effect of stimulation group and differences occurred in the same direction in each task, these results are unlikely to have confounded our results. A Bayesian ANOVA supported this analysis, with the preferred model including terms for Age Group, Task and the Age Group x Task interaction, BF_M = 36.07 (consistent with the principle of marginality: we do not consider models with interaction terms that do not contain all corresponding main effects; (Wagenmakers, Marsman, et al., 2018)). Given the data, this model was 4.89 times more likely than the next best model, which had the additional term for Stimulation Group, and 19.96 times more likely than the model only including the Task main effect.

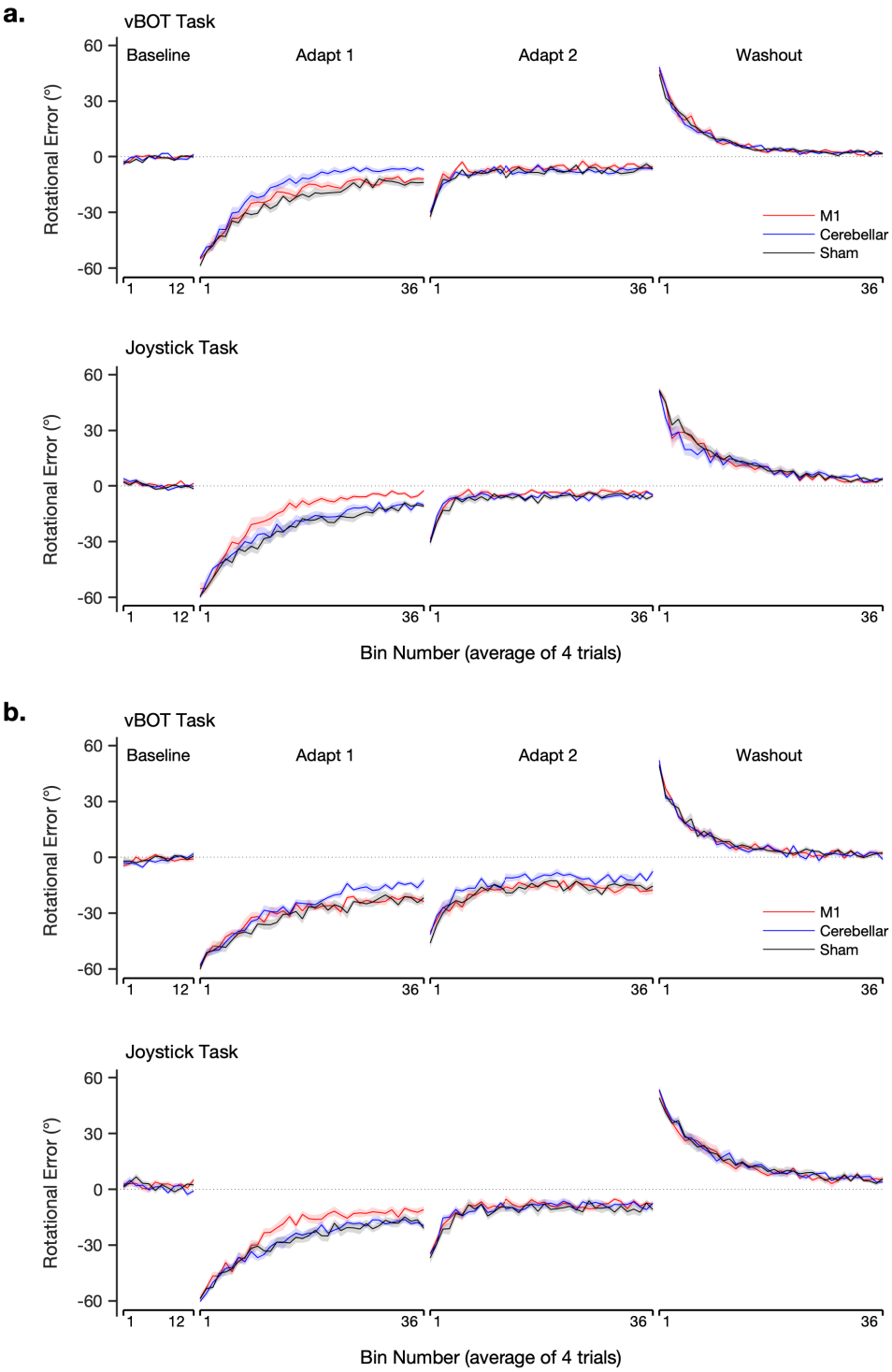


Figure 2.2: *Mean rotational error (± standard error), averaged every four trials into bins, for young (**a**) and older adults (**b**) during Baseline (no rotation), Adapt 1 (60° CCW rotation), Adapt 2 (60° CCW rotation) and Washout trials (no rotation) in M1, cerebellar and sham stimulation groups and both the vBOT and joystick tasks.*

2.3.2 Older adults were impaired in motor adaptation compared to younger adults

In order to investigate differences in adaptation between age and stimulation groups, the area under the curve (a measure of total error within each block) for each participant was compared in 3-way ANOVAs (Age Group x Task x Stimulation Group) for the different adaptation phases (Adapt 1, 2 and Washout). During both Adapt 1 and 2 older adults displayed impaired adaptation performance compared to younger adults (Figure 2.3). Additionally, in Adapt 1 there was a significant main effect of Age Group ($F(1, 150) = 80.94, p < 0.001, \eta_p^2 = 0.35$) and a significant Age Group x Task interaction ($F(1, 150) = 4.85, p = 0.03, \eta_p^2 = 0.031$). Post-hoc tests revealed that older adults made significantly more error in the vBOT task compared to the joystick task ($p = 0.002$), with no differences between younger adults with respect to task ($p = 0.81$). Additionally, older adults made more errors in both the vBOT ($p < 0.001$) and joystick ($p < 0.001$) tasks. This difference was confirmed using a Bayesian ANOVA with models containing a main effect of Age Group demonstrating extreme evidence of an effect (BF = 5.2 x 10^{12}; compared with matched-models without this term), whilst models containing the Age Group x Task interaction showed anecdotal evidence of an effect (BF = 1.896). Similarly in Adapt 2, there was a significant main effect of Age Group ($F(1, 150) = 165.37, p < 0.001, \eta_p^2 = 0.52$) and a significant Age Group x Task interaction ($F(1, 150) = 15.38, p < 0.001, \eta_p^2 = 0.093$). Post-hoc tests showed that performance was significantly worse for older adults in both tasks (vBOT: $p < 0.001$, joystick: $p < 0.001$). Again, the main effect of Age Group demonstrated extreme evidence in the Bayesian ANOVA (BF = 2.8 x 10^{20}), with the Age Group x Task interaction now also demonstrating extreme evidence of an effect (BF = 117.7).

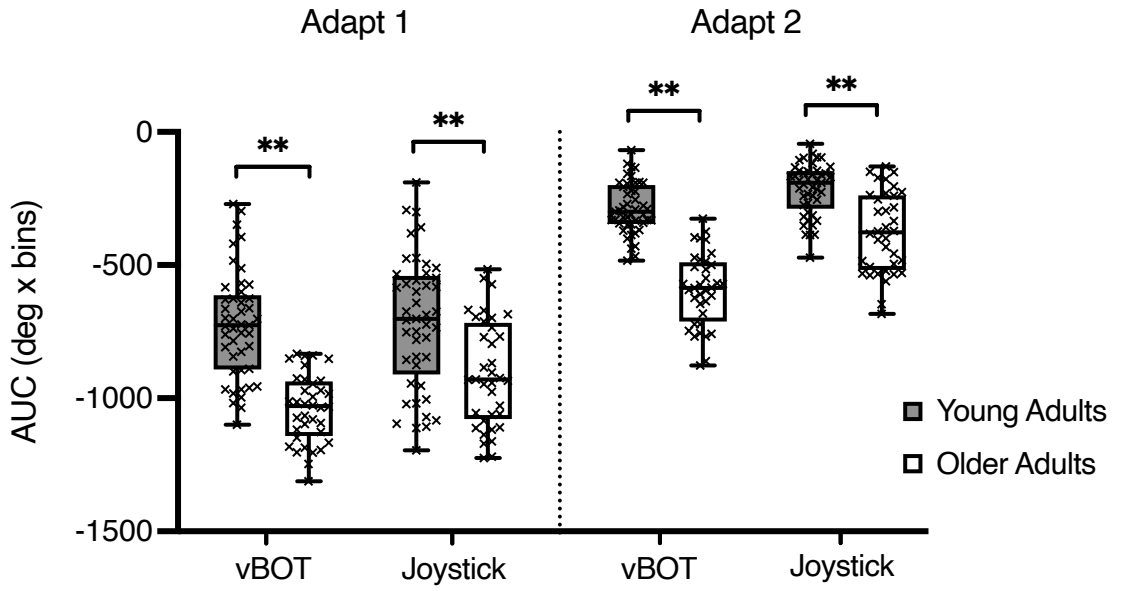


Figure 2.3: *The area under the curve (cm x bins) collapsed across the three stimulation groups, comparing adaptive performance for both younger and older adults during Adapt 1 and 2 of the vBOT and joystick tasks. Box plots indicate the mean, upper and lower quartiles; the range is shown by the error bars and all individual participant values in each group marked by an 'x'). Significant differences are indicated via* $^{*} = p < 0.05$, $^{**} = p < 0.001$*) following Bonferroni corrected multiple comparisons. Values closer to zero represent less error made during the task.*

2.3.3 Cerebellar TDCS improved adaptation during the vBOT task, whereas M1 TDCS improved adaptation during the joystick task in both age groups

We next sought to investigate the differences in adaptation between the stimulation groups in the different tasks, seen in Figure 2.2. In the same 3-way ANOVA as above (Age Group x Task x Stimulation Group), there was a significant main effect of Stimulation Group ($F(2, 150) = 12.44, p < 0.001, \eta_p^2 = 0.14$) and a significant Task x Stimulation Group interaction ($F(2, 150) = 13.28, p < 0.001, \eta_p^2 = 0.15$) for Adapt 1. Post-hoc tests showed that for the vBOT task participants in the cerebellar groups displayed significantly less error than the M1 ($p = 0.009$) and sham groups ($p < 0.001$), with no differences between the M1 and sham groups ($p = 0.4$). For the joystick task,

post-hoc tests revealed that M1 stimulation significantly improved adaptive performance compared to cerebellar ($p < 0.001$) and sham ($p < 0.001$) stimulation, with no difference between cerebellar and sham ($p > 0.99$). There was however, no significant interaction of Age Group with Stimulation Group ($F(2, 150) = 0.54, p = 0.58, \eta_p^2 = 0.007$), suggesting that the stimulation effects were consistent regardless of age (Figure 2.4 & 2.5). In the Bayesian ANOVA, there was an extreme influence of Task x Stimulation Group (BF = 5917.1). Indeed, the winning model across all 19 models (see Methods) included the three main effects of Age Group, Task, and Stimulation Group, as-well as Age Group x Task, and Task x Stimulation Group interactions (BF_M = 24.2); it did not include the Age Group x Stimulation Group interaction, or the three-way interaction (the full model was 31.3 times less likely, given the data). To understand the specific effect of the Task x Stimulation Group interaction, we compared the winning model to the analogous model lacking only the Task x Stimulation Group term; the winning model proved 6468.3 times more likely given the data, and thus provides extremely strong evidence that Stimulation imposes a Task-specific effect.

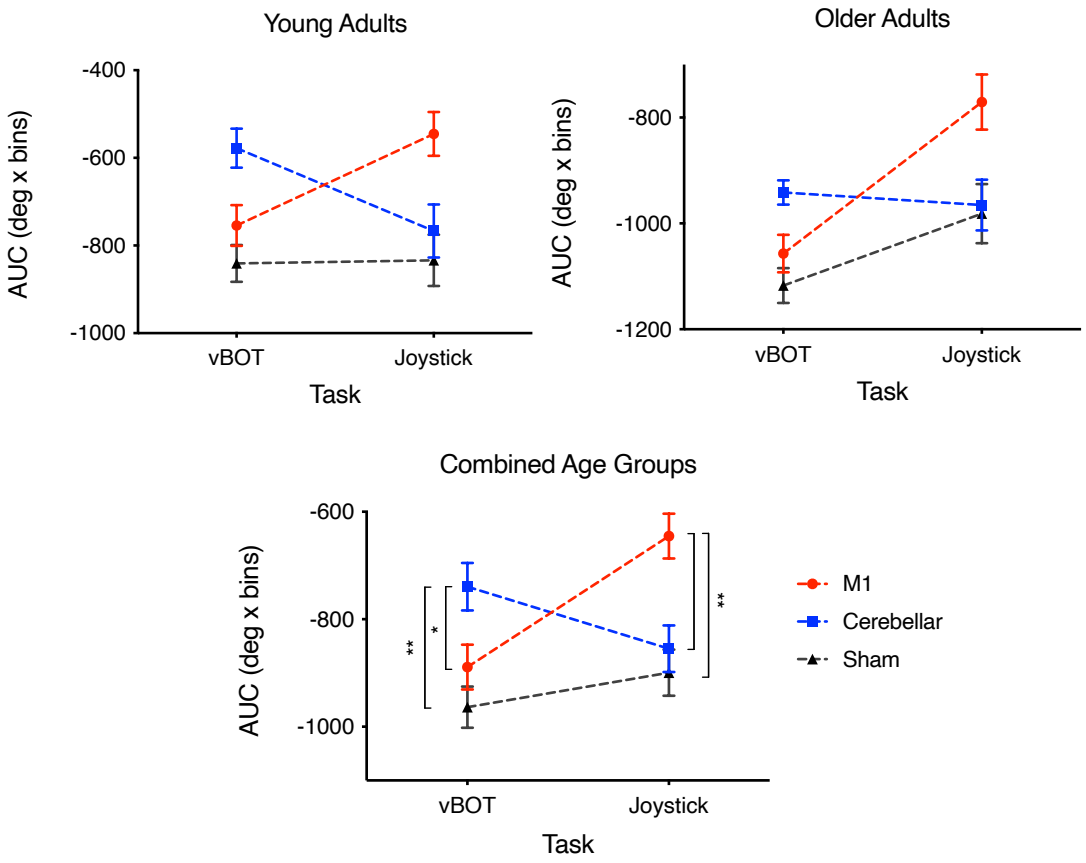


Figure 2.4: *Area under the curve (mean AUC ± standard error) for each stimulation group (M1, cerebellar and sham) in both the vBOT and joystick tasks during Adapt 1. Initially separated by Age Group (upper panel: Young adults, Older adults) and then combined (lower panel) with significance displayed ($^{*} = p < 0.05$, $^{**} = p < 0.001$) following 3-way ANOVA post-hoc tests.*

In Adapt 2 there remained a main effect of Stimulation Group ($F(2, 150) = 3.92, p = 0.02, \eta_p^2 = 0.05$) but there was no Task x Stimulation Group interaction ($F(2, 150) = 1.59, p = 0.21, \eta_p^2 = 0.021$). Post-hoc tests showed that cerebellar groups displayed significantly less error than sham groups ($p = 0.035$), with no further significant differences between M1 and cerebellar groups or M1 and sham groups (all $p > 0.073$). The differences between Stimulation Groups may be anecdotally ascribed to reduced error for older adults receiving cerebellar stimulation in the vBOT task (Figure 2.5b). Bayesian analysis supported a winning model containing the three main effects (Age Group, Task and Stimulation Group), as-well as Age Group x Task, and Age Group x Stimulation Group interactions ($BF_M = 10.945$).

This proved 4.5 times more likely than the full model, and 2.2 times more likely than the same model containing a Task x Stimulation Group interaction.

For Washout trials there was no significant main effect of Stimulation Group ($F(2, 150) = 0.23, p = 0.79, \eta_p^2 = 0.003$) and no Task x Stimulation Group interaction ($F(2, 150) = 0.19, p = 0.83, \eta_p^2 = 0.002$), suggesting that TDCS had no effect on de-adaptation during the tasks (Figure 2.5). Again, the Bayesian ANOVA supports this with extreme evidence of a Task effect (BF = 7.7 x 10^{12}), and the winning model contained Task as the only term (BF_M = 14.1). The Task x Stimulation Group interaction demonstrated moderate evidence against its inclusion (BF = 0.121).

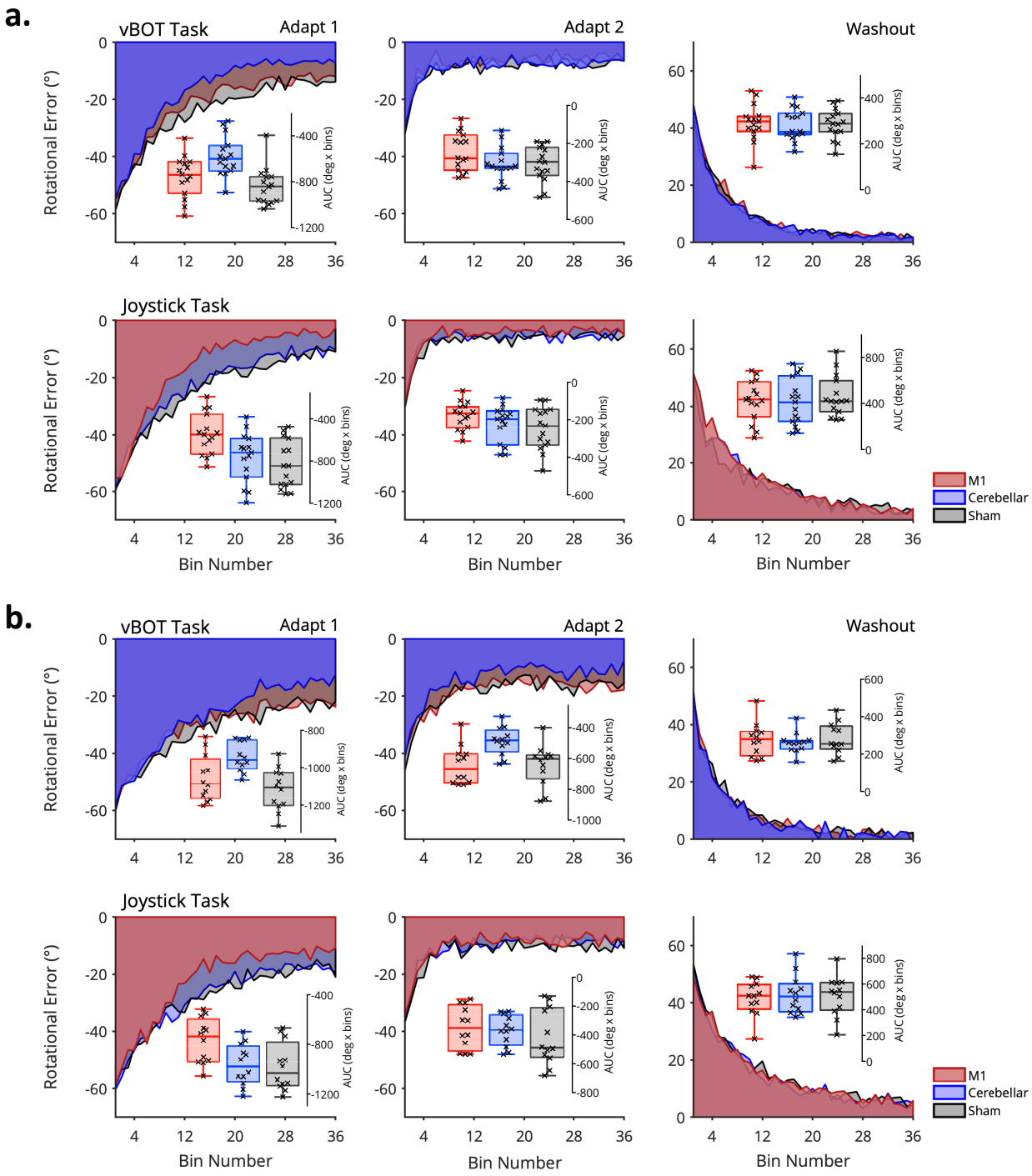


Figure 2.5: *Visualisations of the area under the curve (AUC) for younger adults (**a**) and older adults (**b**) in all stimulation groups for both the vBOT and joystick tasks. Box plots inserts represent the area under the curve for each stimulation group during the different phases of the tasks (with the box indicating mean, upper and lower quartiles; the range shown by the error bars; and individual participant values in each group marked by an 'x')*

2.3.4 Adaptation performance differed between the two tasks for both older and younger adults

During Adapt 1 there were significant differences in performance between the two tasks for older adults, but not for the younger adults. The 3-way ANOVA revealed a significant main effect of Task ($F(1, 150) = 6.38, p = 0.01, \eta_p^2 = 0.041$) and a significant Age Group x Task interaction ($F(1, 150) = 4.85, p = 0.029, \eta_p^2 = 0.031$). Post-hoc testing showed that older adults made significantly greater errors during the vBOT task (arm movements) compared to the joystick task (hand movements): $p = 0.002$, with no differences for younger adults ($p = 0.81$, Figure 2.6). Models containing an Age Group x Task interaction demonstrated anecdotal evidence of an effect (BF = 1.8), with the winning model also proving 1.8 times more likely than the analogous model with the interaction excluded. For Adapt 2 there was again a main effect of Task ($F(1, 150) = 61.16, p < 0.001, \eta_p^2 = 0.29$) and an Age Group x Task interaction ($F(1, 150) = 15.38, p < 0.001, \eta_p^2 = 0.093$). Post-hoc tests revealed that both younger and older adults made significantly more error during the vBOT task ($p = 0.004$ and $p < 0.001$ respectively). Models containing an Age Group x Task interaction demonstrated extreme evidence for inclusion (BF = 115.2), with the winning model proving 17.9 times more likely than the analogous model with this term excluded. During Washout trials, the ANOVA also revealed a main effect for Task ($F(1, 150) = 82.81, p < 0.001, \eta_p^2 = 0.36$) and an Age Group x Task interaction ($F(1, 150) = 4.25, p = 0.04, \eta_p^2 = 0.028$). Post-hoc tests revealed that less error was made during the vBOT task compared to the joystick task for both age groups (both $p < 0.001$), suggesting that adaptation in the joystick task caused greater after-effects. During Washout, there was anecdotal evidence for inclusions of the Age Group x Task interaction (BF = 1.5), with the winning model (Task term only) proving 1.5 times more likely than the analogous model with Age Group and Age Group x Task Interaction.

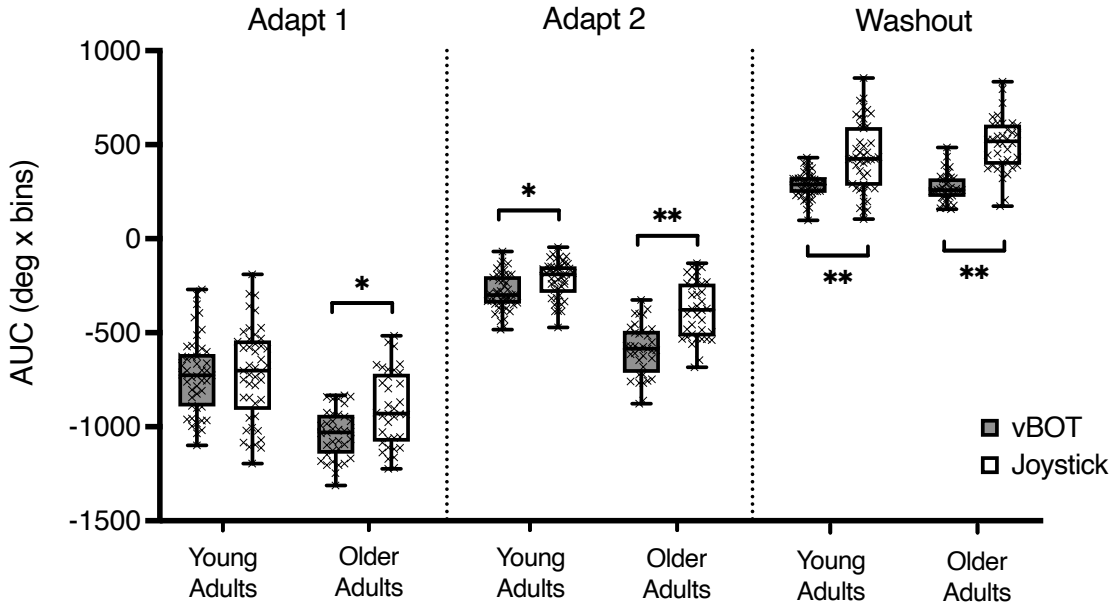


Figure 2.6: *The area under the curve (cm x bins) collapsed across the three stimulation groups for both younger and older adults from Adapt 1, Adapt 2 and washout, comparing adaptation performance during the vBOT and joystick tasks. Box plots contain the mean, upper and lower quartiles; the range is indicated by the error bars and all individual participant values in each group marked by an 'x'). Significant differences are indicated via* $^{*} = p < 0.05$, $^{**} = p < 0.001$*) following Bonferroni corrected multiple comparisons. Values closer to zero represent less error made during the task.*

2.3.5 No differences in perceived comfort or confidence in stimulation

To ensure sufficient blinding to the stimulation type received (active or sham), all participants rated their perceived comfort and their confidence in receiving active stimulation on a 10-point visual analogue scale (VAS), shown in Table 2.2. A 3-way ANOVA (Age Group x Task x Stimulation Group) showed that all participants reported similarly high levels of comfort with no main effect of Stimulation Group ($F(2, 150) = 1.07, p = 0.34, \eta_p^2 = 0.014$) and no interaction with Age Group ($F(2, 150) = 1.79, p = 0.17, \eta_p^2 = 0.023$). There was a significant main effect of Age Group ($F(1, 150) = 59.37, p < 0.001, \eta_p^2 = 0.28$), and post-hoc comparisons revealed that older adults reported significantly higher levels of comfort during session than younger adults ($p < 0.001$). Bayesian analysis revealed extreme evidence for an effect of Age on comfort (BF = 6.6 x 10^9, with all other terms producing BFs in the range 0.1-0.5). Unsurprisingly, the model with only a single term (Age Group) was preferred (BF_M = 41.8, proving 6.9 x 10^9 times more probable than the null model, given the data). Additionally, all participants reported high levels of confidence that they were in the active stimulation group. There were no main effects of Age Group ($F(1, 150) = 0.31, p = 0.58, \eta_p^2 = 0.002$), Task ($F(1, 150) = 0.05, p = 0.83, \eta_p^2 < 0.001$) or Stimulation Group ($F(2, 150) = 0.54, p = 0.59, \eta_p^2 = 0.007$) and no significant interactions (all $p > 0.49$). In this case, Bayesian analysis supported the null model as the most likely (BF_M = 32.8), with all terms producing BFs in the range 0.092 [Stimulation Group] - 0.220 [Age Group x Task].

Young Adults					
Perceived Comfort					
vBOT Task			Joystick Task		
M1	Cerebellar	Sham	M1	Cerebellar	Sham
3.27	3.07	3.53	3.13	3.33	3.07
±1.16	±1.16	±1.06	±1.13	±1.11	±1.22
Confidence in Stimulation					
8.27	7.60	7.80	7.87	7.93	7.87
±1.67	±1.18	±1.37	±1.51	±1.91	±1.68
Older Adults					
Perceived Comfort					
2.17	1.92	1.25	2.25	1.67	1.67
±0.72	±1.68	±0.45	±1.66	±0.89	±1.15
Confidence in Stimulation					
7.75	8.17	7.42	7.67	8.08	7.17
±2.05	±1.8	±3.06	±2.93	±2.5	±2.69

Table 2.2: *Average ratings (± SD) of perceived comfort (1–10 VAS, 1 = no discomfort, 10 = very high discomfort) and confidence in detecting stimulation (1–10 VAS, 1 = low confidence in receiving real stimulation, 10 = high confidence in receiving real stimulation) for both age group and tasks after the stimulation period. All three younger adult groups contained 15 participants; all three older adult groups contained 12 participants.*

2.4 Discussion

The aim of this study was to investigate whether TDCS targeted at the motor cortex or the cerebellum could specifically improve motor adaptation in tasks dominated by movement of the distal versus proximal upper limb, respectively. In line with our hypothesis, derived from the anatomy and physiology of these motor systems, we demonstrated that stimulation of the cerebellum can selectively improve motor

adaptation using arm movements, whereas M1 TDCS selectively improves adaptive performance when using the hand/fingers. This effect was found in two separate age groups.

Both M1 and cerebellar TDCS have previously been shown to improve adaptive motor learning in visuomotor rotation tasks (Galea, Vazquez, et al., 2010; Block & Celnik, 2013; Hardwick & Celnik, 2014; Panouillères et al., 2015). However, to our knowledge this is the first study to show that selective stimulation of different brain areas can have specific effects on the proximal or distal upper limb. We found that cerebellar TDCS improves adaptation for both younger and older adults when using reaching movements to complete the task, which coincides with the fact that the cerebellum is an important neural substrate in multi-joint upper limb control. Many previous studies have shown that accurate and coordinated whole arm reaching movements are dependent on the cerebellum and deficits in reach behaviour result from cerebellar degeneration (Schweighofer, Arbib, & Kawato, 1998; Bastian & Thach, 1995; Zackowski, Thach, & Bastian, 2002; Bhanpuri, Okamura, & Bastian, 2014). The cerebellum is also thought to be heavily involved in the sensorimotor processes that adapt movements of the arm (Tseng et al., 2007; Izawa, Criscimagna-Hemminger, & Shadmehr, 2012; Tzvi, Loens, & Donchin, 2021), although there is current debate as to the effectiveness of cerebellar TDCS on adaptation (Galea, Vazquez, et al., 2010 vs Jalali et al., 2017). A point to which we will return later.

In contrast, we found that M1 and not cerebellar TDCS enhanced adaptation for both age groups when the task was executed with the fingers/hand. This result supports findings that M1 stimulation can improve adaptive performance in a visuomotor rotation task (Panouillères et al., 2015) and other forms motor learning in tasks predominantly using distal muscles (Nitsche, Schauenburg, et al., 2003; Reis et al., 2009; Kantak, Mummidisetty, & Stinear, 2012; Karok, Fletcher, & Witney, 2017). As M1 dominates in control of relatively independent hand and finger movements (Porter & Lemon, 1993) and projections from M1 terminate more densely among motor

neuron pools controlling the hand and digits than any other cortical or sub-cortical region (Armand, Olivier, Edgley, & Lemon, 1997; Maier et al., 2002), we suggest it may play a greater role in the mechanisms that adapt movements of the hand.

The double dissociation revealed here between the cerebellum/reaching and M1/hand movements is generally consistent within the extant literature on visuomotor adaptation and TDCS use. Galea et al. (2010), Block and Celnik (2013) and Hardwick and Celnik (2014) all found a significant effect of cerebellar stimulation on visuomotor adaptation using reaching tasks (with either whole arm movements of a digitised pen/tablet or robotic manipulandum), whereas Panouillères et al. (2015) showed M1 TDCS to enhance adaptation using a hand-held joystick (an effect replicated in the present study). However, the efficacy of TDCS has recently been called into question by some studies that have not found improved adaptation in visuomotor rotation tasks as a result of TDCS or have reported inconsistent effects (Hulst et al., 2017; Jalali et al., 2017; Mamlins et al., 2019). These studies also add to the growing body of evidence which suggests that stimulation parameters and study protocols are critical variables in TDCS research (Buch et al., 2017). For example, one difference between our study and the studies listed above is the degree of rotational perturbation: 60° vs 30°. It should be noted that a robust effect of M1 TDCS on this hand/finger 60° visuomotor rotation protocol has been demonstrated by replication in our lab between separate studies and age groups (Panouillères et al., 2015), and we conjecture that the additional difficulty in the task imposed by the greater visual rotation is important. Hence the dissociation we show here between proximal and distal control may help to further clarify the currently confused view of whether TDCS has significant effects in motor adaptation tasks. Given the large rotation size used, it is probable that a large percentage of learning was achieved via explicit processes (Taylor & Ivry, 2011; Bond & Taylor, 2015). As we did not attempt to assay the different processes which contribute to successful adaptation, we cannot confidently conclude which process/s (implicit, explicit or both) were modulated. The addition of tasks which can accurately

measure implicit and explicit processes (e.g., Morehead, Taylor, Parvin, and Ivry, 2017 and Taylor et al., 2014) could help to clarify this potential confound.

It is difficult to speculate on the exact mechanisms in play during the present study, especially as the underlying mechanisms of TDCS induced effects remain relatively unknown. However, stimulation improved performance in the tasks only when applied to structures that are most allied to the control of either arm movements (cerebellum-brainstem) or hand and finger movements (M1-corticospinal tract). This result seems to align with the proposed TDCS activity-selectivity mechanism of action (Bikson & Rahman, 2013; Fertonani & Miniussi, 2017), whereby stimulation preferentially modulates circuits in the brain that activated by a particular task or behaviour. Therefore, neural circuits activated more so by each of the respective tasks (and their associated behavioural demands) are more likely to be facilitated by TDCS. Yet, whether these effects act to improve adaptation indirectly, by improved performance of the specific movements, or more directly, via increased plasticity in the stimulated areas cannot be separated by this study and thus remain relatively unknown.

We also acknowledge that, although our rationale for this study has a sound functional foundation, it is reductionist in nature and other factors may have played a part in the results presented here. Despite strong evidence for some segregation in the control of fractionated hand/finger and proximal upper limb movements in lesion studies (Lawrence & Kuypers, 1968a, 1968b; Baker & Perez, 2017), we cannot refute that in the intact brain both M1 and the cerebellum will play some part in both proximal and distal motor control. Microstimulation of both the corticospinal and reticulospinal (which receives input from the cerebellum) tracts elicit responses in distal and proximal muscles (Riddle, Edgley, & Baker, 2009) and as previously stated the cerebellum contains motor representations for both the hands and arms (Mottolese et al., 2012). Additionally, the complex relationship and connectivity between M1 and the cerebellum is known to change during motor skill learning and adaptation (Schlerf,

Galea, Spampinato, & Celnik, 2014; Spampinato & Celnik, 2017), which may have had some bearing on our results. That being said, a lack of an exact mechanism does not detract from the behavioural data presented which shows a clear and obvious double dissociation between effector and stimulation site.

There is great interest in the therapeutic utility of TDCS for stroke rehabilitation. A number of studies have identified TDCS as a potential adjunct therapy after stroke, with some positive results for upper limb deficits (Hummel et al., 2005; Boggio et al., 2007; Bolognini et al., 2011; Allman et al., 2016). However, overall results have proven less promising than expected. It should be noted that these studies combined M1 TDCS with clinical tests that measure the functional improvement of the movements of the whole upper limb. Our results raise the possibility that stimulation of M1 may only improve the performance of the distal arm, which may not have been captured by clinical measures of whole arm use. We suggest that M1 and cerebellar TDCS could be directed to specific subgroups, or potentially used in combination to produce more robust functional improvements of the whole upper limb, especially as proximal and distal upper limb motor recovery post-stroke may be mediated by somewhat functionally dissociated pathways (Schambra et al., 2019). Additionally, in a recent review Wessel and Hummel (Wessel & Hummel, 2018) introduce the potential benefits of cerebellar TDCS to motor recovery after stroke, where previously only M1 stimulation seems to be considered. The authors suggest that the cerebellum could be an attractive target for TDCS due to its unique plasticity mechanisms, multiple connections to cortical regions and its successful use in the rehabilitation for cerebellar ataxia (Benussi et al., 2017, 2018; Maas et al., 2019) and the motor symptoms of other neurological disorders (Miterko et al., 2019).

In conclusion we have displayed that TDCS over the cerebellum improves motor adaptation using the whole arm, whereas M1 TDCS enhances adaptation using hand and finger movements. These findings suggest that stimulation of different neural substrates - which exert high levels of control over fractionated hand or whole arm

reaching movements - drives better adaptation in the respective tasks. They also further highlight the potential for TDCS to be used to ameliorate motor declines in ageing and present new ideas for more robust upper limb rehabilitation post-stroke.

Chapter 3

Direct and indirect effects of cathodal cerebellar TDCS on visuomotor adaptation of hand and arm movements

3.1 Introduction

Work from the previous chapter demonstrated that anodal transcranial direct current stimulation (TDCS) targeted at the primary motor cortex (M1) or cerebellum selectively improved motor adaptation of distal versus proximal upper limb movements respectively (Chapter 2: Weightman et al., 2020). Our rationale was derived from the differential level of control M1 and the cerebellum exert over fractionated hand and finger, as oppose to whole-arm movements. M1 is essential for the control and production of independent hand and finger movements (Bortoff & Strick, 1993; Porter & Lemon, 1993; Lemon, 2008). Direct damage or lesions to M1 or the corticospinal tract result in severe and permanent deficits in dexterous hand and finger use (Lawrence & Kuypers, 1968a; Lang & Schieber, 2003; Baker & Perez, 2017). The importance of the cerebellum in controlling and adapting gross movements of the arm is also well documented (Bastian & Thach, 1995; Schweighofer et al., 1998; Zackowski et al., 2002; Tseng et al., 2007; Shadmehr et al., 2010; Izawa et al., 2012). Cerebellar output also projects heavily and reciprocally to areas in the parietal cortex known to be important for reaching behaviours and has major connections via the brainstem (e.g., red nucleus and reticular formation) to descending pathways controlling the limbs (Lawrence & Kuypers, 1968b; Clower et al., 2001; Prevosto, Graf, & Ugolini, 2010).

Although the exact mechanisms of TDCS are still poorly understood, especially in terms of driving behavioural changes, a prevailing theory is that stimulation is believed to modulate circuits in the brain which are concomitantly active (Reis & Fritsch, 2011; Bikson & Rahman, 2013; Fertonani & Miniussi, 2017). Given the types of movement demanded by each of the tasks performed in our previous study (fine hand and finger vs whole-arm reaching) and thus the circuits proposed to be preferentially active (M1-corticospinal tract vs cerebellum-brainstem), we predicted (and found, Weightman et al., 2020) that TDCS would have differential effects on hand vs arm movement, when applied to M1 or the cerebellum.

Notwithstanding these prior results, M1 and the cerebellum are richly

interconnected and interplay between them is critical to dexterous use of the limbs. Both TDCS and transcranial magnetic stimulation (TMS) can influence the excitability of pathways between M1 and the cerebellum (Pinto & Chen, 2001; Oliveri, Koch, Torriero, & Caltagirone, 2005; Galea et al., 2009) and connectivity between these structures is also know to change during motor adaptation and skill learning. It has been shown previously that connections between M1 and the cerebellum are lateralised with regards to handedness, as right-handed individuals have a stronger connection between the right cerebellum and left M1 (Schlerf, Galea, Spampinato, & Celnik, 2015). Additionally, Jayaram, Galea, Bastian, and Celnik (2011) and Spampinato and Celnik (2017) found that learning during motor adaptation tasks resulted in a decrease in cerebellar inhibition of M1 (specifically during early learning) and occlusion of M1 plasticity during later learning (Spampinato & Celnik, 2017). Given this, we sought to further our investigation of the effector-specific influence of TDCS observed in our previous study (Weightman et al., 2020), to test whether cathodal stimulation exerts a similarly divergent influence over each of these structures during visuomotor adaptation.

Although it is likely an oversimplification of the effects, studies recording motor-evoked potentials or measuring neuronal firing rates have shown that anodal stimulation increases neural excitability of the targeted area, whereas cathodal TDCS results in a diminution in excitability (Bindman et al., 1964; Nitsche & Paulus, 2000; Nitsche, Nitsche, et al., 2003). However, while there is evidence that both M1 and cerebellar anodal TDCS can enhance motor adaptation (Galea, Vazquez, Pasricha, Orban de Xivry, & Celnik, 2011; Block & Celnik, 2013; Panouillères et al., 2015; Patel et al., 2019; Weightman et al., 2020), there is far less or mixed evidence of the behavioural effect of cathodal TDCS. Mechanistically, this has been anecdotally attributed to the conflict between increased levels of neural excitability associated with motor adaptation and the reduction in excitability induced by cathodal stimulation, resulting in a potential zero-sum effect (Reis & Fritsch, 2011). Nevertheless, some

studies have reported findings showing a decrease in motor learning and adaptive performance as a result of both M1 and cerebellar cathodal TDCS (Stagg, Jayaram, et al., 2011; Jayaram et al., 2012; Panico, Sagliano, Grossi, & Trojano, 2016; Fernandez et al., 2017). Determining whether direct current stimulation does indeed have polarity specific effects on motor adaptation of proximal and distal movements would inform on the mechanistic interplay of these systems, and guide rehabilitative strategies.

We therefore aimed to combine cathodal TDCS targeting M1 and the cerebellum with motor adaptation tasks that required either hand/finger movements or whole-arm movements (Weightman et al., 2020). Given the known anatomical connections, bias in activity of the associated circuits, and in the context of our previous results, we hypothesised that cathodal cerebellar stimulation would decrease adaptation in a task that predominantly necessitates arm movements, but have no or little effect on a task involving fine-finger/hand movements. In contrast, cathodal TDCS of M1 would impair adaptive performance in the task requiring fine hand/finger movements, and have little to no effect on adaptation involving predominantly arm movements.

3.2 Materials & Methods

3.2.1 Participants

A total of ninety-two healthy right-handed (self-reported) participants were recruited to take part in the study (aged 18-26 years, mean age = 19.9 $\pm$ 1.4 years; 37 females). All participants gave written informed consent in line with ethical approval at the University of Birmingham (Science, Technology, Engineering and Mathematics Ethical Review Committee, University of Birmingham). Participants were all undergraduate students at the University of Birmingham and were offered course credits for participating. Prior to starting the study, safety screening questionnaires for TDCS and TMS were completed. All participants had normal or corrected to normal vision,

reported no history of neurological disease and were not taking any centrally acting medication.

Participants were pseudo-randomised into either a whole-arm (vBOT) or hand/finger (joystick) movement task, and then again into one of three stimulation sub-groups: M1 cathodal TDCS, Cerebellar cathodal TDCS or a Sham stimulation group (Table. 3.1). Data from the two sham stimulation sub-groups were the same as reported in our previous study (Chapter 2: Weightman et al., 2020); none of the participants receiving active stimulation had been included in the previous study.

vBOT Task			Joystick Task		
M1	Cerebellar	Sham	M1	Cerebellar	Sham
n = 16	n = 15	n = 15	n = 15	n = 16	n = 15
(4 females)	(6 females)	(9 females)	(6 females)	(5 females)	(7 females)

Table 3.1: *Summary table of the different experimental groups. Participants received either M1, cerebellar or sham stimulation and completed a motor adaptation task using either a robotic manipulandum (vBOT) or hand-held joystick.*

3.2.2 Apparatus

vBOT Task

Participants assigned to the vBOT task sat comfortably in front of a custom-built two-dimensional planar robotic manipulandum (Howard et al., 2009). With their right hand, they used a power grip to grasp the vertical handle of the manipulandum, which allowed movement in the horizontal plane (Figure 3.1a). 10-15cm movements of the handle were required for the task and were typically achieved via motion of the shoulder and elbow, with limited wrist flexion/extension. The task display was reflected from a computer monitor (Mac Cinema HD Display) onto a horizontal screen (60 x 76 cm) directly below, to appear aligned to the motion of the top of the vBOT handle. Vision of participant's upper arm was restricted using a curtain attached to the vBOT frame and the room was darkened prior to starting the task. The position of the vBOT handle was measured and digitised at 1000Hz.

Joystick Task

For the joystick task, participants sat comfortably in front of a vertical computer monitor (22.5 cm x 30.5 cm) and grasped a small low-profile sprung joystick (APEM 9000 Series, height = 6.5cm, width = 2cm) with their index finger and thumb (See Figure 3.1b). The joystick was located to the right of the computer monitor and was fixed to the desk. 2-3cm motion of the joystick was attained by index finger and thumb movements with very slight wrist abduction/adduction. Joystick motion was sampled at 75Hz. An opaque box was used to block vision of participant's hand and forearm during the task.

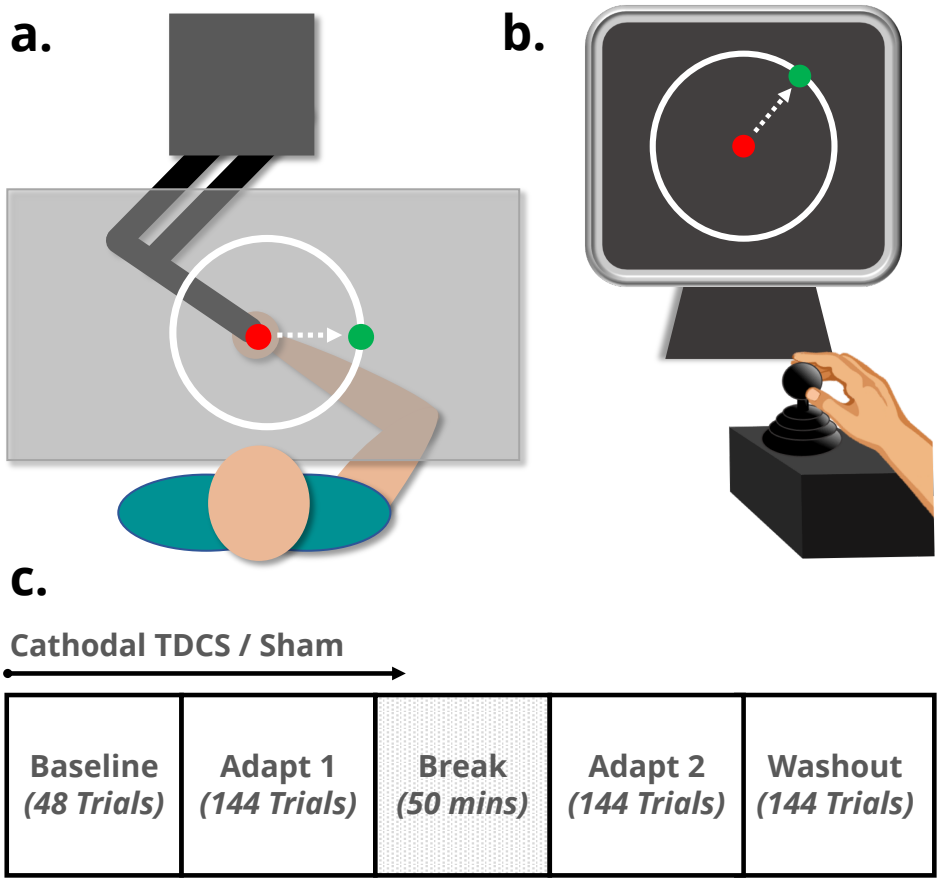


Figure 3.1: *Experimental set up for* ***a:*** *the vBOT task and* ***b:*** *the joystick task, with example screen displays.* ***c:*** *A time course of the study protocol. For each trial, targets would appear at one of eight equidistant locations around the perimeter of the circle, in a pseudorandomised order. In Adapt 1 and Adapt 2, a 60° rotation of the cursor was imposed, with respect to movement of the vBOT handle/joystick. TDCS was started at the beginning of baseline (1.75 minutes), continued during Adapt 1 (5.25 minutes) and then was turned off 10 minutes into the break period. After the break, participants completed Adapt 2 and Washout phases (5.25 minutes each).*

3.2.3 Visuomotor Rotation Paradigm

The display, stimulus-timings and trial/block protocol of the task were exactly the same for both the vBOT and joystick task. The task display contained a white outline circle (12 cm diameter) which was located in the centre of the screen. Using the vBOT handle or joystick, participants controlled a circular red cursor (0.5 cm diameter). During the task a green target circle (0.5 cm diameter) would 'jump' between the

centre position of the circle and one of eight equidistant target locations spaced around the perimeter of the circle (Figure 3.1a & b). The target had a dwell time of 1 second at each location. Participants were instructed to make fast, straight movements with the vBOT handle/joystick in order to direct the cursor towards and through the target before returning to the central home position. They were asked to avoid making curved movements or correcting the trajectory of their movements once initiated. The position at which the cursor crossed the circle perimeter was marked by an open red circle to indicate participant's final angle, which remained on screen until the target moved back to the central home position.

The task included baseline trials, two visuomotor adaptation phases (Adapt 1 and Adapt 2) and washout trials (Figure 3.1c). During baseline and washout trials participants received veridical cursor feedback, thus the on-screen cursor movement matched that of the vBOT handle/joystick. A 60° counter-clockwise (CCW) rotation was applied to the cursor throughout the two adaptation phases. A 50-minute period separated the Adapt 1 and Adapt 2 phases, where the participant remained seated at rest. Prior to the start of the task participants were instructed that at some point a perturbation would be applied to the cursor, however, they were not informed about its nature or when it would be implemented. Participants were instructed to try their best to hit or get as close to the target on every trial and were not told, or asked to employ, any explicit strategies.

3.2.4 TDCS

2 mA of cathodal TDCS (cTDCS) was delivered through two saline soaked sponge electrodes (5 cm x 7 cm) using a DC-Stimulator (neuroConn, Ilmenau, Germany). For the M1 TDCS group, we used a canonical montage: the cathodal electrode was placed over the hand area of the left motor cortex and the anodal electrode was positioned on the contralateral supraorbital ridge (Nitsche & Paulus, 2000; Nitsche, Nitsche, et al., 2003). The hand motor 'hotspot' was identified in each participant using single pulses

of TMS (Magstim Radpid2 stimulator; Magstim Ltd, UK), delivered just above threshold intensity in order to elicit a visible twitch from the first dorsal interosseous muscle. For cerebellar stimulation the cathode electrode was positioned over the right cerebellum, 3 cm lateral to the inion (Galea et al., 2009; Hardwick & Celnik, 2014) and the anodal electrode attached to the upper aspect of the ipsilateral trapezius muscle. This extra-cephalic return electrode was used - as in our previous study (Weightman et al., 2020) - in order to maximally stimulate the cerebellar hemisphere and reduce current spread (Ferrucci et al., 2013; Ferrucci & Priori, 2014). For the sham groups, each participant was pseudo-randomly assigned to either the M1 or cerebellar electrode montage arrangement.

For both the M1 and cerebellar cTDCS groups the current was ramped up over 10 seconds at the beginning of baseline trials, held at 2mA for 17 minutes and then ramped down over 10 seconds. The stimulation lasted throughout the entirety of baseline, Adapt 1 and 10 minutes into the break period (Figure 3.1c). Sham stimulation was delivered at 2mA for 30 seconds at the start of baseline trials with 30 seconds ramping (Russo et al., 2013). After the task participants were asked to rate their levels of perceived comfort and confidence in receiving active stimulation on a ten-point visual analogue scale (VAS), in order to determine the level of blinding achieved.

3.2.5 Data Analysis

Movements of the vBOT handle/joystick were recorded trial-by-trial and analysed using custom MATLAB analysis (version R2018b, Mathworks). The main outcome measure: rotational error, was defined as the angular distance between the target location and the direction of cursor movement at peak velocity. Rotational error calculations were checked trial-by-trial and individual trials were rejected and removed from further analysis if participants failed to follow task instructions e.g. failed to make a movement, made more than one movement, changed their aiming

direction mid movement etc. (0.36% of trials were rejected).

Error was averaged every 4 trials into bins to be used for subsequent analysis. Area under the error curve (AUC error) was calculated for each participant in Adapt 1, Adapt 2 and Washout to determine the total rotational error made during each phase of the task. Statistical analyses were performed in MATLAB and SPSS Statistics (IBM, version 26). ANOVAs were carried out in general linear model form; any significant main effects and interactions were followed up with Bonferroni-corrected multiple comparisons (post-hoc tests) and statistical significance was set at $p < 0.05$. We report partial eta squared (η_p^2) effect sizes. Separate two-way ANOVAs (Task = 2 levels (vBOT/joystick) x Stimulation Group = 3 levels (M1/Cerebellar/Sham TDCS)) were performed for each of the four task phases. We do not include phase as a factor in a broader omnibus test (e.g. a 3-way ANOVA) as there are obvious differences between these phases that are simply due to adaptation and after-effect, that would confound the ANOVA. It is only the relative differences between groups at each phase that is of interest. For clarity we initially report the results from each task separately with regards to adaptation, however these were run in a single two-way ANOVA in order to avoid accruing type I errors.

3.3 Results

3.3.1 No differences between groups in baseline performance

Mean error in the last six bins of the baseline phase was compared across the experimental groups. The two-way ANOVA (Task x Stimulation Group) revealed no significance main effects for Task ($F(1, 86) = 0.44, p = 0.51, \eta_p^2 = 0.005$) or Stimulation Group ($F(2, 86) = 3.07, p = 0.052, \eta_p^2 = 0.067$) and no significant Task x Stimulation Group interaction ($F(2, 86) = 0.41, p = 0.67, \eta_p^2 = 0.009$). These results suggest that all participants were performing similarly towards the end of the baseline (Figure 3.3), making certain that any differences during the adaptation phases were not due to

differences in baseline performance.

3.3.2 Adaptation and de-adaptation performance varied between the two tasks

Two-way ANOVAs revealed a significant main effect of Task in each of the Adapt 1, Adapt 2 and washout phases (Adapt 1: $F(1, 86) = 4.27, p = 0.042, \eta_p^2 = 0.047$, Adapt 2: $F(1, 86) = 11.05, p = 0.001, \eta_p^2 = 0.14$ and washout: $F(1, 86) = 7.03, p = 0.01, \eta_p^2 = 0.076$). Comparisons showed that participants in the joystick task made less error during Adapt 1 and 2 compared to the vBOT task ($p = 0.042$ and 0.001 respectively), whereas they made greater error during washout trials ($p = 0.01$), suggesting that the vBOT version of the task is harder to learn, and has less after-affect (Figure 3.2). However, as we never directly compare adaptation between the two tasks this difference does not present a confound when analysing results further.

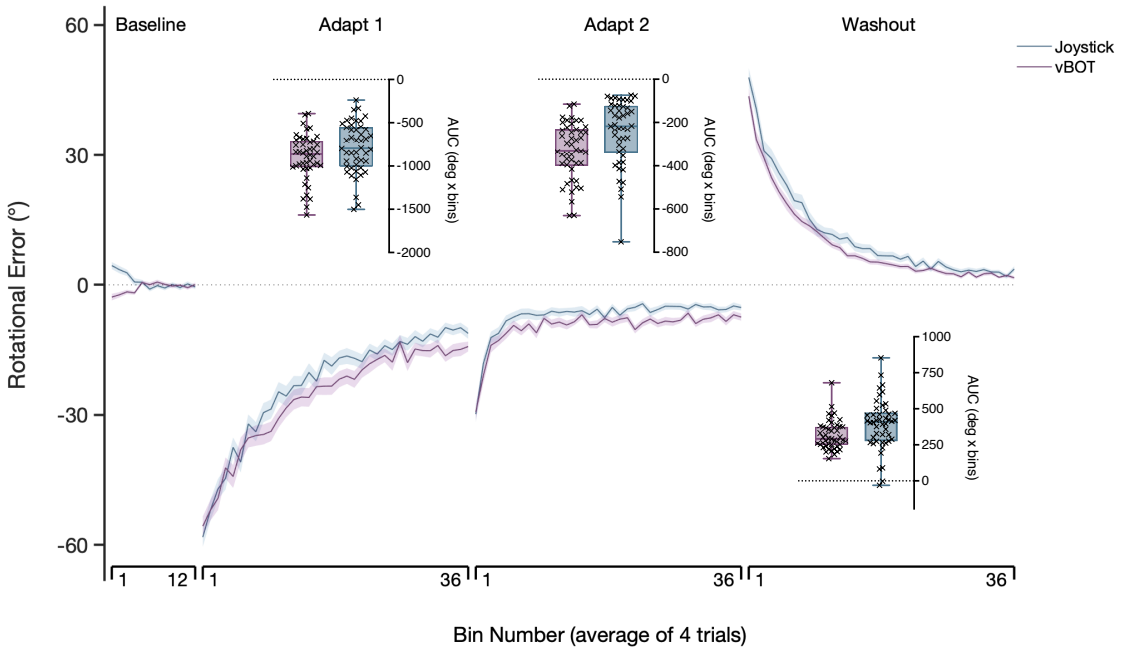


Figure 3.2: *Mean rotational error curves (error over bins of 4 trials, ± standard error = shaded region) for all participants completing the vBOT and joystick tasks (regardless of stimulation group). Box plot inserts depict the average area under the curve (AUC error, degrees x bins) for each task in the three adaptation phases, with individual data points marked by an 'x' (the box indicates mean, upper and lower quartiles; the range shown by the error bars).*

3.3.3 Cerebellar cTDCS decreased adaptation in the vBOT task

During Adapt 1 cathodal cerebellar TDCS decreased adaptive performance in the vBOT task compared to the M1 and sham group (Figure 3.3a). Post-hoc tests on AUC error (Bonferroni corrected for multiple comparisons) following a significant Task x Stimulation Group interaction: $F(2, 86) = 15.33, p < 0.001, \eta_p^2 = 0.26$, revealed adaptation was significantly different between the cerebellar and M1 group ($p = 0.019$) while a strong trend was found for the cerebellar and sham group difference ($p = 0.059$). There was no significant difference between AUC error for the M1 and sham groups ($p > 0.99$).

A two-way ANOVA also revealed a significant Task x Stimulation Group interaction during Adapt 2 ($F(2, 86) = 13.001, p < 0.001, \eta_p^2 = 0.23$). Post-hoc tests showed that the

cerebellar group continued to make significantly more error than the M1 group ($p < 0.009$), with again a trend between cerebellar and sham AUC errors ($p = .0.072$) and no difference between M1 and sham ($p > 0.99$). During washout, despite a significant Task x Stimulation Group interaction; $F(2, 86) = 4.97, p = 0.009, \eta_p^2 = 0.1$, there were no differences in AUC errors between any of the stimulation groups (all $p > 0.63$). These findings suggest that all participants in the vBOT task made a similar amount of errors during washout, likely stemming from them reaching comparable levels of adaptation at the end of Adapt 2. The significant interaction was driven by differences in washout performance in the joystick task (next section).

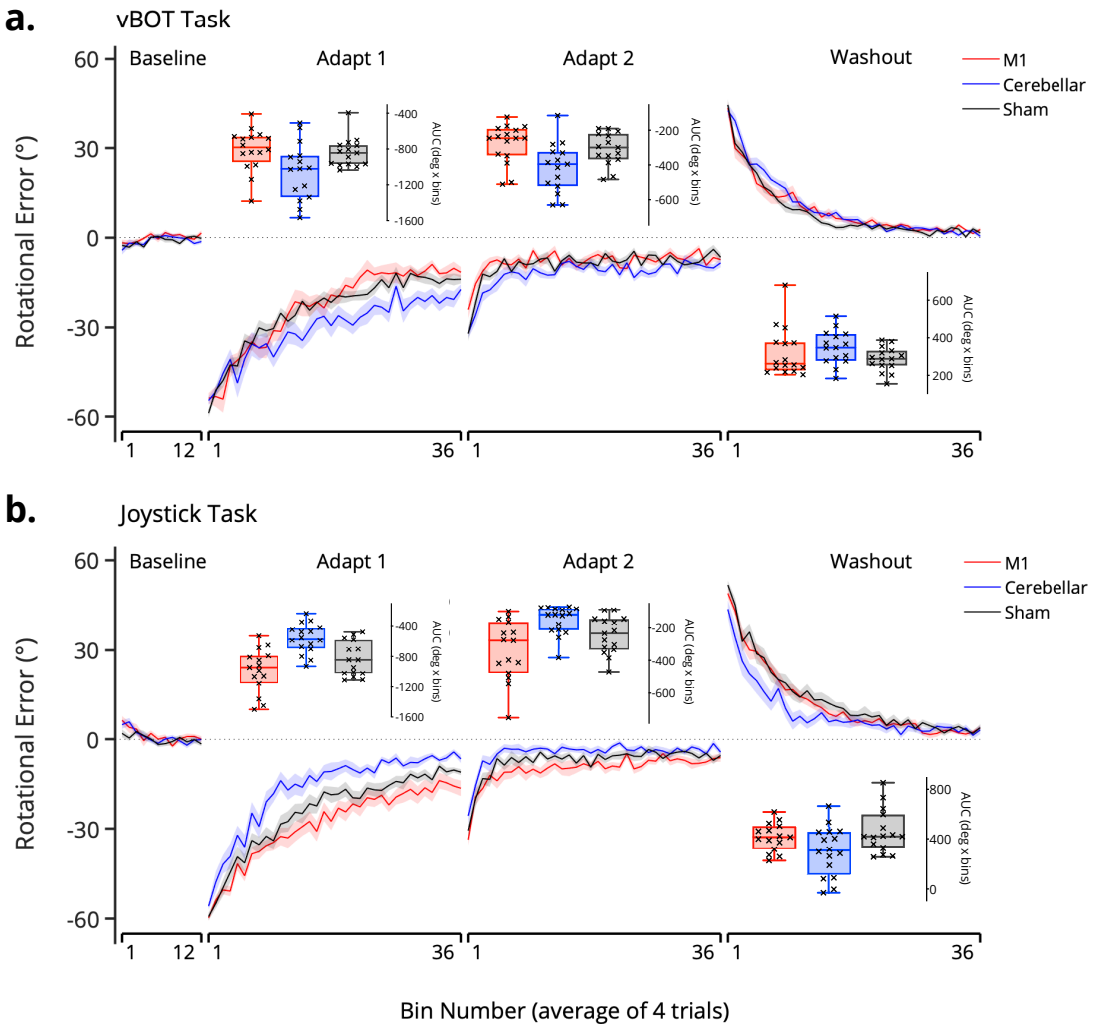


Figure 3.3: *Mean rotational error curves (error over bins of 4 trials, ± standard error = shaded region) for* ***a:*** *the vBOT task and* ***b:*** *the joystick task. Box plot inserts depict the average area under the curve (AUC error, degrees x bins) for each group in the three adaptation phases, with individual data points marked by an 'x' (the box indicates mean, upper and lower quartiles; the range shown by the error bars).*

3.3.4 Cerebellar cTDCS improved adaptation in the joystick task

Contrary to our hypothesis for the joystick task, participants in the cerebellar group displayed significantly less error during Adapt 1 than the M1 and sham groups (post-hoc tests: $p < 0.01$ and $p = 0.009$ respectively, following a significant Task x Stimulation Group interaction from the two-way ANOVA, $F(2, 86) = 15.33, p < 0.001, \eta_p^2 = 0.26$). Despite a slight decrease in performance compared to the sham group (Figure 3.3b),

the effect of cathodal M1 stimulation was not statistically significant ($p = 0.28$).

Post-hoc tests following the significant Task x Stimulation Group interaction ($F(2, 86) = 13.001, p < 0.001, \eta_p^2 = 0.23$), showed at the cerebellar group continued to make less error than the M1 group during Adapt 2 ($p < 0.001$), with no other differences between the M1 and sham group ($p = 0.15$) or cerebellar and sham group ($p = 0.13$). For washout trials, post-hoc tests following a significant Task x Stimulation Group interaction, $F(2, 86) = 4.97, p = 0.009, \eta_p^2 = 0.1$, showed no differences in de-adaptation between the M1 and either the sham ($p = 0.084$) or cerebellar ($p > 0.99$) groups. There was however, a significant difference between the cerebellar and sham groups ($p = 0.007$), as participants in the cerebellar group made less error during de-adaptation (Figure 3.3b).

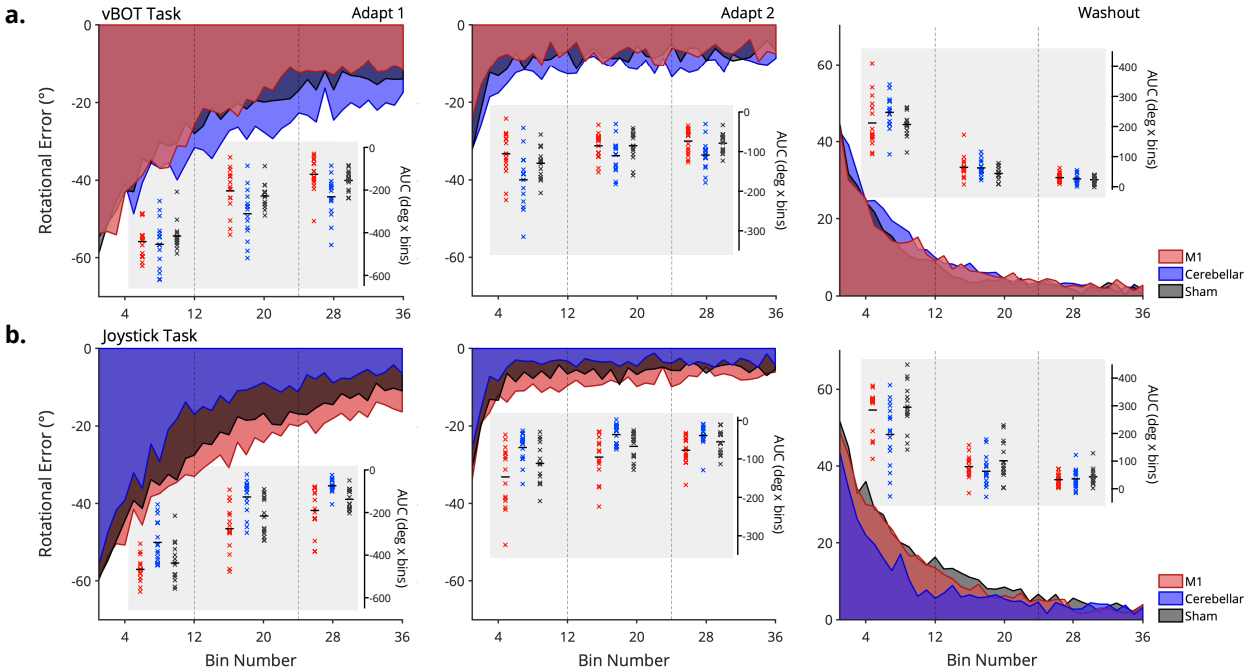


Figure 3.4: *Visualisations of the area under the curve (AUC; degrees x bins) for each adaptation phase in* ***a:*** *the vBOT task and* ***b:*** *joystick task. Scatter plot inserts represent the individual data for each participant in each section of the task phase, with group means shown as short black dashes. Vertical dashed lines signify where the overall data is split into the 3 equal sections.*

3.3.5 Exploratory analyses of adaptation time-course

As cerebellar cTDCS produced significant behavioural changes when analysed at the task-phase level, we performed exploratory analyses to further understand how differences in error between the stimulation groups evolved over time. Each of the adaptation and washout phases were split into three equal sections and the AUC error calculated for each third. These sub-phase errors (for the 1st, 2nd and 3rd area under the curve sections) were analysed separately for each task phase using two-way ANOVAs (Task x Stimulation Group).

During Adapt 1 there was a significant Task x Stimulation Group interaction for all 3 sub-sections of the adaptation phase (1st section: $F(2, 86) = 6.3, p = 0.003, \eta_p^2 = 0.13$, 2nd section: $F(2, 86) = 14.2, p < 0.001, \eta_p^2 = 0.25$ and 3rd section: $F(2, 86) = 17.93, p < 0.001, \eta_p^2 = 0.29$). Post-hoc tests revealed that there were no significant differences between the three stimulation groups in the vBOT task during the first section of Adapt 1 (all $p > 0.69$), suggesting that all groups performed similarly during early adaptation (Figure 3.4a). Conversely, for the joystick task, post-hoc tests showed that the cerebellar group displayed significantly less error than both the M1 and sham groups during the first section ($p < 0.001$ and $p = 0.009$ respectively), with no differences between the M1 and sham groups ($p > 0.99$), see Figure 3.4b. For the second section of Adapt 1, in the vBOT task, cathodal cerebellar TDCS blunted adaptation performance significantly compared to the M1 group ($p = 0.008$) with a near significant decrease compared to the sham group also found ($p = 0.063$). There remained no significant differences between performance in the M1 and sham groups, $p > 0.99$. For the joystick task, the cerebellar group continued to display significantly less error than the M1 ($p < 0.001$) and sham ($p = 0.035$) groups, with no differences between the latter two groups ($p = 0.28$). In the third section of Adapt 1, participants in the cerebellar group made significantly more error than both the M1 ($p < 0.001$) and sham ($p = 0.016$) groups, suggesting cathodal cerebellar TDCS had a greater effect on the final adapted level in the vBOT task. As adaptation started to plateau in the joystick task, post-hoc test revealed that there was

only a difference between the cerebellar and M1 groups ($p < 0.001$), with the cerebellar group making significantly less error. The mean difference in area under the curve between the sham and cerebellar group was 63.3 (degrees x bins), but this failed to reach statistical significance ($p = 0.056$). There was again no difference between M1 and sham groups, $p = 0.16$. In summary, exploratory analysis revealed that cathodal cerebellar TDCS impaired late adaptation to a greater extent during Adapt 1 in the vBOT task. Whereas for the joystick task, it resulted in a greater reduction of error during early and middle adaptation.

Repeating this analysis for the sub-sections within Adapt 2 revealed a significant Task x Stimulation Group interaction for all the respective sections (First: $F(2, 86) = 11.54, p < 0.001, \eta_p^2 = 0.21$, Second: $F(2, 86) = 8.81, p < 0.001, \eta_p^2 = 0.17$ and Third: $F(2, 86) = 10.55, p < 0.001, \eta_p^2 = 0.19$. Post-hoc tests for the first section of Adapt 2 showed that there was only a significant difference between the M1 and cerebellar groups in both the vBOT and joystick task ($p = 0.007$ and $p = 0.001$ respectively), with the cerebellar group making significantly more error in the vBOT task and significantly less error in the joystick task. All other comparisons were non-significant, $p > 0.16$ (Figure 3.4). For the second section, there were no differences in adaptation between any of the stimulation groups in the vBOT task (all $p > 0.26$). In the joystick task the cerebellar group continued to make significantly less error than the M1 group ($p < 0.001$), with no differences between any of the other groups (M1 vs Sham: $p = 0.18$, Cerebellar vs Sham: $p = 0.103$). Post-hocs for the third section of Adapt 2 showed that, similarly to Adapt 1, participants in the cerebellar group made significantly more error at the end of the adaptation phase compared to M1 and sham groups ($p = 0.008$ and $p = 0.036$ respectively) in the vBOT task. As in the previous sections of Adapt 2, there was only a significant difference in adaptation performance between cerebellar and M1 groups ($p = 0.004$) in the joystick task. All other groups performed similarly, $p > 0.18$. Further analyses of Adapt 2 showed relatively inconclusive results, however there appears to be a clear trend of reduced error following cathodal cerebellar TDCS

in the joystick task.

Finally, during washout trials a two-way ANOVA revealed a significant Task x Stimulation Group interaction for the first and second sections of washout trials (1st and 2nd sections: $F(2, 86) = 6.67, p = 0.002, \eta_p^2 = 0.13$ and $F(2, 86) = 3.17, p = 0.047, \eta_p^2 = 0.069$, respectively), but not the third section ($F(2, 86) = 1.09, p = 0.34, \eta_p^2 = 0.025$). Post-hoc tests showed that the cerebellar group in the joystick task displayed significantly less error during the first third of washout trials than the M1 ($p = 0.011$) and sham ($p = 0.004$) groups. This result suggests that participants were able to reduce error to a greater extent early in de-adaption following cathodal cerebellar TDCS (Figure 3.4). There were no other significant differences between stimulation groups for either the joystick task or vBOT task for any of the other sections of washout ($p < 0.065$), suggesting that de-adaptation occurred relatively similarly across groups regardless of stimulation.

3.3.6 Ratings of perceived comfort and confidence in stimulation levels

All participants rated relatively low levels of discomfort (vBOT task means: M1 = 3.06 $\pm$ 1.61; Cerebellar = 3.0 $\pm$ 1.65; Sham = 3.53 $\pm$ 1.06, Joystick task means: M1 = 2.87 $\pm$ 1.3; Cerebellar = 3.44 $\pm$ 1.71; Sham = 3.07 $\pm$ 1.22) on the 10-point VAS (1 = no discomfort, 10 = very high discomfort). A two-way ANOVA (Task x Stimulation Group) revealed there were no significant differences in participant's rating of comfort during the task. The main effects of Task and Stimulation Group were non-significant (Task: $F(1, 86) = 0.61, p = 0.81, \eta_p^2 = 0.001$, Stimulation Group: $F(2, 86) = 0.45, p = 0.64, \eta_p^2 = 0.01$) and no significant Task x Stimulation Group interaction ($F(2, 86) = 0.78, p = 0.46, \eta_p^2 = 0.02$).

Likewise, participants in all three stimulation conditions reported reasonably high levels of confidence on the 10-point VAS (1 = low confidence, 10 = very confident) that they received active TDCS rather than sham/placebo stimulation (vBOT task means: M1

= 7.69 $\pm$ 1.3; Cerebellar = 7.53 $\pm$ 1.19; Sham = 7.8 $\pm$ 1.37, Joystick task means: M1 = 8.13 $\pm$ 1.99; Cerebellar = 8.31 $\pm$ 1.3; Sham = 7.87 $\pm$ 1.68). There was no main effect of Task ($F(1, 86) = 1.9, p = 0.17, \eta_p^2 = 0.022$) or Stimulation Group ($F(2, 86) = 0.032, p = 0.97, \eta_p^2 = 0.064$) and no interaction of these terms ($F(2, 86) = 0.43, p = 0.65, \eta_p^2 = 0.01$). This result suggests that effective blinding of the stimulation condition was achieved.

3.4 Discussion

In this study we aimed to differentially disrupt motor adaptation of movements made with either the whole arm or the hand, by inhibiting M1 or cerebellar function with cathodal TDCS (cTDCS). Based on previous work in our lab, the physiology of motor systems, and the proposed activity-selective effects of stimulation, we hypothesised that cerebellar cTDCS would impair adaptation of arm movements mainly involving the proximal shoulder and elbow joints, whereas M1 cTDCS would impair adaptive performance using fine hand and finger movements.

Indeed, when compared across the experimental phases, cerebellar cTDCS significantly impaired motor adaptation of the proximal upper limb compared to M1 stimulation, which failed to reach statistical significance compared to the sham condition (p=0.056). This latter difference became more obvious with time, and an exploratory analysis indicated that by the end of the first phase, the cerebellar effect was also significantly different from the sham group. Thus, participants who received cathodal cerebellar stimulation continued to make larger errors, while both the sham and M1 groups approached a lower error asymptote. As the cerebellum is known to be crucial in the control and adaptation of arm movements (Schweighofer et al., 1998; Tseng et al., 2007), reducing its excitability via cathodal TDCS is likely to compromise adaptive performance when using whole-arm reaching movements, as displayed here. Herzfeld and colleagues (2014) likewise reported an impairment of performance in a force field reaching task following cerebellar cTDCS, while Jayaram et al., (2012) have

shown disrupted gait adaptation. Depressing cerebellar excitability with repetitive TMS has also been shown to impair cerebellar-dependent adaptation of saccadic eye movements (Jenkinson & Miall, 2010). It is also reported that increasing cerebellar excitability using anodal TDCS, enhances adaptation of whole-arm reaching movements (Galea et al., 2011; Block & Celnik, 2013; Hardwick & Celnik, 2014; Weightman et al., 2020), complementing our present results. Additionally, patients with cerebellar impairments often display severe deficits in the accuracy and control of whole-arm reaching behaviour and adaptation (Zackowski et al., 2002; Bhanpuri et al., 2014; Panouillères et al., 2017). There is however, a current debate surrounding the effectiveness of TDCS on motor behaviour, with an increasing number of studies reporting null effects or failing to replicate previous findings (Hulst et al., 2017; Jalali et al., 2017; Marquez et al., 2017; Mamlins et al., 2019). We believe that the results presented here, coupled with our previous results (Weightman et al., 2020), suggest that TDCS is very sensitive to a combination of stimulation target site and task demands; specifically, regarding biases in activity of neural circuits associated with the particular movements required.

As M1 dominates the control of dexterous hand movements (Lemon, 2008) and previous research in our lab has shown that anodal TDCS increases adaptation performance when the task requires fine hand and finger movements (Panouillères et al., 2015; Weightman et al., 2020), we predicted that cathodal TDCS of M1 would impair performance in the joystick task. Contrary to this hypothesis, despite a trend towards lower levels of error reduction, there were no significant differences between the M1 and sham group at any point during the task. This result is not out of place within the extant literature on M1 cTDCS and motor skill learning/performance (Nitsche, Schauenburg, et al., 2003; Galea et al., 2009; Reis et al., 2009). One possible explanation for the lack of effect is competition between increased M1 excitability associated with motor learning (Muellbacher, Ziemann, Boroojerdi, Cohen, & Hallett, 2001; Bagce, Saleh, Adamovich, Krakauer, & Tunik, 2013) and the depressive effects of

cTDCS (Reis & Fritsch, 2011), thus preventing significant change in performance. Given that all participants in the current study were healthy young adults, floor effects may also have had some bearing on the results, especially as adaptation performance was more complete in the joystick task compared to the vBOT task.

However, we also observed an unexpected enhancement of motor adaptation in the joystick task following cerebellar cTDCS, compared to both M1 and sham stimulation. Thus, cerebellar cTDCS impaired adaptation of the arm, and enhanced adaptation of the hand and fingers. Although not hypothesised, there is a clear physiological foundation for the latter effect when considering the connectivity between M1 and the cerebellum. As discussed previously, increased excitability of M1 can improve motor learning and adaptation, particularly when using the hand/fingers (Nitsche, Schauenburg, et al., 2003; Panouillères et al., 2015; Weightman et al., 2020). It is well established that there are functional connections between the cerebellum and M1 (see review Allen and Tsukahara, 1974). Purkinje cells, which are the sole output neurons of the cerebellar cortex, have inhibitory connections with the dentate nucleus (the largest of the deep cerebellar nuclei), which in turn projects to M1 via disynaptic excitatory pathways through the thalamus. These complex connections form the cerebello-thalamo-cortical pathway, one of the major output systems of the cerebellum (Allen & Tsukahara, 1974; Kelly & Strick, 2003; Daskalakis et al., 2004). At rest this pathway exerts an overall inhibitory tone over the motor cortex, termed cerebello-brain inhibition (CBI). It is believed that TDCS modulates Purkinje cell excitability to either increase or decrease CBI, depending of the polarity of stimulation used (Nitsche & Paulus, 2000; Galea et al., 2009). For example, Ugawa and colleagues (1991) applied anodal electrical currents across the cerebellum, which resulted in short-lasting inhibition of the contralateral M1 (i.e. an increase in CBI). More recently, Galea et al., (2009) showed that modulation of M1-cerebellar connectivity is polarity specific: anodal cerebellar TDCS enhanced CBI, whereas cathodal TDCS decreased it, disinhibiting M1 and therefore increasing excitability. Given these findings, we

speculate that cerebellar cTDCS increased M1 excitability (via reduced CBI) and thus indirectly facilitated adaptation of fine hand and finger movements.

Many studies have investigated the relationship between M1 and the cerebellum during motor adaptation and skill learning (Jayaram et al., 2011; Torriero et al., 2011; Schlerf et al., 2015; Spampinato & Celnik, 2017; Spampinato, Block, & Celnik, 2017). But to our knowledge no study has reported a significant motor effect linked to CBI modulation (see Pope and Miall, 2012 & 2014 for a related cognitive effect). Further research must be conducted in order to mechanistically link the behavioural effect displayed here to a decrease in CBI. It may be particularly interesting to probe the excitability of the motor system with TMS, pre and post intervention, in order to better understand the interaction between TDCS induced changes in neural excitability of different brain regions and motor learning. The capability to improve hand and finger use via stimulation of a brain area distant from M1 may have important practical implications for TDCS use in rehabilitation. Especially when direct targeting of an injured brain area – following stroke or traumatic brain injury etc. – may be best avoided due to contraindications, such as inducing seizures.

Recently, it has become clear that implicit and explicit learning processes contribute to successful adaptive behaviour (Mazzoni & Krakauer, 2006; Taylor et al., 2014; McDougle et al., 2015; McDougle, Ivry, & Taylor, 2016; Voets, Panouilleres, & Jenkinson, 2020). Implicit processes drive gradual adaptation to small discrepancies between predicted and actual consequences of movements, by updating internal models of the imposed perturbation (see review Shadmehr, Smith, and Krakauer, 2010). Implicit sensorimotor adaptation is cerebellar dependent, and thought to constitute the slow process of adaptation (Smith, Ghazizadeh, & Shadmehr, 2006; Tseng et al., 2007). Explicit processes on the other hand, allow a strategic component to the adaptation of large and sudden perturbations. Learners detect the perturbation and consciously select appropriate actions in order to counter it (Heuer & Hegele, 2008; Taylor & Ivry, 2011). Explicit processes are believed to be more involved during

the fast process of adaptation and to be under greater cortical control (McDougle et al., 2015). Results from the present study, especially our exploratory analysis of the time course of the adaptation phases, suggest that cerebellar cTDCS impairs late adaptation to a greater extent in the vBOT task and promotes error reduction early in the joystick task. Given that we suggest the increased performance in the joystick task is the result of CBI-driven disinhibition of the neocortex, and that TDCS of the cerebellum is not focal, one could argue that the cerebellar cTDCS may have facilitated frontal areas outside of M1 (Pope & Miall, 2012). The prefrontal cortex is classically associated with the explicit component of sensorimotor adaptation, due to its role in cognitive control and working memory (Anguera, Reuter-Lorenz, Willingham, & Seidler, 2010; Taylor & Ivry, 2014). In contrast, cathodal cerebellar stimulation impaired performance during late adaptation in the vBOT task, which may reflect a disruption of the direct cerebellar dependent slower process of learning (although the cerebellar contribution to motor learning is not solely confined to the latter stages (Schlerf, Galea, Bastian, & Celnik, 2012; Spampinato & Celnik, 2017)). However, we did not specifically aim to probe the various processes of motor adaptation, so these conclusions must be only speculative. Modelling these data using a two-rate state-space model (Smith et al., 2006; McDougle et al., 2016) to directly investigate a distinction between implicit and explicit processes could help to provide some clarity on this matter.

In summary, we have shown that adaptation of arm reaching movement is impaired following cathodal cerebellar stimulation, consistent with our previous work that argued the cerebellum was more responsible for adaptation of movements involving the proximal musculature, whereas M1 was more involved in adaptation of distal hand/finger movements. Paradoxically, then, we also found that fine hand and finger adaptation was enhanced by cathodal cerebellar TDCS, and we propose this is due to disinhibition of M1 via a reduction in CBI. In other words, we suggest a direct effect of cerebellar cTDCS on proximal control and an indirect effect on distal control. We found no evidence however, for a significant effect of cathodal M1 TDCS on either arm

or hand adaptation, suggesting a single-session of stimulation using these parameters in healthy individuals had null effects. Our results provide additional evidence to support an emerging framework, which suggests TDCS affects neural circuits in an activity-specific manner, consistent with a bias in activity within the motor hierarchy for control of proximal and distal movement (Figure 3.5).

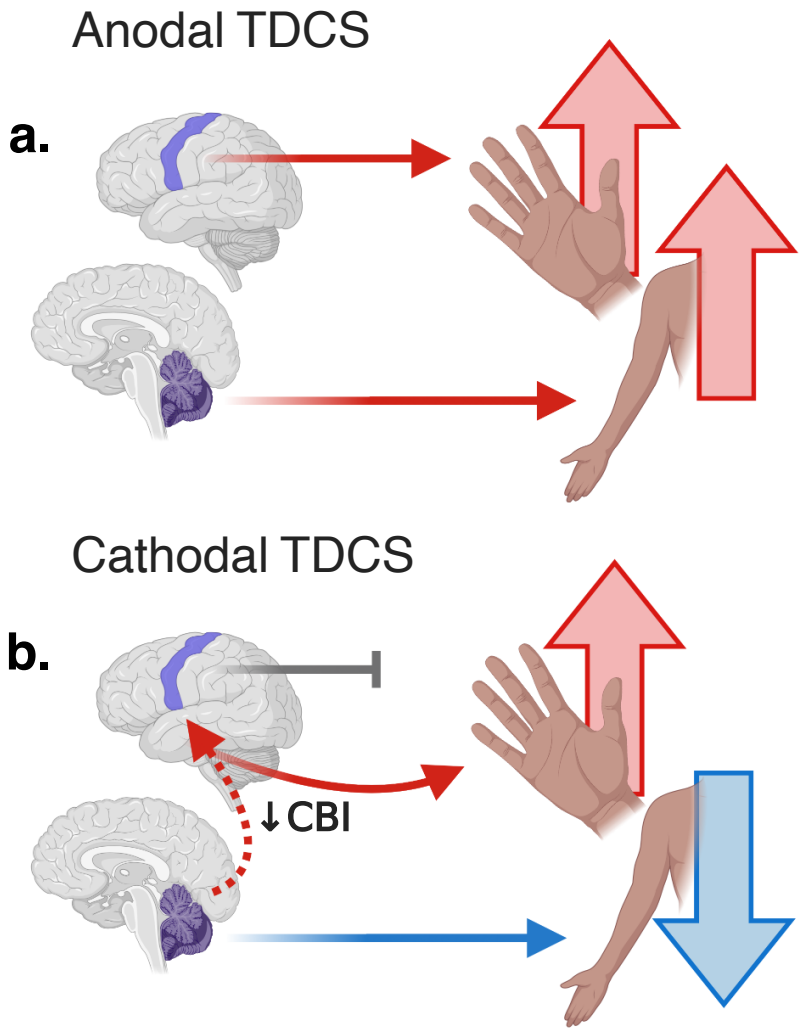


Figure 3.5: *A schematic diagram of the proposed framework of TDCS effects, devised from current and previous results. Panel* ***a:*** *depicts the dissociated effects of anodal TDCS on upper limb motor adaptation reported in Chapter 2 (Weightman et al., 2020), whereby M1 TDCS selectively enhanced adaptation of dexterous hand movements and cerebellar stimulation enhanced adaptation of whole-arm reaches. Panel* ***b:*** *portrays results from the present study. As hypothesised cathodal cerebellar TDCS impaired adaptation of reaching movements, however with no significant effect of M1 cathodal TDCS on hand and finger movements. We also found cathodal cerebellar TDCS indirectly improved adaptation of dexterous hand movements, which we suggest to be a result of disinhibition of M1 via a reduction in cerebello-brain inhibition (CBI). Created with BioRender.com*

Chapter 4

Timing is everything: event-related transcranial direct current stimulation (er-TDCS) improves context-dependent motor learning

4.1 Introduction

The foundational theories of motor learning are based upon coincident, time-dependent mechanisms of plasticity. Donald Hebb (1949) was the first to formalise this idea in its modern form. He proposed that simultaneous activity in the pre and post synaptic membranes of neurons selectively and specifically strengthens those synaptic connections and forms the basis of Hebbian plasticity. Despite some refinement of these theories (Kandel & Hawkins, 1992; Shatz, 1992), the temporal association of events remains key to the understanding of motor learning. Evidence of cellular and synaptic changes have been observed during classical conditioning (one of the simplest forms of Hebbian learning), which are dependent on temporally aligned spiking activity (Hawkins, Abrams, Carew, & Kandel, 1983; Hawkins, 1984). The Hebbian mechanisms behind these behavioural changes are thought to be dependent on long-term potentiation (LTP) and long-term depression (LTD) -like processes. Various forms of LTP and LTD are ubiquitous throughout the mammalian brain, including the hippocampus, cerebellum, and sensory-motor cortices (Ito, 2001; Malenka & Bear, 2004), and are thought to underpin all forms of learning and memory. Yet, protocols for non-invasive brain stimulation intended to promote motor learning and rehabilitation - particularly transcranial direct current stimulation (TDCS) - largely ignore these timing-dependent mechanisms.

TDCS is a non-invasive form of brain stimulation often used to induce plasticity in the motor system by modulating neural excitability. Studies measuring the physiological effects of TDCS using transcranial magnetic stimulation (TMS), electroencephalogram (EEG), functional MRI (fMRI), magnetic resonance spectroscopy (MRS) etc. have reported alterations in neural excitability that are dependent on the polarity of stimulation (Nitsche & Paulus, 2000, 2001; Kwon et al., 2008; Stagg et al., 2009; Kwon & Jang, 2011; Pellicciari, Brignani, & Miniussi, 2013). Changes in neuronal excitation have been shown to be almost instantaneous in terms of increases in firing rates (Bindman et al., 1964; Landau, Bishop, & Clare, 1964;

Purpura & McMurtry, 1965) and motor evoked potentials (Priori et al., 1998; Nitsche & Paulus, 2000) following the application of TDCS and other forms of polarising currents. However, these changes in neural excitability do not always reliably translate into modulation of motor behaviour, including motor learning. One potential reason for these apparently inconsistent results may be the low temporal resolution of stimulation. In many studies, 15-20 minutes of stimulation is typically administered before and/or during a behavioural task and to date, most investigations have focussed on the potential effects of these tonic stimulation bouts (Patel et al., 2019). Despite knowledge of the importance of time-dependent mechanisms for driving the plasticity that underpins successful motor learning, to our knowledge, no other studies have aimed to deliver TDCS in a more temporally specific manner with the intention of facilitating motor learning. If TDCS can instantaneously modulate neural activity, applying short duration epochs of TDCS temporally aligned with movement has the potential to specifically and selectively enhance learning, by driving coincident mechanisms of plasticity in the circuits of the brain that are active during the movement.

We therefore aimed to deliver short epochs of TDCS coincident with one of two movements during a context-dependent motor learning task - a stimulation protocol we termed event-related TDCS (er-TDCS). It has been shown that without contextual information, individuals are unable to adapt to opposing dynamic environments simultaneously and considerable interference of learning is observed (Brashers-Krug, Shadmehr, & Bizzi, 1996; Krakauer, Ghilardi, & Ghez, 1999; Karniel & Mussa-Ivaldi, 2002; Caithness et al., 2004). However, when provided with unique visuospatial contextual cues, associated to the opposing dynamic environments that perturb movement, it is possible to adapt to both simultaneously and significantly reduce interference (Wada et al., 2003; Richter, Jansen-Osmann, Konczak, & Kalveram, 2004; Hwang, Smith, & Shadmehr, 2006; Cothros, Wong, & Gribble, 2009; Addou, Krouchev, & Kalaska, 2011; Hirashima & Nozaki, 2012; Howard, Ingram, Franklin, & Wolpert,

2012; Howard, Wolpert, & Franklin, 2013, 2015; Sheahan, Franklin, & Wolpert, 2016). In our study, participants adapted to two opposing velocity-dependent force-fields, applied on interleaved trials in a random order, and contextually distinguished by a leftward or rightward shift in the visual display (Howard et al., 2013). er-TDCS was applied over the cerebellum or M1 in brief (< 3 second bouts) during movements through only one of the two force-fields. Thus, only one of the learning contexts was performed with simultaneous stimulation.

Using this paradigm we demonstrate (and replicate) that brief epochs of stimulation, applied over the cerebellum and in synchrony with movement, selectively enhanced motor adaptation whilst, importantly, leaving adaptation of the non-stimulated (yet interleaved) movements unaffected. We believe this novel stimulation protocol harnesses mechanisms of Hebbian plasticity, resulting in the selective, transient, potentiation of those neurobehavioural circuits that are active concomitant with stimulation (Bikson & Rahman, 2013; Fertonani & Miniussi, 2017; Bikson et al., 2019).

4.2 Materials and Methods

4.2.1 Participants

A total of seventy-eight participants (aged 18-32 years, mean = 20.6 $\pm$ 3.0 years; 39 male) gave written informed consent to take part in the study (approved by the Science, Technology, Engineering and Mathematics Ethical Review Committee at the University of Birmingham). All participants were right-handed, had normal or corrected to normal vision and completed a safety screening questionnaire for TMS and TDCS prior to the beginning of the the session. For the main experiment, sixty participants were pseudo-randomised into one of three experimental groups: M1 er-TDCS group (n = 20; mean age = 19.7 $\pm$ 0.8 years, 10 males), Cerebellar er-TDCS group (n = 20; mean age = 19.8 $\pm$ 1.9 years, 11 males) or a Sham TDCS group (n = 20; mean age = 19.5 $\pm$ 0.8

years, 9 males). A further eighteen naive participants (n = 18, mean age = 23.9 ± 4.7 years, 9 males) were recruited for an additional experimental group. Participants in this additional group also received cerebellar er-TDCS. Importantly, data from the additional experimental group were collected after the conclusion of the main experiment, in an attempt to replicate the initial effect.

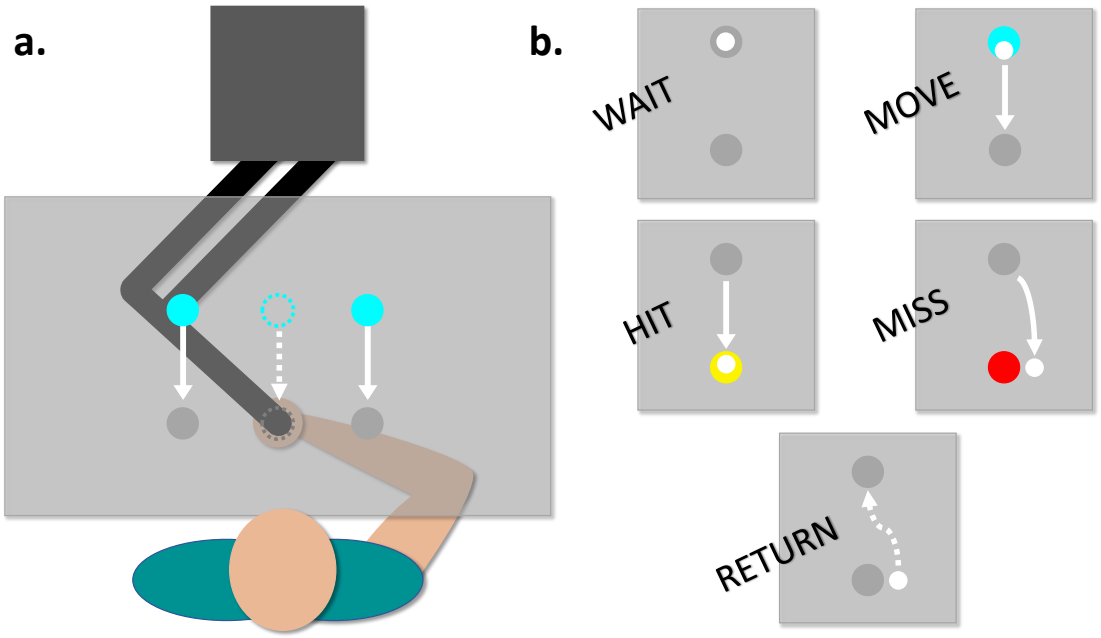


Figure 4.1: ***a:*** *A schematic of the task set-up, with an example screen display. Movements were always made in the midline position, but the cursor and task display would be shifted either 10cm to the right or left.* ***b:*** *Visualisation of the basic task instructions and trial elements. At the start of every trial, participants were required to position the cursor and remain in a distal home position until it changed colour (from grey to blue). Once blue, participants were required to make a straight fast movement towards the target. Trial success was indicated by a yellow (hit) or red (miss) flash of the target marker. Once the movement had been completed the vBOT motor passively moved the handle back toward the home position, ready for the next trial.*

4.2.2 Experimental Design

Participants were seated in an armless chair so they could comfortably reach and manipulate the handle of a custom-built robotic manipulandum (vBOT; Howard et al. (2009)) with their right arm. The vBOT measured and stored the position of the handle at 1000Hz, only allowing movements in the horizontal plane. The task display (Mac Cinema HD Display) was reflected in a horizontal mirror (60 x 76 cm) located directly below to appear as a virtual image co-planar with the manipulandum. The screen displayed two grey circular markers (2 cm diameter) which represented the home position and the target, located 20 cm and 10 cm away from the edge of the screen respectively. The screen also displayed a white cursor (1 cm diameter) which was controlled by movement of the vBOT handle. The home and target markers were displaced 10cm left or right of the screen midline, depending on the context of the trial, and the cursor was displaced 10cm left or right of the vBOT handle (Figure 4.1a).

Participants were told that the aim of the task was to make fast movements from the home marker to the target marker, so that the cursor moved in a straight line between the two (10 cm movement). At the beginning of each trial the participant entered the home position and were held there for 3 seconds by stiff spring forces on the vBOT handle, before being allowed to move. The home marker then changed from grey to blue indicating that participants were allowed to make their movement and the forces were released. During the hold period participants were asked to keep relaxed and not to 'pull' or 'lean' on the handle. To encourage fully completed movements, participants were told that it was acceptable to overshoot the target slightly, but were discouraged from making excessively large movements. If the movement was accurate and hit the target marker it would flash yellow for 1 second indicating a successful trial (Figure 4.1b). If the movement failed to hit the target or deviated $\pm$ 2 cm from the midline at any point during the movement path the target would flash red for 1 second, indicating an unsuccessful trial. Once the movement was completed, the vBOT would passively move the handle back to the home position, ready for the next trial to start. Each

trial took roughly 5 seconds from start to finish (3 second hold, 1 second movement, 1 second return). Vision of the upper arm was blocked during the task using a curtain and all lights extinguished prior to starting the task.

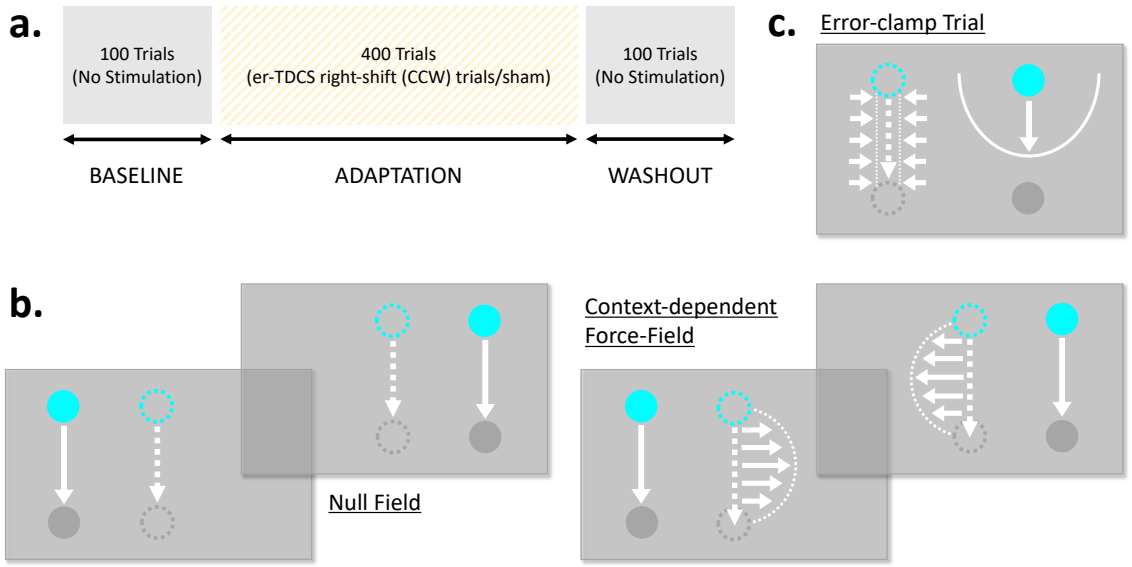


Figure 4.2: ***a:*** *A time course of the study. Baseline included 100 trials in a null field with no stimulation applied. During adaptation (400 trials), a CW or CCW force-field was imposed to the vBOT handle, which was associated with a leftward or rightward shift in task display respectively. er-TDCS was only applied on right-shift (CCW) trials (total of 200 trials). 100 washout trials immediately followed which were unstimulated and were again completed in a null field.* ***b:*** *The task display during null field (left) and context-dependent force-field (right) trials.* ***c:*** *During error-clamp trials participants' movements were constrained to a virtual channel between the home position and target marker. Participants were not given visual feedback regarding the lateral position of the cursor, but observed an expanding semi-circle which indicated their distance from the start location/target.*

4.2.3 Behavioural Protocol

The behavioural task consisted of 600 trials and was split into three phases: Baseline (100 trials), Adaptation (400 trials) and Washout (100 trials), see Figure 4.2a. On each trial, in all three phases, the task display would either be presented with a 10 cm leftward or rightward shift from the midline position. The order of this shift was pseudo-randomised, so that there was an equal number of leftward and rightward shift trials in each phase and no more than 3 consecutive trials with the same contextual shift. The trial/shift order was the same for all participants. During baseline trials no forces were imposed on the handle so participants could move between the home marker and the target unperturbed (Figure 4.2b). For adaptation trials the leftward or rightward contextual shift in the task display was consistently associated with either a clockwise (CW, for left-shift) or counter-clockwise (CCW, for right-shift) velocity sensitive curl force-field (Figure 4.2b) - thus creating two distinct trial contexts. The strength of both imposed force-fields was 12 N/m/s (see equation 4.1).

$$\begin{bmatrix} F_x \\ F_y \end{bmatrix} = \begin{bmatrix} 0 & -12 \\ 12 & 0 \end{bmatrix} \begin{bmatrix} V_x \\ V_y \end{bmatrix} \tag{4.1}$$

Washout trials immediately followed the adaptation phase, which were once again performed without any forces i.e. identical to baseline. Participants were not given any explicit information regarding the link between the visual shift and associated direction of force-field.

In order to measure compensatory forces applied against the curl field, 60 error-clamp trials were pseudorandomly interleaved throughout the task (10% of all trials). These trials were distributed proportionally throughout the three task phases. During error-clamp trials, movements were constrained to a 'virtual channel' between the home

position and target marker, so that forces produced against the channel walls could be measured (Figure 4.2c). Error-clamp trials took place twice every 20 trials and the contextual shift was pseudorandomly ordered so that no more than two successive error-clamp trials were of the same shift. Additionally, error-clamp trials only occurred on trials where there was a switch in context and not after one or two trials of the same shift. To avoid directional feedback, the vBOT position was indicated via an expanding semi-circle representing only its the distance from start location (Lago-Rodriguez & Miall, 2016). At the end of the task each participant was asked if they had noticed the relationship between the visuospatial context and direction of the force in order to understand their explicit knowledge during the task.

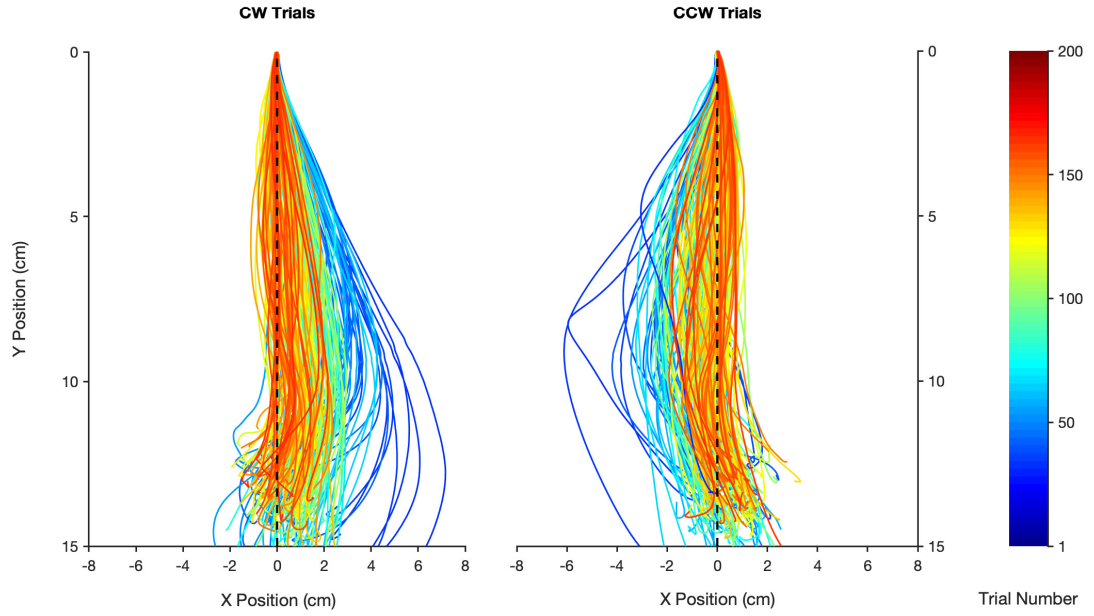


Figure 4.3: *Representative lateral deviation trajectory paths (cm) of an individual participant separated by movements through the CW (left) and CCW (right) force-fields. Trajectory path colour is matched to the trial number indicated by the colour bar (cooler colours = early trials, warmer colours = later trials).*

4.2.4 TDCS

Anodal TDCS was delivered via two sponge electrodes (5 x 7 cm) soaked in saline solution, using a nurostym tES device (Neuro Device Group S.A., Poland). For cerebellar stimulation the anodal electrode was placed over the right cerebellar cortex (3 cm lateral to the inion; Galea et al. (2009)) and the cathode was positioned on the superior aspect of the right trapezius muscle (Panouillères et al., 2015; Weightman et al., 2020). For M1 stimulation the anodal electrode was positioned over the hand area of the left motor cortex, identified by single pulse TMS (Magstim Rapid2 stimulator; Magstim Ltd, UK) delivered at suprathreshold stimulus intensity so as to elicit a visible twitch of the first dorsal interosseous muscle. The cathode electrode was placed on the skin over the contralateral supraorbital ridge (Nitsche & Paulus, 2000). TDCS was only delivered during the adaptation phase, the parameters of which depended on the stimulation group. Once the task had ended, participants rated their perceived comfort and confidence in their belief that they received real stimulation on a 10-point visual analogue scale (VAS). They were also asked if they noticed anything specific regarding the timing of the stimulation, with respect to the task.

er-TDCS

For the main experiment, participants in the M1 and cerebellar stimulation groups received brief epochs of TDCS during the adaptation phase, with each epoch, temporally overlapping with movements made through the CCW force-field, when the task display was shifted to the right. Stimulation was ramped up over 1 second during the hold period (1 second prior to the movement cue). It was then held at 2mA for 1 second during the movement and then ramped down over 1 second as the vBOT returned the participant's hand to the home position. TDCS was applied on both force-field and error-clamp trials. In the additional experimental group, the er-TDCS protocol was conducted as per the main experiment, however, stimulation was only applied over the cerebellum and concurrently with movements made during the CW

force-field and associated left-shift in visual display. Data from this additional stimulation group served as an attempt to replicate the effects found in the main experiment, with stimulation applied during movements through the opposing force-field direction.

Sham Stimulation

For the sham group, stimulation was ramped up over 10 seconds at the start of the adaptation phase, held at 2mA for 10 seconds and then ramped down over a further 10 seconds. The electrode montage was randomly assigned to either M1 or cerebellar prior to starting the session. This sham protocol was chosen to minimise the length of stimulation administered (as we suggest excitability changes can occur after very short periods of TDCS) and is generally accepted to be sufficient within the literature (Fonteneau et al., 2019).

4.2.5 Data Analysis

Data collected from the vBOT were analysed offline in MATLAB (The Mathworks, version R2018b). The lateral deviation (LD) of movements at peak velocity was calculated for null and force-field trials and subsequently averaged into bins. For error-clamp trials, a force compensation ratio (FC) was calculated, see equation 4.2.

$$\frac{\int_{t0}^{tend} actual\ force}{\int_{t0}^{tend} ideal\ force} \times 100 \tag{4.2}$$

Actual force was the forces generated against the channel walls, integrated across the movement; ideal force was the force required to fully compensate for perturbation in force-field trials (ideal force: velocity $\times$ field constant). Any LD or FC values that

fell outside ± 2 SD of the mean across the group were excluded prior to averaging and thus removed from further analysis. LD and FC values were analysed separately for the two contexts. Area under the learning curve for LD and FC during each phase of null, force-field and error-clamp trials was calculated to be used for statistical analysis, providing a measure of total error/adaptation during the task.

Statistical analyses were conducted in MATLAB, R (R Core Team, version 3.6.3) and SPSS (IBM, version 26). All ANOVAs were run in general linear model format and followed up with Bonferroni-corrected multiple comparisons, when a significant main effect or interaction was found. Estimation statistics were conducted as per Ho, Tumkaya, Aryal, Choi, and Claridge-Chang (2019), reporting paired Cohen's d effect sizes and bias-corrected and accelerated confidence intervals (following 5000 bootstrap samples).

Data from the additional experimental group were processed and analysed separately as they were collected after the main experiment and was not included in the original study design.

4.3 Results

Main Experiment

4.3.1 Cerebellar er-TDCS selectively improved context-dependent force-field adaptation

We first sought to determine any differences in adaptation between trial contexts for each stimulation group during the task. We measured the area under the learning curve (calculated from lateral deviation of movements from the target midline; see methods for further details) in order to compare adaptation performance on trials performed with simultaneous stimulation and those without, using a 3x3x2 mixed-design ANOVA. The ANOVA contained within-subject factors of Adaptation

Phase (baseline, adaptation, washout) and Trial Context (CW (left-shift), CCW (right-shift)) and the between-subject factor of Stimulation Group (M1 er-TDCS, cerebellar er-TDCS, sham). The ANOVA revealed significant main effects of Adaptation Phase, Stimulation Group and a significant interaction between the three variables ($F(2, 342) = 1312.45, p < 0.001, \eta_p^2 = 0.89$, $F(2, 342) = 18.93, p < 0.001, \eta_p^2 = 0.1$ and $F(4, 342) = 3.44, p = 0.009, \eta_p^2 = 0.04$, respectively). Bonferroni corrected multiple comparisons revealed that, during adaptation, participants who received cerebellar er-TDCS made significantly less error, and thus adapted better, on stimulated CCW trials compared to unstimulated CW trials, $p < 0.001$ (Figure 4.4). In contrast, we found no evidence of enhanced adaptation following M1 er-TDCS (Figure 4.4), as participants made similar levels of error on both stimulated and unstimulated trials ($p = 0.97$). Similarly, participants in the sham group adapted comparably during left and right-shift trials ($p = 0.72$), suggesting there was no in-built task bias (Figure 4.4).

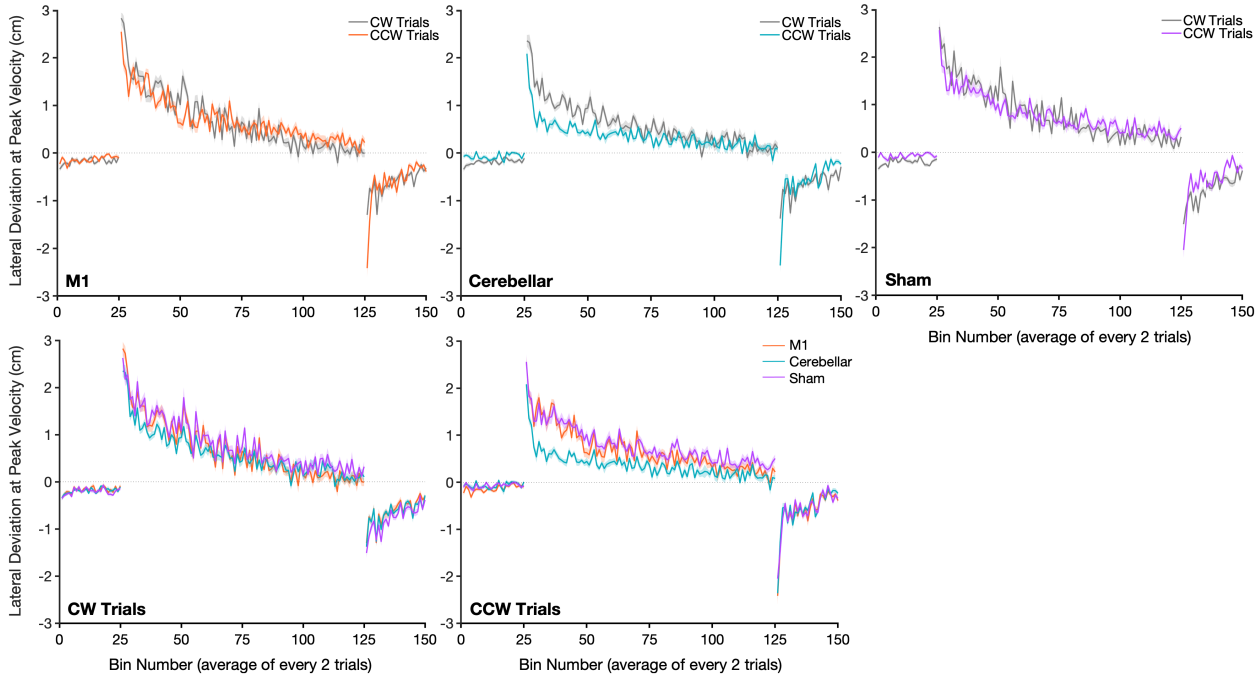


Figure 4.4: *Top panel: Mean lateral deviation for CW (left-shift) and CCW (right-shift) trials (± standard error, shaded regions), averaged into bins of two trials for (from left to right) the M1 er-TDCS, cerebellar er-TDCS and sham stimulation groups. The M1 and cerebellar groups received er-TDCS on CCW trials during the adaptation phase. Lower panel: mean LD (bins of two trials) for all three stimulation groups during either CW or CCW contextual trials.*

Testing the robustness of these effects using estimation statistics (Ho et al., 2019), confirmed that er-TDCS applied to the cerebellum selectively improved the adaptation on CCW trials, while CW trials were unaffected. The effect size for this comparison was substantial (paired Cohen's d = -1.3) with 95.0% confidence intervals (CI) that did not overlap zero ([-2.05, -0.53]; Figure 4.5). Conversely, the paired Cohen's d between CW and CCW trials for the M1 er-TDCS group was close to zero, which fell well within the CI (d = -0.0059, 95.0% CI = [-0.66, 0.64]); for the sham group d = -0.061 and 95.0% CI = [-0.69, 0.57].

Further multiple comparisons from the three-way interaction suggest that there were no differences in adaptive performance between trial contexts during baseline for any of the stimulation groups (all $p > 0.504$), indicating that any differences during adaptation were not a result of uneven performance during baseline (Figure 4.4). There were

also no differences in de-adaptation between trial contexts during washout trials (all $p > 0.23$), which is likely a result of similar levels of learning reached towards the end of the adaptation phase. Additionally, when considering overall adaptation (adaptation to both CW and CCW trials, sign transformed and combined), results from the ANOVA revealed that participants in the cerebellar er-TDCS group made significantly less error compared to the M1 er-TDCS and sham group (both $p < 0.001$), with no significant differences between the latter two groups, $p = 0.078$ (Figure 4.4).

These results show that event-related stimulation of the cerebellum selectively enhanced adaptation of stimulated CCW trials compared to CW trials, with no effect of M1 er-TDCS on context-dependent adaptation or task bias (indicated by sham data). The reduction of error on CCW (right-shift) trials following cerebellar er-TDCS also contributed to (at least in part) an overall improvement in adaptation during the task (Figure 4.4).

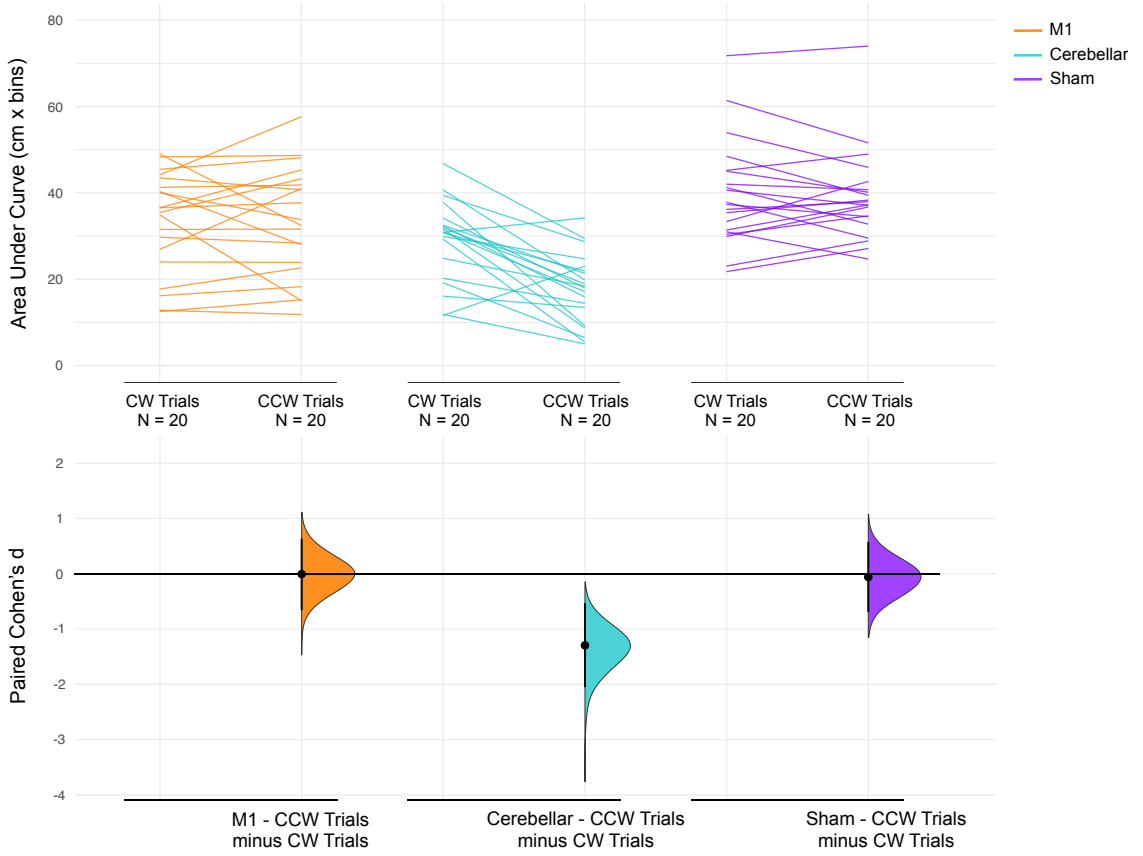


Figure 4.5: *Top panel: area under the curve (cm x bins) for CW vs CCW trials for each participant during the adaptation phase, with each participant's data connected by a line. Lower panel: paired Cohen's d plotted as a bootstrap sampling distribution. Mean differences are depicted as dots, with 95.0% CIs indicated by black vertical bars.*

4.3.2 Event-related Cerebellar TDCS improved overall force compensation during error-clamp trials, but with no context specific effects

The predictive forces applied against the channel walls during error-clamp trials were computed as a percentage of ideal force required to fully compensate for the force-field applied during the task (force compensation ratio, see methods). Force compensation should be close to zero during baseline and washout phases of the task, as no forces were applied. Area under the curve was then calculated (AUC-compensation) for each participant in each task phase and trial context, in order to compare performance. A

3x3x2 (Task Phase x Stimulation Group x Contextual Shift) mixed-design ANOVA revealed significant main effects of Task Phase ($F(2, 342) = 873.68, p < 0.001, \eta_p^2 = 0.84$) and Stimulation Group ($F(2, 343) = 10.78, p < 0.001, \eta_p^2 = 0.06$), but no significant three-way complex interaction ($F(4, 342) = 0.66, p = 0.99, \eta_p^2 = 0.001$). There were no differences between force compensation on CW vs CCW trials for any of the stimulation groups, all $p > 0.072$, suggesting er-TDCS had no specific effect on performance during error-clamp trials. The ANOVA, however, did reveal a significant interaction between Phase and Stimulation Group ($F(4, 342) = 9.92, p < 0.001, \eta_p^2 = 0.1$). Multiple comparisons showed that the three stimulation groups performed similarly on error-clamp trials during baseline and washout phases (all p > 0.99), yet during the adaptation phase, participants in the cerebellar er-TDCS produced greater levels of force compensation compared to the M1 er-TDCS and sham group, both $p < 0.001$ (Figure 4.6), with no difference between the latter two group ($p = 0.39$). These results may suggest that er-TDCS over the cerebellum had a global effect on force compensation during error-clamp trials, rather than the specific timing-dependent effect observed for lateral deviation error-reduction.

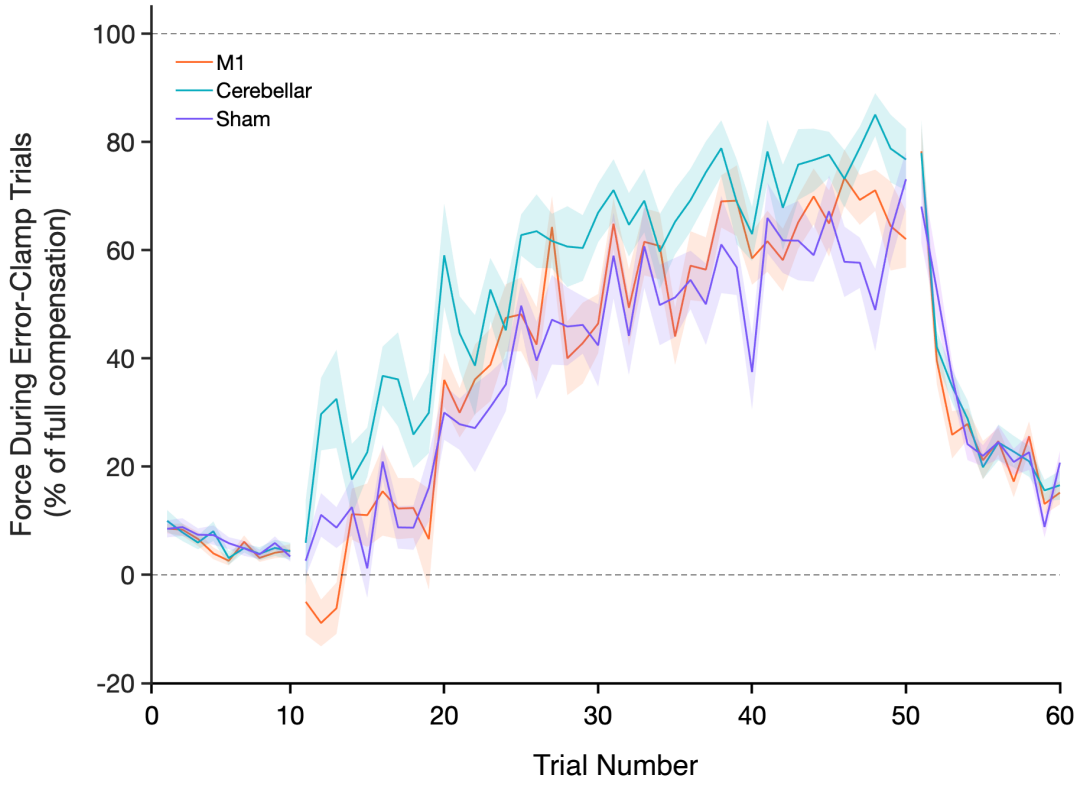


Figure 4.6: *Average force compensation during error-clamp trials (± standard error, shaded region) in each task phase for all three stimulation groups. Data is sign adjusted to show the percentage of full compensation for both expected CW (left-shift) and CCW (right-shift) error-clamp trials*

4.3.3 Cerebellar er-TDCS increased overall hit rate, but without significant context specific effects

Accuracy during the task was determined by whether the participant hit or missed the target. If a participant's movement failed to land on or pass through the target marker or deviated laterally from the midline by more than 2cm at any point on the movement trajectory, a miss was recorded for that trial. A further 3x3x2 mixed-design ANOVA of the percentage of missed trials during the task displayed significant main effects of Task Phase ($F(2, 342) = 245.013, p < 0.001, \eta_p^2 = 0.59$) and Stimulation Group ($F(2, 342) = 15.021, p < 0.001, \eta_p^2 = 0.081$), and a significant 3-way interaction

($F(4, 342) = 2.64, p = 0.034, \eta_p^2 = 0.03$). Despite missing the target less on CCW stimulated trials (a reversal of the trend for the M1 er-TDCS and sham groups), this difference did not prove statistically significant, $p = 0.33$ (Figure 4.7b). In fact, the significant three-way interaction seems to be driven entirely by differences in miss percentage in the sham group during adaptation and washout, with those participants making more task errors on right-shift (CCW) trials during adaptation ($p = 0.004$) and on left-shift trials during washout ($p = 0.03$). These differences in the sham group hit rate are likely due to greater terminal errors rather than early trajectory errors, as no significant differences in lateral deviation were observed for any of the task phases. There were no further significant differences between trial contexts for any other group in any of the task phases (all $p > 0.23$). The ANOVA did reveal a significant interaction between Phase and Stimulation Group interaction ($F(4, 342) = 5.28, p < 0.001, \eta_p^2 = 0.06$), which showed that during adaptation participants in the cerebellar er-TDCS group were more accurate on both CW and CCW trials than the M1 er-TDCS or sham groups (both $p < 0.001$, Figure 4.7a).

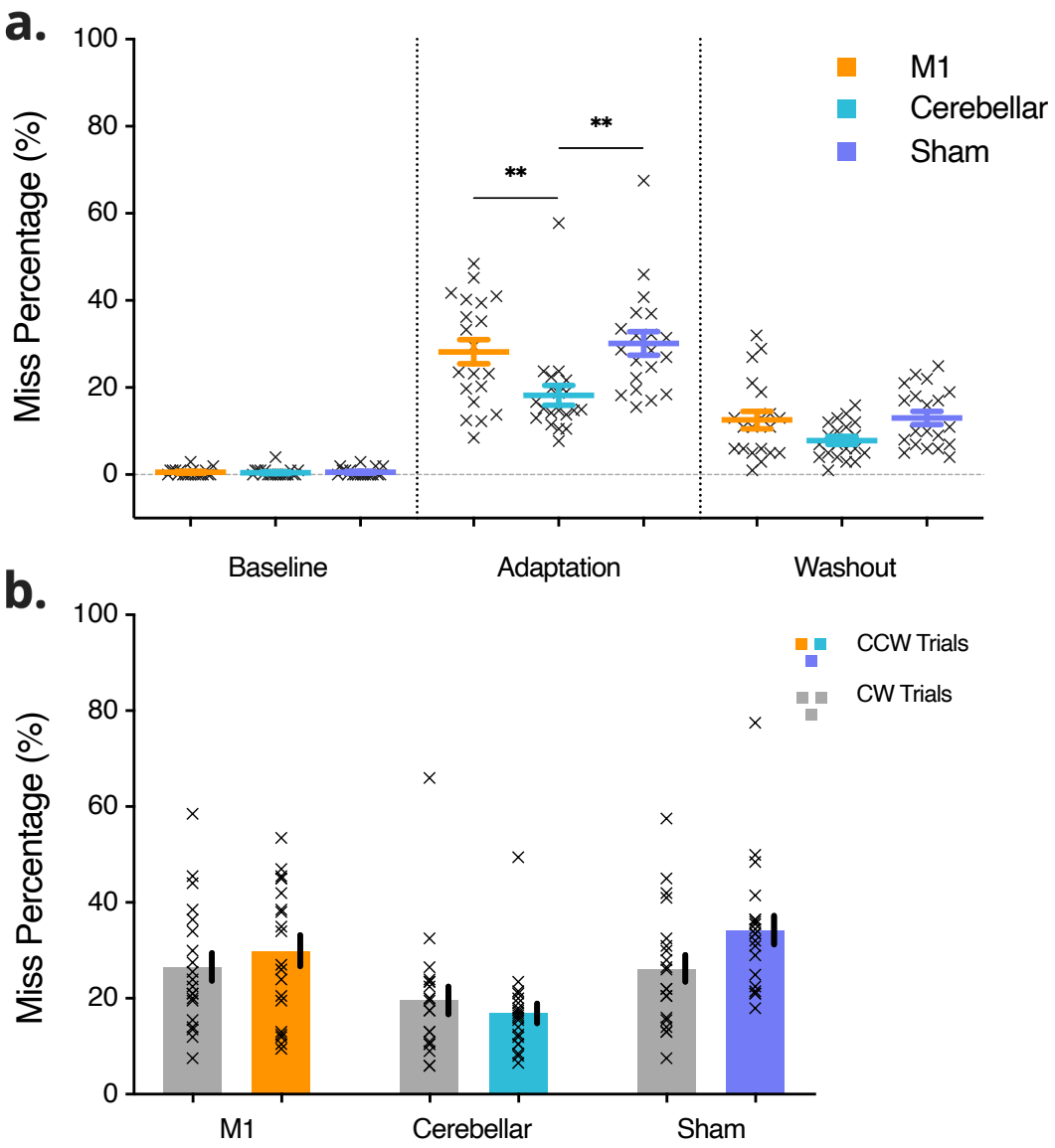


Figure 4.7: ***a:*** *The percentage of trials recorded as missed during each phase of the task for every participant, on both CW and CCW contextual trials combined. Horizontal lines represent the group mean, with standard error bars plotted above and below. Significant differences between stimulation groups are indicated following Bonferroni corrected multiple comparisons (* = $p < 0.05$, ** = $p < 0.001$).* ***b:*** *Shows the percentage of missed trials during the adaptation phase only, separated into movements through the CW force-field and CCW force-field. Individual data points in each group are marked by an 'x', with standard error bars displayed.*

4.3.4 Stimulation and task self-report measures

Participants in all groups reported low levels of discomfort and high levels of confidence that they were receiving active TDCS (Table. 4.1). Importantly, there were no significant differences between these self-report measures of stimulation perception, suggesting successful blinding to the stimulation group (active vs sham) was achieved (Table 4.1). Given that this er-TDCS protocol is relatively novel, it is pleasing that both blinding was effective and that the short bouts of TDCS did not cause excessive discomfort due to rapid onset/offset (similar comfort levels were reported in Weightman et al. (2020) after 17 minutes of anodal TDCS). Additionally, only one participant (in the M1 er-TDCS group) noticed that the stimulation only occurred on trials with a right-shift in task display and corresponding CCW force-field. This suggests that awareness of stimulation timing had little effect on adaptation during the task or resulted in increased attention towards right-shift (CCW) trials.

Participants were also asked if they noticed anything specific regarding the relationship between the force-field direction and contextual workspace shift. A relatively low percentage of participants in all three stimulation groups claimed they were aware of the link between the force direction and context during the task: M1 = 33.3%, Cerebellar = 33.3%, Sham = 25.0%, with no significant differences in awareness between the groups following a one-way ANOVA ($F(2, 57) = 0.089, p = 0.92, \eta_p^2 = 0.003$). This result indicates that participants in all groups had fairly low levels of explicit awareness of - or found it equally difficult to verbalise - the contextual link between workspace shift and force-field, despite being able to adapt to both force-fields reasonably successfully.

	M1	Cerebellar	Sham	One-way Anova Results
Age (Years)	19.75 (±0.85)	19.8 (±1.85)	19.45 (±0.83)	$F(2,57) = 0.44, p = 0.64, \eta_p^2 = 0.015$
Task Duration (Minutes)	51.34 (±0.72)	51.64 (±1.18)	51.59 (±1.23)	$F(2,57) = 0.45, p = 0.64, \eta_p^2 = 0.016$
Confidence in Stimulation	7.6 (±1.9)	7.55 (±1.88)	7.65 (±1.57)	$F(2,57) = 0.016, p = 0.98, \eta_p^2 < 0.001$
Perceived Comfort	3.7 (±2.13)	2.8 (±1.20)	3.4 (±1.54)	$F(2,57) = 1.51, p = 0.23, \eta_p^2 = 0.05$

Table 4.1: *Participant and task information (mean, ± standard deviation) with results from one-way ANOVAs reported. Confidence in Stimulation and Perceived Comfort were recorded after the task in debrief via a 10-point VAS (1 = low confidence/low discomfort, 10 = high confidence/high discomfort).*

Additional Experimental Group

4.3.5 Cerebellar er-TDCS selectively improved adaptation in both lateral deviation and force compensation.

Results from our additional experimental group helped to confirm the findings from our main experiment. We found that er-TDCS over the cerebellum enhanced adaptation of movements through the stimulated context compared to the unstimulated control - a replication of the effect initially found (See Figure 4.8a). Area under the learning curve was compared in a 3x2 way ANOVA (Task Phase: baseline, adaptation, washout; Trial Context: CW (left-shift), CCW (right-shift)), and revealed significant main effects of Task Phase ($F(2,102) = 248.23, p < 0.001, \eta_p^2 = 0.83$), Trial Context ($F(1,102) = 12.49, p < 0.001, \eta_p^2 = 0.11$) and a significant interaction

($F(2, 102) = 6.05, p = 0.003, \eta_p^2 = 0.11$). Bonferroni corrected multiple comparisons showed that during the adaptation phase participants made significantly less error on stimulated CW trials, compared to CCW trials ($p < 0.001$). We found no evidence to suggest performance during the two trial contexts were different during baseline or washout phases (both $p > 0.53$). Estimation statistics affirmed this result revealed a large effect size (paired cohen's d = 0.82, 95% CI = [0.095, 1.43]), with zero falling outside the 95% CI range (see Figure 4.8b).

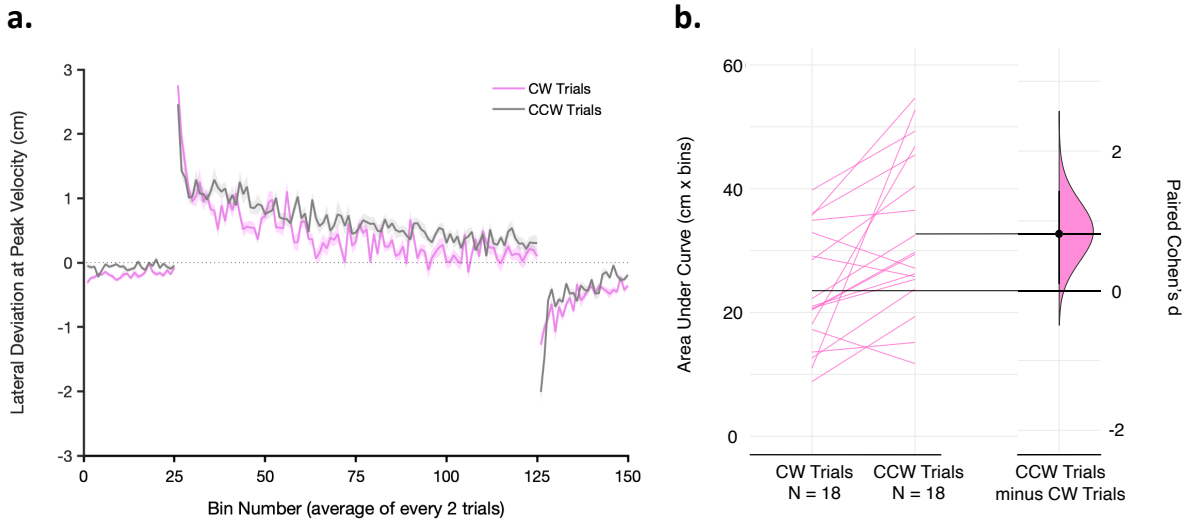


Figure 4.8: ***a:*** *Mean lateral deviation for CW (left-shift) and CCW (right-shift) trials (± standard error, shaded regions), averaged into bins of two trials for the additional experimental group. Participants in this group received er-TDCS over the cerebellum during CW adaptation trials. Panel* ***(b)*** *depicts the area under the curve (cm x bins) for CW vs CCW trials for each participant during the adaptation phase, with each participant's data connected by a line in a Paired Gardner-Altman plot, with the paired Cohen's d plotted as a bootstrap sampling distribution alongside. The mean difference is shown as a dot, with 95.0% CIs indicated by black vertical bars.*

Unlike the main experiment, we found that the specific enhancement in adaptation on stimulated trials, when considering lateral deviation, also occurred in force compensation during error-clamp trials in the additional experimental group. Thus, participants applied more force against the channel wall during expected CW adaptation trials than CCW trials (Figure 4.9). Area under the curve during error-clamp trials were compared in a 3x2 way ANOVA (Task Phase x Trial Context) and revealed significant main effects for Phase ($F(2, 102) = 192.26, p < 0.001, \eta_p^2 = 0.79$), Context ($F(1, 102) = 4.24, p = 0.042, \eta_p^2 = 0.04$) and a significant interaction between Trial Phase and Context ($F(2, 102) = 5.7, p = 0.005, \eta_p^2 = 0.1$). Comparisons from this interaction showed greater compensation on stimulated CW compared to CCW trials ($p < 0.001$) during the adaptation phase, with no differences for baseline and washout trials (all $p > 0.83$).

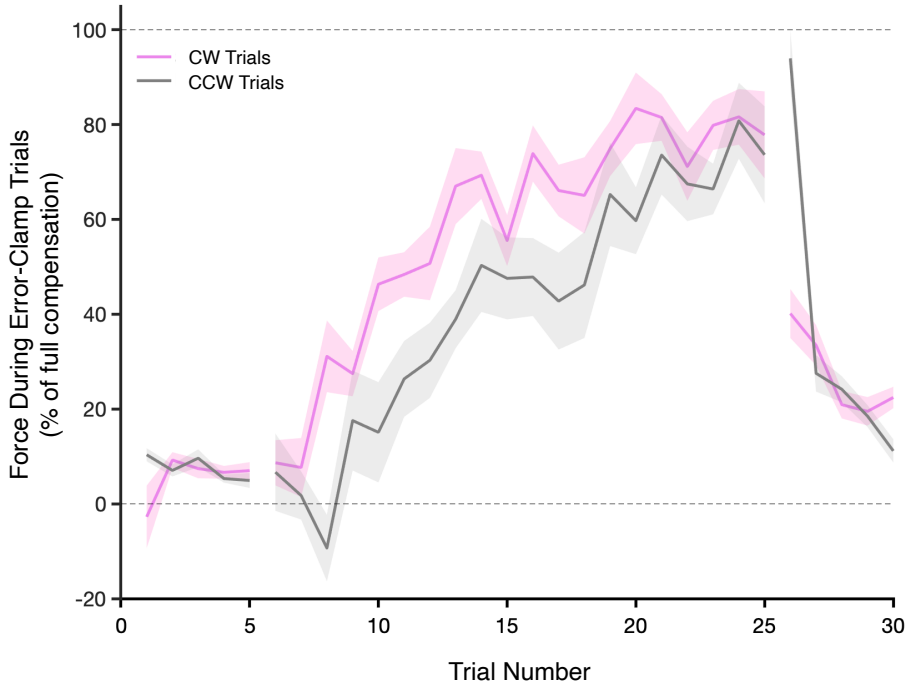


Figure 4.9: *Average force compensation during CW and CCW error-clamp trials (± standard error, shaded region) for data from the additional experimental group. Cerebellar er-TDCS was applied on CW (right- shift) error-clamp trials during the adaptation phase only (trials 6-25 on figure).*

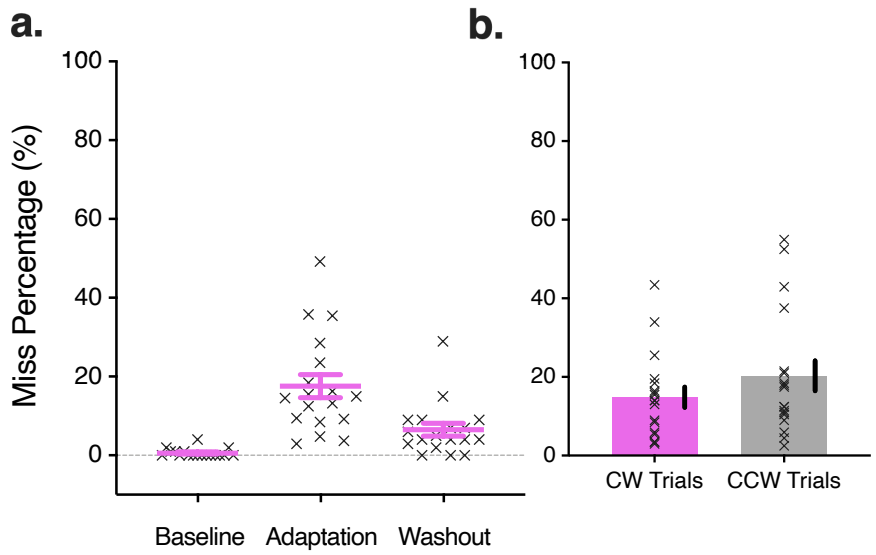


Figure 4.10: ***a:*** *The percentage of trials recorded as missed during each phase of the task for every participant, on both CW and CCW contextual trials combined. Horizontal lines represent the group mean, with standard error bars plotted above and below.* ***b:*** *Depicts the percentage of missed trials during the adaptation phase only, separated into movements through the CW force-field and CCW force-field. Individual data points in each group are marked by an 'x', with standard error bars displayed.*

4.3.6 Miss percentage was reduced on stimulated CW trials during adaptation

Accuracy during the task for the additional experimental group was assessed in a further 3x2 way ANOVA. Results revealed a significant main effect of Task Phase ($F(2, 102) = 32.62, p < 0.001, \eta_p^2 = 0.4$), which unsurprisingly showed that miss percentage significantly increased from the baseline to the adaptation phase ($P < 0.001$) and then decreased again during washout ($p < 00.1$), but not to pre-adaptation levels (baseline vs washout: $p = 0.021$, Figure 4.10a). Neither the main effect of Trial Context, nor the task Phase x Trial context revealed significant effects ($F(1, 102) = 0.46, p = 0.502, \eta_p^2 = 0.004$ and $F(2, 102) = 1.47, p = 0.24, \eta_p^2 = 0.028$ respectively). Despite participants increasing their accuracy on stimulated CW trials during the adaptation phase (Figure 4.10b), the ANOVA revealed no significant difference in miss percentage between the two trial contexts ($p = 0.082$). There is a

potential that is binary metric of success during the task is too gross to capture the more intricate differences in performance, despite revealing trends in both this data and the main experiment.

4.3.7 Self-report TDCS and task information

Participants in the additional experimental group rated their comfort during the task similarly to those in the main experiment (Perceived Comfort = 2.5 $\pm$ 1.3) and had a comparable level of certainty that they received real (vs sham/placebo) stimulation (Confidence in Stimulation = 7.83 $\pm$ 2.2). Importantly, no participants were able to identify that stimulation was only applied on CW trials during the adaptation phase, suggesting that the increase in adaptation was not due to additional attention towards CW trials or other attentional factors. Only 22.2% of participants (4/18) were able to accurately describe the contextual link between force direction and visual workspace shift, despite all showing successful adaptive performance (again similar levels to the main experiment). The average task length during the additional data collection was 51.61 minutes.

4.4 Discussion

Here we have shown that brief periods of TDCS applied over the cerebellum and in synchrony with movement can selectively and specifically improve motor adaptation of that movement, while leaving adaptation of interleaved movements unaffected. In both our main experiment and replication attempt, cerebellar er-TDCS improved adaptation and reduced lateral deviation error during stimulated compared to unstimulated trials. This effect was less clear with respect to force compensation, with a non-specific increase in predicted forces applied in the main experiment following cerebellar stimulation and an event-related effect in our additional experimental group.

Although many studies have reported positive effects of TDCS on motor learning and rehabilitation, when applied continuously for 10-20 minutes (Hummel et al., 2005; Fregni et al., 2006; Galea, Vazquez, et al., 2010; Hardwick & Celnik, 2014; Allman et al., 2016; Benussi et al., 2017; Chiou, Morris, Gou, Alexander, & Gay, 2020; Weightman et al., 2020), there are a growing number of studies reporting null or mixed effects (Jalali et al., 2017; Hulst et al., 2017; Mamlins et al., 2019; Wiltshire & Watkins, 2020), leading to uncertainty around the effectiveness of TDCS (Horvath, Forte, & Carter, 2015a). During continuous stimulation, for 10-20 minutes, any number of different behaviours may be performed alongside the specific task that is the 'target' of stimulation. The concatenation of all these behaviours under the same stimulation conditions may lead to non-specific changes in excitation levels in multiple cortical circuits that confound the results, contributing to some of the conflicting findings (Antal, Terney, Poreisz, & Paulus, 2007). In contrast, event-related TDCS may selectively modulate only those circuits and task-related synapses that are contemporaneously active and undergoing concurrent plasticity (Bikson & Rahman, 2013; Kronberg et al., 2017). As such, er-TDCS could prove beneficial when long experimental or rehabilitative protocols are required, as recent research suggests that long continuous bouts of TDCS may cause the modulatory effects of TDCS to reverse over time, i.e. from excitation to inhibition (Hassanzahraee et al., 2020a). Neural recording studies have also found that the effects of direct current stimulation may attenuate during long stimulation blocks. Such decreases have been seen in spontaneous neural activity and evoked potentials, due to short-term habituation-like adaptation processes (Creutzfeldt et al., 1962; Kunori & Takashima, 2019; Asan, Lang, & Sahin, 2020).

The exact mechanisms of plasticity responsible for the specific improvement in performance of movements following er-TDCS in the present study are difficult to definitively identify. However, Hebbian-like mechanisms of synaptic plasticity, such as LTD are particularly important in cerebellar driven behaviours, for example:

vestibular-ocular reflexes (Ito, 1982); eyeblink conditioning (J. J. Kim & Thompson, 1997); and even more complex forms of motor adaptation (Ito, 2001). Cerebellar LTD is believed to be contingent on activity at the parallel fibre-purkinje cell synapse (Linden & Connor, 1993) and correlated with climbing fibre signals, to update future behaviour (Marr, 1969; Albus, 1971; Ito, 2001). Disruption to this activity results in blocked LTD induction and subsequent impairment of learning and adaptation (Kashiwabuchi et al., 1995; Martin et al., 1996; Yanagihara & Kondo, 1996). Therefore, we propose that (1) pulsing TDCS during a movement - in this case reaching movements in a context-dependent force-field adaptation task - enhances plasticity by boosting the neural activity within the circuit associated with and activated by this specific behaviour. This increased activity in turn potentiates the synapses within this circuit that are 'eligible' for Hebbian change during this stimulated behaviour. (2) By providing brief er-TDCS, it is more likely that only those circuits involved in the particular (concurrent) behavioural context are the ones that are potentiated. In essence, er-TDCS provides transient heightened potentiation that 'focuses' Hebbian learning onto specific neurobehavioural circuits to facilitate learning. (Kronberg et al., 2017, 2020).

We should also note that there is some non-uniformity in the apparent mass of the vBOT when moving in different directions due to the direction of the 'elbow' joint (Figure 4.1a). This may have resulted in a small disparity in the errors between the two movement conditions when the CW and CCW forces were first introduced, as seen for example in the sham group data (Figure 4.4). However, this difference was quickly overcome in the sham and M1 group, and we found significantly improved adaptation in both CW and CCW cerebellar conditions, so it is unlikely to have had major impact on the overall results.

Hebbian-like plasticity can also be induced in the motor cortex, for example using paired associative stimulation (PAS) protocols (Ziemann, Iliać, Pauli, Meintzschel, & Ruge, 2004; Rosenkranz, Kacar, & Rothwell, 2007; Koch, Ponzo, Di Lorenzo,

Caltagirone, & Veniero, 2013). However, we found no specific or general effect of M1 er-TDCS on adaptation. Adaptation of left (CW) and right-shift (CCW) trials were not significantly different and participants performed similarly to the sham stimulation group. The lack of effect following M1 er-TDCS may be explained by the nature of the task. Reach adaptation to force-fields is believed to be predominantly cerebellar-dependant (Maschke et al., 2004; Tseng et al., 2007; Rabe et al., 2009; Criscimagna-Hemminger, Bastian, & Shadmehr, 2010; Donchin et al., 2012), and so targeting M1 may have had little effect on the processes governing motor adaptation/performance during the task.

The results presented here highlight novel ways in which TDCS could be utilised in research and rehabilitation, with focus on increased temporal resolution. er-TDCS could be used in conjunction with tasks or protocols comprising of precise temporal epochs, with scope beyond the motor modality e.g., memory encoding and recall tasks (Javadi, Cheng, & Walsh, 2012; MacDonald, Brittain, Spitzer, Hanslmayr, & Jenkinson, 2019). Where TMS protocols have been assumed to be the most viable time/event-dependent non-invasive brain stimulation intervention to date, er-TDCS should now be considered, especially given that stimulation has the potential to be delivered in an excitatory or inhibitory manner. There may also be potential to combine er-TDCS with EEG or electromyography (EMG) in a closed-loop type paradigm (Zrenner, Belardinelli, Müller-Dahlhaus, & Ziemann, 2016; Thut et al., 2017; Jochumsen, Navid, Rashid, Haavik, & Niazi, 2019), where stimulation is triggered via changes in brain state or muscular activity. The addition of these physiological triggers would further increase temporal selectivity of er-TDCS. Comparing these results to a 'standard' TDCS group would be beneficial to determine if er-TDCS can improve performance over and above the generally accepted stimulation protocol, which is a necessary next-step for this line of research. In addition, the use of different control or sham stimulation groups e.g., applying er-TDCS before or after movement would help to further tease apart which learning processes which may be responsible for this

enhanced adaptation.

One apparent discordance in the present study is the lack of difference in force compensation in the main experiment during CW and CCW error-clamp trials, despite an overall improvement for the cerebellar er-TDCS group. This is in contrast to a significantly and selective reduction in lateral deviation error on stimulated force-field trials and the effect found in the additional experimental group. Conventionally, lateral force generation measured in error-clamp trials serves as a proxy for adaptation, indicating how well participants are able to predict the dynamics of the perturbed environment experienced during force-field trials (Scheidt, Reinkensmeyer, Conditt, Rymer, & Mussa-Ivaldi, 2000; Herzfeld et al., 2014). Error-clamp trials also help to dissociate field-specific compensatory forces from a non-specific increase in limb stiffness, which would also reduce lateral deviation errors (Osu et al., 2002; Franklin, Osu, Burdet, Kawato, & Milner, 2003; Franklin et al., 2007). A decrease in lateral deviation error with no concomitant increase in force compensation would suggest participants are simply stiffening their limb when moving, rather than learning to adapt to the force-fields. However, as all three groups in the current study achieved greater than 60% force compensation by the end of the adaptation phase, in accordance with similar studies (Howard et al., 2012, 2013), we can rule out a non-specific change in stiffness. There are a number of different possible factors which may have contributed to these mixed findings. The low number or error-clamp trials and the altered feedback during movement (expanding semi-circle vs veridical cursor feedback), may have contributed somewhat to the mixed force compensation findings. Clamp-trials made up only 10% of the overall task and thus their infrequency, alongside the unexpected change in task feedback may have resulted in altered or nosier behaviour. In other words, the semi-circular cursor designed to avoid directional feedback may have provided a strong cue that the error-clamp trials were different from the normal force-field trials, effectively casting them in a different context to the much more frequent force-adaptation trials. Additionally, the ratio calculated in order

to determine force compensation is a derivative of behaviour rather than a direct measure of motor performance during the task and therefore might be less specific than other more direct measures e.g., lateral deviation. However, these explanations fall short of explaining why we found specific effects during error clamp trials during one experiment but no effect in another. At present we have insufficient evidence to satisfactorily reconcile these conflicting results. Notwithstanding, the lack of reliable differences in force compensation does not diminish the highly selective effect we found of cerebellar er-TDCS on force-field adaptation, but rather highlights how task design can influence TDCS mediated behavioural effects.

In summary, we have shown that brief epochs of TDCS over the cerebellum can selectively modulate motor adaptation when delivered coincidentally with reaching movements. We suggest that the coupling of stimulation and movement influences mechanisms of Hebbian-like plasticity and thus facilitates learning in the stimulated context. These results open up new possibilities for the use of TDCS in both research and clinical settings, to improve its effectiveness and specificity. They also demonstrate that stimulation can be applied in very short bouts without inducing severe discomfort or side-effects, and without the participants' explicit knowledge of the specific stimulation protocol.

Chapter 5

Residual errors in visuomotor adaptation persist despite extended motor preparation periods

5.1 Introduction

The ability of our sensorimotor system to recalibrate and adjust planned movements in response to changes in one's body or environment is essential for accurate and successful motor performance. This phenomenon - termed sensorimotor adaptation - occurs frequently during our everyday lives, when for example, we experience injury or fatigue, or walk on an uneven or slippery surface. In all of these instances, prior motor commands that would have resulted in successful performance now fall short and must be adapted in order to restore accuracy (for reviews, see Shadmehr et al., 2010; Krakauer et al., 2011).

Sensorimotor adaptation can be studied in a number of different lab-based tasks, for example: prism glasses (Martin et al., 1996), novel force-fields (Shadmehr & Mussa-Ivaldi, 1994), split-belt treadmills (Reisman et al., 2005), and perhaps most commonly, visuomotor rotations (Krakauer et al., 2000). In this latter task, individuals adapt reaching movements to counter rotated visual feedback in the attempt to attain pre-rotation baseline levels of movement accuracy. Initial large errors are quickly reduced, followed by more gradual adjustments until a plateau occurs - creating a typical adaptation curve response. However, a stereotypical observation in visuomotor rotation data is a lack of full compensation when performance plateaus a few degrees below complete adaptation. This stereotypical incomplete adaptation is routinely seen regardless of rotation magnitudes (Fernandez-Ruiz, Wong, Armstrong, & Flanagan, 2011; Huberdeau, Haith, & Krakauer, 2015; van der Kooij, Brenner, van Beers, & Smeets, 2015; Vaswani et al., 2015; Weightman et al., 2020; Langsdorf, Maresch, Hegele, McDougle, & Schween, 2021), with residual errors ranging from approximately 5-15°, depending on the size of imposed rotation.

Residual errors at the end of learning are commonly described as an in-built feature of visuomotor adaptation, where trial-by-trial error-dependent learning and forgetting reach an equilibrium below that of the imposed cursor displacement. State-space models of learning have been used to accurately capture this incomplete compensation

(Smith et al., 2006; Kording, Tenenbaum, & Shadmehr, 2007). In these mathematical models, opposing parameters for learning, which reflect updated estimations of the environment, and forgetting (or a reversion to baseline) equilibrate below optimal performance and thus result in the commonly observed undershoot. Recent research leveraging state-space models has suggested that residual errors in motor adaptation can be attributed to implicit learning processes, which modify sensitivity to errors dependent on the variance of the perturbation and the consistency of prior errors (Albert et al., 2021).

That being said, Vaswani and colleagues (2015) demonstrated that under certain manipulated feedback conditions, individuals have the ability to disengage from this limited error-dependent learning in an attempt to attain greater task success. In one of their experimental conditions, Vaswani et al. (2015) 'clamped' visual feedback after an initial learning block, such that a small, fixed, visual error was presented, regardless of movement accuracy. They found that under these conditions, participants appeared to select an alternative, more exploratory learning policy, which enabled them to close the errors and even to overcompensate for the rotation (which differed from the partial reversion to baseline predicted by the state-space model). While, under standard visuomotor rotation feedback conditions the state-space model accurately predicted incomplete adaptation. The authors suggested that the altered feedback distribution triggered alternative exploratory learning processes (and enabled the elimination of residual errors), which are usually suppressed during naturalistic feedback conditions.

More recently, Langsdorf et al. (2021) presented an alternative theory to explain why under normal, non-clamped environments, the central nervous system fails to eliminate residual errors during motor adaptation. They suggested an intrinsic speed-accuracy trade-off: where time consuming planning processes are interrupted by the onset of movement prior to completion, resulting in more fast, but inaccurate movements. In their study, they showed that when an obligatory 2.5 second wait period between target presentation and movement initiation was introduced,

participants were able to fully adapt to a 45° rotation, leaving no persisting errors at the end of learning. However, if this wait period was not enforced or was introduced at the end of the movement, when no planning was assumed to be taking place, participants failed to fully counteract the rotation. The authors highlighted mental rotation as a time-consuming cognitive process potentially involved in the planning of visuomotor adaptation.

For some time now, visuomotor adaptation has been framed as a combination of distinct learning processes (Mazzoni & Krakauer, 2006; Taylor et al., 2014; Bond & Taylor, 2015; McDougle et al., 2015; Voets et al., 2020). These processes are customarily described as implicit and explicit learning. The implicit component adapts slowly and is driven by sensory prediction errors (Smith et al., 2006; Tseng et al., 2007). The explicit component is a fast adaptation process and involves, among other processes, strategic re-aiming to counter the detected perturbation (Taylor & Ivry, 2011; Heuer & Hegele, 2008; McDougle et al., 2015). Such strategies are thought to include a form of metal rotation (McDougle & Taylor, 2019). Langsdorf et al. (2021) suggest that under naturalistic feedback conditions, parametric mental rotations from the target to the intended movement goal are prematurely terminated (despite no time constraints) and result in aimed movement trajectories falling short of the imposed rotation.

Mental rotation has primarily been studied in the context of visual perception, however, evidence from both behavioural and neurophysiological research suggests a role of mental rotation in the planning of movements made at angles from visually defined targets (Georgopoulos & Massey, 1987; Bhat & Sanes, 1998; Georgopoulos, Lurito, Petrides, Schwartz, & Massey, 1989; Lurito, Georgakopoulos, & Georgopoulos, 1991; Pellizzer & Georgopoulos, 1993). Neuronal population vectors recorded in the monkey motor cortex gradually rotate from a stimulus direction to a cued movement direction during the planning of a reach (Georgopoulos et al., 1989; Lurito et al., 1991). Additionally, the completion of mental rotation tasks require long reaction

times with larger magnitudes of rotation (Fernandez-Ruiz et al., 2011; Haith, Huberdeau, & Krakauer, 2015; McDougle & Taylor, 2019); a signature of cognitive strategies. (Shepard & Metzler, 1971; Georgopoulos & Massey, 1987).

Given this knowledge, we aimed to replicate and extend the findings of Langsdorf et al. (2021), in order to further understand the roles of extended planning periods and mental rotation in attaining full adaptation. We designed an online visuomotor adaptation task, where participants had either long (2.5 seconds), medium (1 second) or short (0.35 seconds) enforced preparation periods between target presentation and movement onset, and were required to adapt to either a small (30°), moderate (45°) or large (60°) visuomotor rotation. Previous studies (Langsdorf et al., 2021) suggest that the 45° rotation would be fully corrected with the longest preparation period; errors for the middle interval would be greater; and a substantial residual error should be found for the shortest preparation interval. This negative relationship between preparation interval and residual error should be most obvious for the 60° rotation; the smallest rotation (30°) might allow full compensation even at the shortest preparation interval. In other words, the response time could be considered the sum of a mental rotation period linearly related to the rotation magnitude, and a fixed movement initiation period; if the sum exceeds the prescribed preparation interval, then residual errors should be seen.

5.2 Materials and Methods

5.2.1 Participants

A total of 200 participants were recruited via posters, study averts and through personal contact (aged 18-37 years, mean $\pm$ = 22.4 $\pm$ 3.5 years, 89 males); all gave informed consent before participating and either received no remuneration or received course credit which counted towards their university degree mark. The study was approved by the University of Birmingham ethics board (Science, Technology,

Engineering and Mathematics Ethical Review Committee). Participants were self-reported as right-handed (n = 181) or left-handed (n = 19) and used their preferred hand to complete the task (all but 5 of the left-handed participants completed the task using their right hand). All participants had normal, or corrected to normal, vision and reported no history of neurological disease. Initially, 180 participants were pseudorandomised into one of nine experimental groups (each n = 20), which differed in the amount of preparation time provided (0.35, 1 or 2.5 seconds) and the magnitude of cursor rotation (30°, 45° or 60°). These participants formed the online arm of the study (Table. 5.1). To avoid any possible confounds relating to online data collection and only after COVID-19 restrictions relating to in-person human testing were lifted, we also collected data from an additional experimental group who completed the task in a laboratory setting. Participants in this group experienced a 45° cursor rotation, with 2.5 seconds of preparation time (Table. 5.1) - a closer replication of Langsdorf et al. (2021).

	0.35 seconds			1 second			2.5 seconds			
	30°	45°	60°	30°	45°	60°	30°	45°	45° *	60°
N	20	20	20	20	20	20	20	20	20	20
(n male)	(9)	(6)	(8)	(11)	(12)	(4)	(10)	(13)	(7)	(9)
Mean age	23.5	25.4	25.9	21.0	21.5	22.6	20.8	21.0	20.2	22.7
(years, ±SD)	(2.0)	(3.4)	(3.4)	(1.1)	(3.7)	(5.0)	(1.3)	(1.6)	(1.8)	(3.7)

Table 5.1: *Summary table of the different experimental groups. Participants were pseudorandomised into one of nine experimental groups (each n = 20), which differed in the amount of preparation time provided (0.35, 1 or 2.5 seconds) and the magnitude of cursor rotation (30°, 45° or 60°). An additional group of participants were also recruited who completed the task in a laboratory and experienced a 45° rotation with 2.5 seconds of preparation time. * = in-laboratory group*

5.2.2 Task

Online

We developed a visuomotor adaptation task using the online behavioural science experiment platform PsychoPy (Peirce et al., 2019), which was implemented online via Pavlovia (https://pavlovia.org). Participants were required to have access to a desktop or laptop computer with internet connection and a mouse or trackpad to navigate through and complete the task (117/180 participants used a trackpad; 63/180 participants used a mouse). Participants were sent a link to access the task and entered a unique code which determined which combination of preparation time and rotation angle they would encounter. Participants were asked to sit in a location of their choosing, so that they could easily see their computer screen and comfortably reach and manipulate the mouse or trackpad. They made centre-out movements with either their mouse or on their trackpad from an on-screen central starting position to targets which appeared on an invisible circular array surrounding it (Figure. 5.1a). They were told to make one fast and straight 'shooting' movement, aiming to get the on-screen cursor as close as possible to the target. Prior to starting the task, all participants completed a brief tutorial, which included the task instructions and aims. At this point, participants were asked to contact a researcher if they were unclear about any part of the task and/or had any questions relating to the instructions.

Laboratory

Participants sat in an armless chair in front of a computer monitor (21.5 inch iMac, 60Hz refresh rate) and used a trackpad (Apple Magic Trackpad) to control the onscreen cursor. The trackpad measured 0.49-1.09 cm in height, 16 cm in width and 11.49 cm in depth and was fixed to the desk next to the computer screen. A 1 cm movement on the trackpad corresponded to $\sim$3 cm of on-screen cursor movement. Crucially, the participants received the same instructions and completed the same

tutorial before starting the task. The remaining task parameters were exactly as the online paradigm. All 20 participants were right-handed (self-report) and used their right hand to complete the task.

Protocol

At the beginning of every trial the cursor (red filled circle) would be located in the centre of the screen (grey background). The cursor was surrounded by two larger red annuli, which formed a bullseye-like formation (Figure. 5.1b). At a set moment, the outer ring disappeared, followed by the inner ring 0.5 seconds later, and the cursor then changed colour from red to white after a further 0.5 seconds. Participants were told that this sequence of events should be treated as a countdown to movement and that they should aim to time their movement so that it was initiated in synchrony with the cursor changing colour from red to white (Figure. 5.1b). Depending on the experimental group, the target (green filled circle) would appear either 2.5 seconds, 1 second or 0.35 seconds before the movement cue - thus creating three distinct preparation periods. The target could appear at any one of eight possible locations, equally spaced (separated by 45°) around an invisible circular array centred on the start position, and pseudorandomised so that the target appeared at each location once every cycle of eight trials. The position at which the cursor passed the invisible perimeter was displayed for 0.5 seconds as static open white circle, providing feedback of movement accuracy. After an inter-trial interval of 0.5 seconds the cursor would reset to the central position ready for the next trial. Participants were encouraged to move their hand back to a comfortable starting position after each trial. We did not acquire details regarding the different screen sizes used by each participant in the online experiment; therefore, we cannot stipulate the exact dimensions of the various stimuli. However, all elements of the visual display were scaled according to the size of the task window and thus were the same relative size for all participants. Consequently, the physical movement size required varied between participants

depending on their set up and was not recorded beyond input device. For the in-lab experiment, the stimuli dimensions were as follows: cursor diameter = 1 cm, target diameter = 1.2 cm and target circle radius = 10.8 cm. If participants attempted to move 0.15 seconds before or after the go cue, or if movement time exceeded 0.25 seconds, the message "Response too fast/slow" appeared on the screen and the trial was aborted. These measures were to encourage fast movements, initiated correctly with the task instructions.

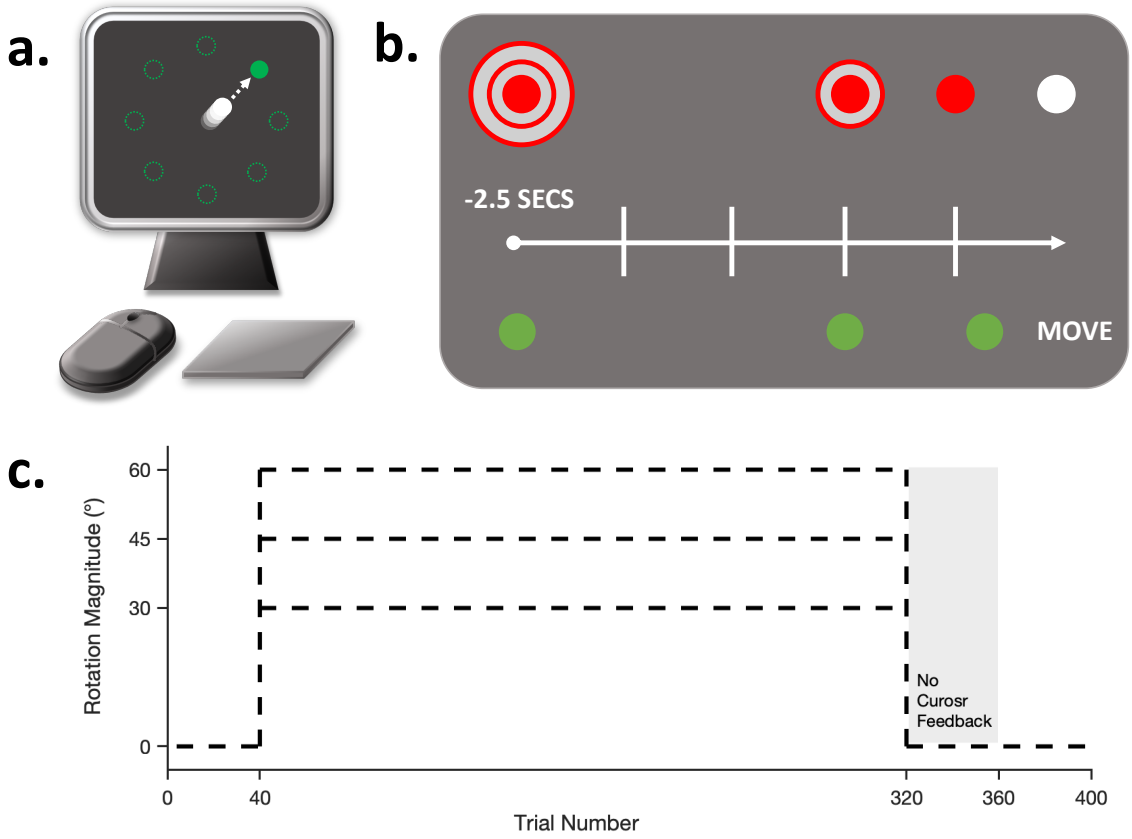


Figure 5.1: *The experimental design.* ***a:*** *Participants used either a mouse or trackpad to direct an on-screen cursor towards targets presented radially around a central starting position.* ***b:*** *An example of the cursor countdown sequence and movement cue. At the beginning of each trial the (red) cursor would appear in the centre of the screen, flanked by two larger (red) rings (shown here on the top row). During the trial the two rings would disappear in sequence and the cursor would change colour to white. Participants were required to initiate their movement in synchrony with the cursor colour change, using the disappearing rings as a countdown. The target (shown on the bottom row) would appear either 2.5, 1 or 0.35 seconds prior to the movement cue, depending on group assignment.* ***c:*** *A time course of the study protocol. Participants completed 40 baseline trials, followed by 280 adaptation trials (where either a 30°, 45° or 60° cursor rotation was imposed), 40 no-feedback trials and finally 40 de-adaptation trials.*

5.2.3 Experimental Design

Participants first performed eight practice trials (one trial at each target location). These trials were performed with veridical cursor feedback and were used to familiarise the participants with the timing of their task version. Data from practice trials was not used in any final analysis. The main task directly followed the practice

trials and included four phases: baseline, adaptation, no-feedback and de-adaptation (with a total of 400 trials, Figure. 5.1c). During baseline trials (n = 40) participants received veridical cursor feedback, such that the on-screen cursor moved in accordance with participants' movements. Adaptation trials immediately followed, in which the cursor feedback was rotated 30°, 45° or 60° clockwise (depending on the experimental group, Table 5.1) relative to participants' movement. This block lasted 280 trials, selected to ensure learning approached its asymptotic limit, based on pilot data collected prior to the present study. While there is some indication that full asymptotic saturation of learning was not achieved in all conditions, regression analysis of the last 40 trials of adaptation indicated that there was no significant trend remaining (all $p > 0.19$, with all slopes between 0.041 and -0.039) and thus we use the term 'asymptote' to refer to the final state reached at the end of the 280 adaptation trials. Following adaptation trials, participants performed no-feedback trials (n = 40). During these trials, participants were told to stop using any strategies they might have employed to achieve the task objectives and try to aim directly for the target. The cursor was hidden at all times during the trial, apart from when located in the central position for the countdown cue. End-point error was not displayed during the no-feedback phase. Veridical cursor feedback and display of end-point error were then restored for the final de-adaptation trials (n = 40).

There were ten participant groups (Table. 5.1), to cover all combinations of preparation time (long: 2.5 seconds, medium: 1 second, short: 0.35 seconds) and the magnitude of cursor rotation (large: 60°, moderate: 45°, small: 30°), with the 2.5 seconds/45° group repeated in a laboratory setting. The preparation time was held constant throughout the whole task; the rotation was applied only during the adaptation phase.

5.2.4 Data Analysis

There were three main outcome variables: reach angle, response time and movement duration. Our primary dependent variable - reach angle - was the angular difference between the target location and participants' movement at end-point (i.e., the difference in angle between the vector linking the starting position and the target marker, and the vector linking the starting position and the point at which participants' movement crossed the target circle perimeter). Participants were excluded from analysis if they either failed to follow task instructions (i.e., ignoring the rotated cursor and not adjusting their aiming direction) or if they violated the timing limits of the task on four successive trials (indicating a lack of concentration or distraction). 17 individuals were excluded based on this criterion and were replaced with new participants in order to achieve the desired sample size. Trials were deemed outliers and removed if they fell 2.5 standard deviations outside the group average on each trial. A total of 1.23% of all trials were removed from further analysis. Data from each participant were then averaged into bins of 4 trials to be used for visual representation and statistical analysis. Response time was defined as the time period between target presentation and movement onset (i.e., cursor movement breaking an invisible line immediately surrounding the starting position) and movement duration was defined as the time period between movement onset and when movement crossed the target circle. Reach angle data was not recorded for trials where the response or movement time limits were violated.

Statistical Analysis

Asymptotic levels of adaptation were defined as the mean error over the last 40 trials of the adaptation phase and compared between groups in a two-way ANOVA (Rotation Magnitude = 3 levels (30°/45°/60°) x Preparation Time = 3 levels (0.35 seconds/1 second/2.5 seconds)), with any significant main effects or interactions followed up with Bonferrroni-corrected multiple comparisons. Asymptotic differences from the imposed

rotation magnitude were compared using a Wilcoxon Signed Rank test, after data from some groups failed normality checks (Shapiro-Wilk test). Mean reach angles across all baseline trials and during the first 16 no-feedback trials for each participant were used for baseline and retention comparisons. Data from the laboratory group were processed and analysed separately from the online data as this group was not factored into the original study design. In-lab data was compared to its online counterpart using unpaired t-tests (two-tailed) and from the degree of imposed rotation using a Wilcoxon Signed Rank test. All statistical analyses were carried out in MATLAB (R2018b) and SPSS (IBM, version 27). All ANOVAs were run as general linear models. The threshold for statistical significance was set at $p < 0.05$ and we report W, F, T and p-values, as well as effect sizes from ANOVAs (partial eta squared (η_p^2)).

5.3 Results

5.3.1 Baseline performance did not differ within or between groups

Differences in reach angle during the baseline phase were assessed in a two-way ANOVA (Rotation Magnitude x Preparation Time), which revealed no significant main effects for Rotation Magnitude ($F(2, 171) = 0.071, p = 0.93, \eta_p^2 = 0.001$), Preparation Time ($F(2, 171) = 0.29, p = 0.75, \eta_p^2 = 0.003$), and no significant Rotation Magnitude x Preparation Time interaction ($F(4, 171) = 0.45, p = 0.77, \eta_p^2 = 0.1$). This result suggests that all groups performed similarly during baseline trials (Figure. 5.2) and thus, group differences are unlikely to influence performance later in the task. We felt this analysis important, given the limited experimenter input associated with online research.

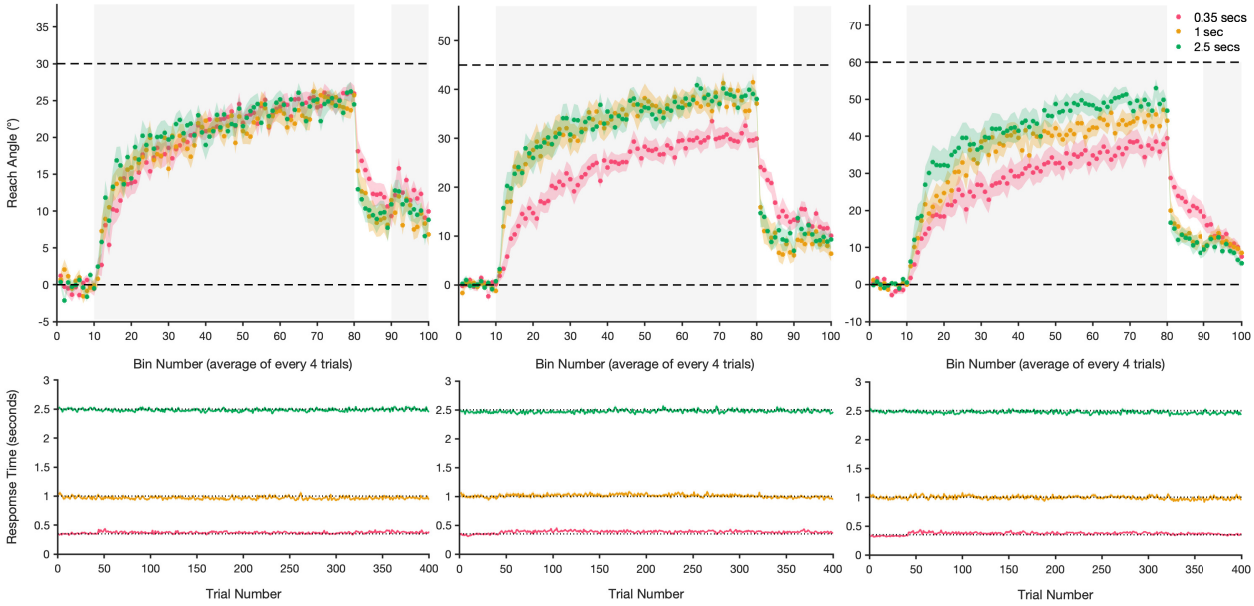


Figure 5.2: *Mean reach angle and response time for each of the online experimental groups. Top panel: Reach error (± standard error, shaded region) is averaged every four trials into bins for (from left to right) the 30°, 45° and 60° groups, during baseline, adaptation (shaded grey background), no feedback and de-adaptation trials (shaded grey background). Zero degrees and the magnitude of imposed rotation are shown by horizontal dashed lines. Bottom panel: Mean response time (time between target presentation and movement initiation), ± standard error (shaded region) for each group. Note, preparation times were predetermined at 0.35, 1 or 2.5 seconds (dotted lines) and were tightly controlled.*

5.3.2 The effect of differing preparation time on asymptotic levels of adaptation

A two-way ANOVA comparing asymptotic levels of adaptation revealed significant main effects for Rotation Magnitude ($F(2, 171) = 121.01, p < 0.001, \eta_p^2 = 0.59$), Preparation Time ($F(2, 171) = 15.17, p < 0.001, \eta_p^2 = 0.15$) and a significant Rotation Magnitude x Preparation Time interaction ($F(4, 171) = 5.24, p < 0.001, \eta_p^2 = 0.11$). Multiple comparisons revealed that in the 45° rotation group, there were some differences between learning asymptotes, with regards to preparation time provided. The 0.35 second preparation time group displayed impaired adaptation compared to the 1 and 2.5 second groups (both $p < 0.001$), with no further differences between the

latter two conditions ($p > 0.99$). However, contrary to Langsdorf et al. (2021), all final levels of adaptation significantly differed from 45° (0.35 seconds: W = -210.0, p < 0.001, 95% CI = [-16.72, -11.32]; 1 second: W = -200.0, p < 0.001, 95% CI = [-9.71, -2.50]; 2.5 seconds: W = -210.0, p < 0.001, 95% CI = [-9.33, 3.18]). The 0.35 seconds preparation time group compensated 67.3% for the rotation, with the 1 and 2.5 second groups achieving 85.1% and 86.1% compensation respectively (Figures 5.2 & 5.3), suggesting that additional preparation time allowed for greater compensation but not the elimination of residual errors.

Similarly, for the 60° rotation condition, shortening planning time to 0.35 seconds significantly reduced the final level of adaptation compared to both 1 and 2.5 second preparation periods (0.35 seconds vs 1 second: p = 0.001, 0.35 seconds vs 2.5 seconds: $p < 0.001$). However, there was no difference between the 1 and 2.5 second groups with respect to final adaptation levels ($p = 0.17$). Participants averaged 62.4% compensation with 0.35 seconds preparation time, 75.0% with 1 second preparation time and 81.7% with 2.5 seconds preparation time (Figures 5.2 & 5.3). Additionally, all asymptotic levels of adaptation significantly differed from the imposed 60° rotation (0.35 seconds: W = -210, p < 0.001, 95% CI = [-31.14, -16.02]; 1 second: W = -210.0, p < 0.001, 95% CI = [-16.27, -10.27]; 2.5 seconds: W = -206.0, p < 0.001, 95% CI = [-16.76, -6.44]).

In the 30° rotation group, there were no differences in asymptotic error between any of the different preparation time groups (all $p > 0.99$, Figure 5.2). Furthermore, all final levels of adaptation differed significantly from 30° (0.35 seconds: W = -210.0, p < 0.001, 95% CI = [-5.35, -2.39]; 1 second: W = -204.0, p < 0.001, 95% CI = [-6.87, -2.98]; 2.5 seconds: W = -210.0, p < 0.001, 95% CI = [-8.09, -3.25]), with adaptation reaching 84.7%, 82.8% and 82.0% of optimum, respectively (Figure 5.3).

In summary, our results support previous work suggesting that mental rotation contributes an interval to the planning process which is proportional to rotation magnitude, and that short periods of preparation interrupt planning, leading the

greater residual errors. However, for the smallest rotation, we found no relationship between preparation time and error, suggesting that mental rotation was completed within the allowed time. But even in these circumstances, there were significant residual errors. In fact, in opposition to results reported by Langsdorf et al. (2021), all groups displayed incomplete adaptation regardless of the preparation time provided.

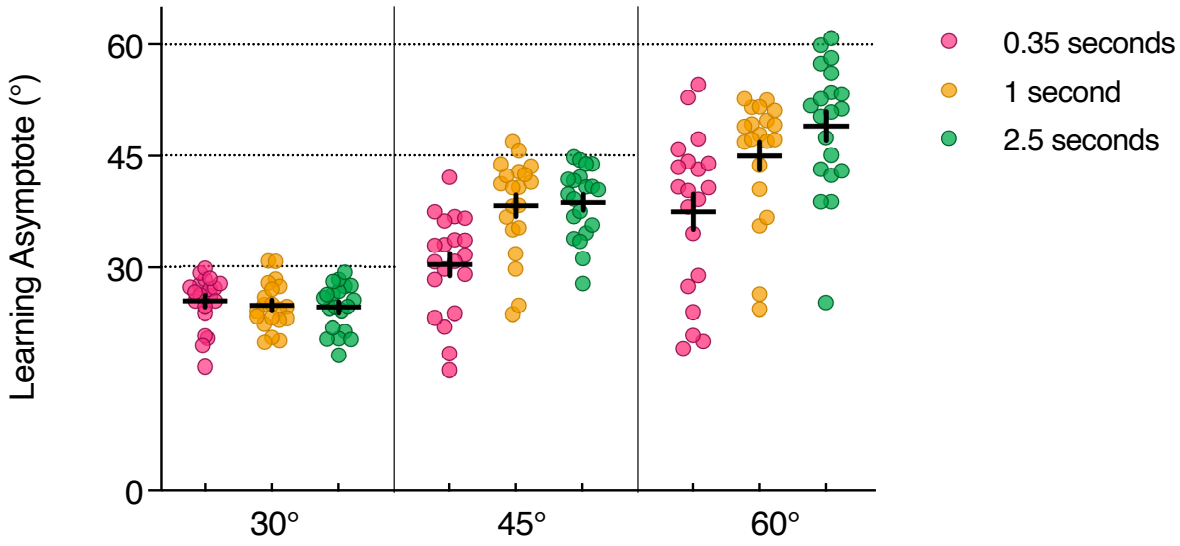


Figure 5.3: *The asymptotic levels of adaptation for each participant in each of the rotation magnitude and preparation time groups (online experiment). Filled circles represent the adaptation asymptote for each participant (defined as the average of the last 40 adaptation trials), with mean values and standard error depicted by horizontal and vertical lines respectively. Dashed horizontal lines depict the imposed cursor rotation for each group.*

5.3.3 Restricting motor preparation time resulted in a stronger implicit retention

Implicit retention (as measured by mean reach angle in the first 16 no-feedback trials, two cycles of reaches to each target location) was compared between groups in a two-way ANOVA (Rotation Magnitude x Preparation Time). Results from the ANOVA revealed a significant main effect of Rotation Magnitude and Preparation Time ($(F(2,171) = 6.71, p = 0.002, \eta_p^2 = 0.07$ and $F(2,171) = 18.33, p < 0.001, \eta_p^2 = 0.18$, respectively), but no significant interaction ($F(4,171) = 1.08, p = 0.37, \eta_p^2 = 0.03$). Multiple comparisons showed that participants in the restricted 0.35 second motor preparation time groups displayed greater retention than both the 1 second ($p < 0.001$) and 2.5 second ($p < 0.001$) groups, with no differences between the latter two ($p > 0.99$).

5.3.4 Input device and handedness had no effect on late adaptation levels

In order to determine whether the input device used (trackpad or mouse), or the handedness of the participant had any effect on our main outcome variable, reach angle, we ran an additional mixed design ANOVA (Rotation Magnitude x Preparation Time) with factors for both input device and handedness (online groups only). The ANOVA revealed no significant main effect of Input Device or Handedness (Input Device: $F(1,150) = 0.9, p = 0.35, \eta_p^2 = 0.006$; Handedness: $F(1,150) = 1.12, p = 0.29, \eta_p^2 = 0.007$). In fact, no interaction that included the term Input Device revealed significance (Rotation Magnitude x Input Device: $F(2,150) = 0.36, p = 0.7, \eta_p^2 = 0.005$; Preparation Time x Input Device: $F(2,150) = 0.23, p = 0.79, \eta_p^2 = 0.003$; Rotation Magnitude x Preparation Time x Input Device: $F(4,150) = 0.3, p = 0.88, \eta_p^2 = 0.008$; Figure 5.4. Similarly, all interaction effects with Handedness included were also non-significant (Rotation Magnitude x

Handedness: $F(2, 150) = 1.55 p = 0.22, \eta_p^2 = 0.02$; Preparation Time x Handedness: $F(2, 150) = 0.75, p = 0.48, \eta_p^2 = 0.01$; Rotation Magnitude x Preparation Time x Handedness: $F(2, 150) = 0.12, p = 0.89, \eta_p^2 = 0.002$). These analyses corroborate our belief that neither the handedness of the participants, nor the input devices they used, confound our results.

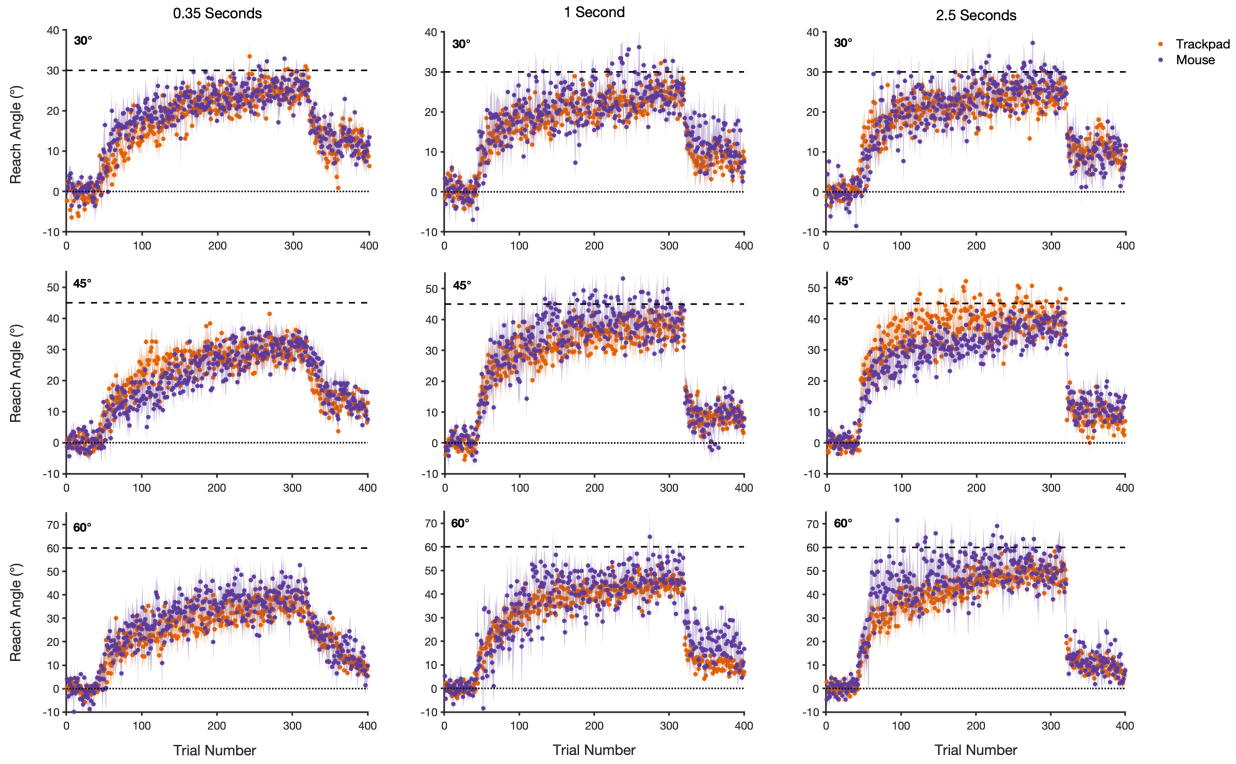


Figure 5.4: *Mean reach angle (coloured markers, ± standard error; shaded region) during baseline, adaptation, no-feedback and de-adaptation trials for all the online experimental groups. Data is separated by the input device used to complete the task (mouse or trackpad). Zero degrees and the magnitude of imposed rotation shown as a dotted and dashed line respectively.*

5.3.5 There were no differences in task performance between the online and in-laboratory groups

To confirm the validity of our results collected using online methodology, we collected data from an additional group of participants who performed the experiment in a laboratory with 2.5 seconds of preparation time and a 45° cursor rotation. Data from this additional in-lab experimental group were compared with the equivalent online group using unpaired t-tests (two-tailed) and revealed no significant differences in baseline, asymptotic or retention performance ($t(38) = 0.89, p = 0.38$; $t(38) = 0.35, p = 0.73$; $t(38) = 1.78, p = 0.084$, respectively). Participants in this group compensated 87.2% for the rotation and importantly, the final level of adaptation was also significantly different from 45° (W = -196.0, p < 0.001, 95% CI = [-8.35, -3.1]), replicating the effect found consistently across our online groups (Figure 5.5). We also found no differences in variance between the laboratory and online groups in each of the experimental phases (F-tests: $F(19, 19) = 1.9, p = 0.17$; $F(19, 19) = 1.04, p = 0.93$; $F(19, 19) = 1.31, p = 0.56$).

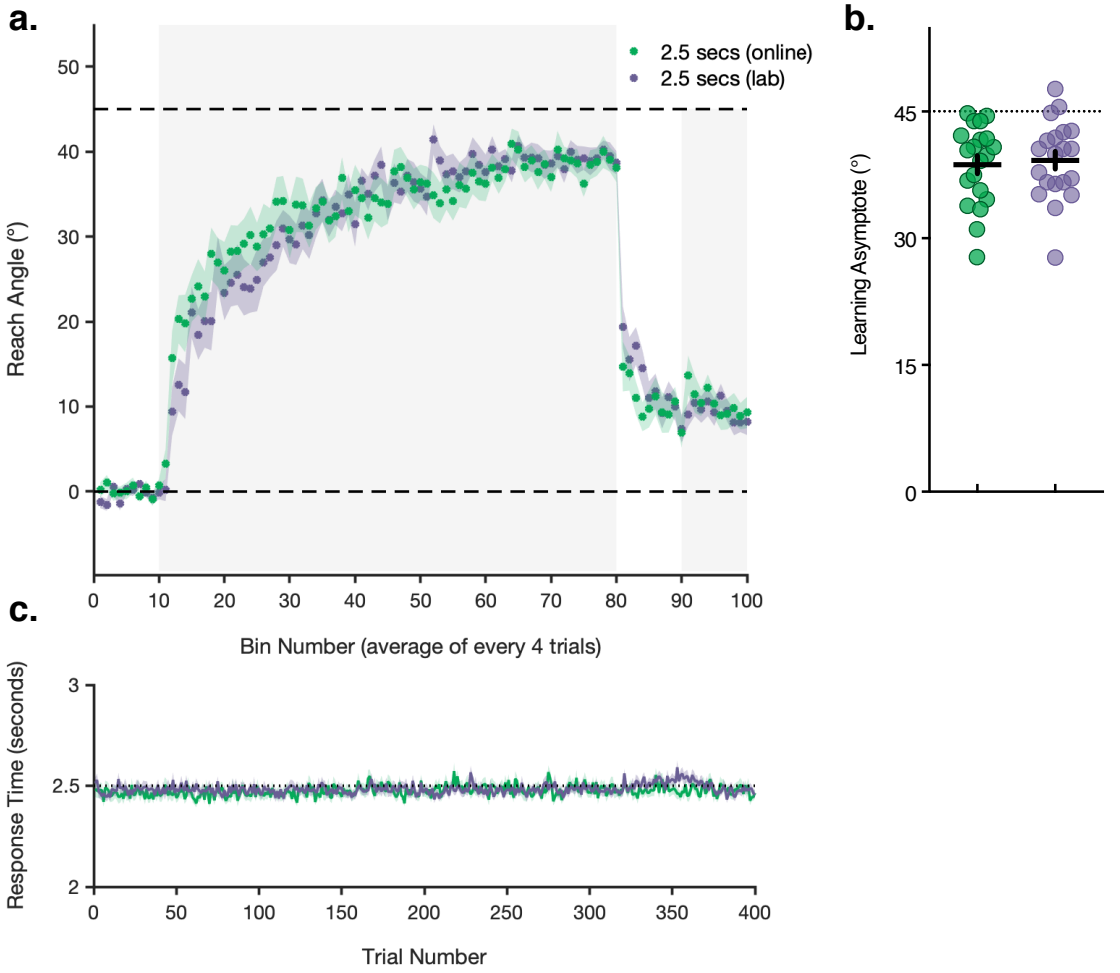


Figure 5.5: *Mean reach angle, response time and learning asymptote for the in-laboratory and comparative online experimental group.* ***a:*** *Reach error (± standard error, shaded region) is averaged every four trials into during baseline, adaptation (shaded grey background), no feedback and de-adaptation trials (shaded grey background) for each group. Zero degrees and the magnitude of imposed rotation are shown by horizontal dashed lines.* ***b:*** *The asymptotic level of adaptation for each participant in both the online and in-lab group. Filled circles represent the adaptation asymptote for each participant (defined as the average of the last 40 adaptation trials), with mean values and standard error depicted by horizontal and vertical lines respectively. Dashed horizontal lines depict the imposed cursor rotation.* ***c:*** *Mean response times (time between target presentation and movement initiation), ± standard error (shaded region) for each group. Preparation time was predetermined and tightly controlled at 2.5 seconds.*

5.3.6 Analysis of movement duration during the task

During the task, participants had 0.25 seconds to complete their movement towards the target. Mean movement durations for each participant in each group (online task)

were analysed in a two-way ANOVA (Rotation Magnitude x Preparation Time). The ANOVA revealed no significant main effect of Rotation Magnitude ($F(2, 171) = 0.98, p = 0.38, \eta_p^2 = 0.011$) and no Rotation Magnitude x Preparation Time interaction ($F(4, 171) = 0.75, p = 0.56, \eta_p^2 = 00.017$). There was however, a main effect of Preparation Time ($F(2, 171) = 11.83, p < 0.001, \eta_p^2 = 0.12$), which indicated that overall participants with 0.35 seconds of preparation time made slower movements than those with 1 and 2.5 seconds of preparation (both $p < 0.001$), with no differences between the latter two groups ($p > 0.99$, Figure 5.6).

An F-test suggested there was a significant difference in the variance of the data between the in-lab and corresponding online group ($F(19, 19) = 7.94, p < 0.001$), despite there being no statistically significant difference in movement duration between the two groups ($t(38) = 2.01, p = 0.052$).

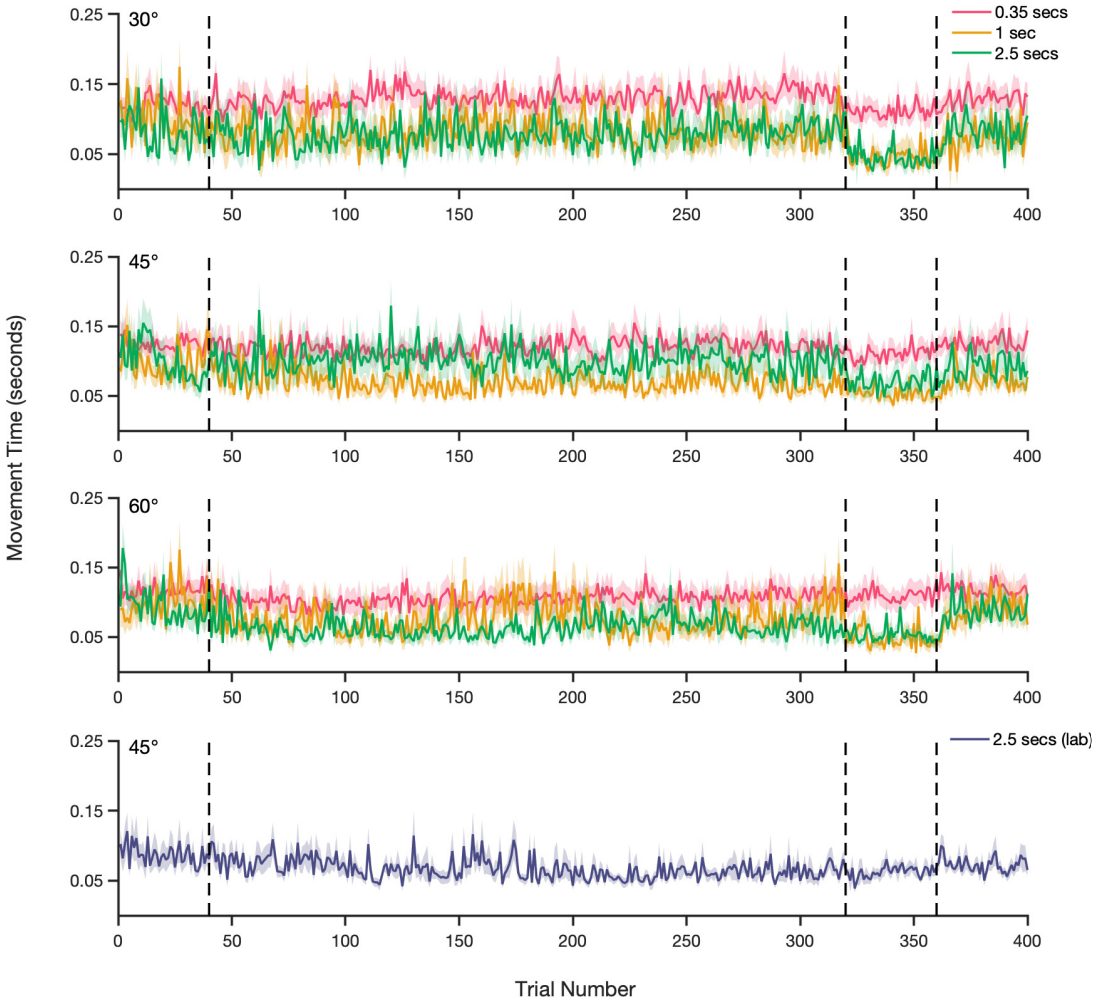


Figure 5.6: *Mean movement duration (defined at the time between movement initiation and the point at which participants' movement crossed the target circle perimeter) ± SE (shaded region), plotted by trial number for each experimental group. Vertical dashed lines depict the different task phases (baseline, adaptation, no-feedback and washout).*

5.4 Discussion

We aimed to test the assumption that increased motor preparation periods may allow for more complete adaptation during visuomotor rotation tasks. As such, we hypothesised that shorter preparation periods would be sufficient to fully counteract a 30° rotation, as a small rotation would require less (and therefore quicker) mental rotation before motor execution. We then predicted that this effect would scale with an increased cursor rotation, so that 45° and 60° would require greater mental rotation and thus more time to fully compensate. Indeed, we did find that restricting planning time for moderate and larger rotations resulted in impaired final adaptation levels and greater implicit retention compared to those groups with more preparation time. However, contrary to research from Langsdorf et al. (2021), we found no evidence to suggest that extended motor preparation periods allow for the elimination of residual errors observed during late stages of adaptation, as all groups displayed final adaptation performance significantly lower than the imposed cursor rotation.

Hence, we failed to replicate the results from Langsdorf et al. (2021), who found that enforcing a 2.5 second planning period between target presentation and reach onset allowed individuals to fully counteract a 45° visuomotor rotation, leaving no residual mean error at asymptote. The authors suggested that the extended planning period allowed for time-consuming cognitive processes, such as mental rotation, to be completed prior to the go-signal and resulted in complete compensation. This theory, centred around a speed-accuracy trade-off, seems plausible given that reaction times increase in a linear fashion when subjects are asked to reach at increasing angles from a target - a relationship that mimics the behaviour seen in mental rotation tasks (Shepard & Metzler, 1971; Georgopoulos & Massey, 1987; McDougle & Taylor, 2019). Accordingly, brain regions activated in both visuomotor adaptation and mental rotation tasks have also been shown to overlap (Anguera et al., 2010), suggesting that mental rotation contributes to visuomotor adaptation. Recent evidence investigating preparatory activity in the motor cortex of non-human primates further suggests the

necessity for motor planning time in visuomotor adaptation (Vyas, O'Shea, Ryu, & Shenoy, 2020). In addition, Langsdorf et al. (2021) found that delaying movement initiation resulted in an overcompensation of the imposed rotation, similar to the overshoot in reach estimation shown by Georgopoulos and Massey (1987), suggesting similar cognitive rotation strategies may have been in play.

Notwithstanding these studies, we found that on average participants' learning plateaued before eliminating error, with asymptotic learning levels statistically different from the degree of imposed rotation for all rotational groups (30°, 45°, 60°), regardless of the amount of preparation time enforced. These findings are consistent with previous reports which have suggested that sustained errors during visuomotor adaptation are a product of the implicit learning system; either suppressing alternative learning mechanisms which may be able to overcome persisting errors (Shmuelof et al., 2012; Vaswani et al., 2015) and/or modulating the system's sensitivity to errors dependent on their size, variability and history (Albert et al., 2021). It should be noted however, that despite regression analysis suggesting the data had reached an asymptote, there is a possibility that with a longer adaptation session, or with multiple sessions, participants may have been able to reduce their error further and get closer to complete compensation. Yet, given the degree of error remaining at the end of these 280 trials, and the non-significant slopes of the regression analyses, it is unlikely that much greater adaptation would be achieved within the bounds of Langsdorf et al's. (2021) study protocol (i.e., with an additional 40 trials). In support of this, estimated asymptotic levels of adaptation modelled from existing mean group data are in close correspondence with the values calculated in our original analysis and suggest all groups would asymptote below the degree of imposed rotation (Figure 5.7).

One factor that may explain the discrepancy between our results and those of Langsdorf et al. (2021), is the level of experimental control. Our study was conducted online, with participants completing the task unsupervised at home, whereas Langsdorf et al. (2021) conducted a laboratory-based study. The disparities associated

with these environments may have contributed to small but significant differences in motivation, attention and behaviour. That said, data from our additional in-laboratory group is at odds with this reasoning. We found no difference in adaptive performance at any phase of the task between the in-lab and corresponding online group, with participants in both groups failing to achieve full compensation. This finding supports previous literature which suggests that kinematic data and results from online motor learning studies are analogous with those collected in a controlled lab environment (Tsay, Lee, Ivry, & Avraham, 2021) and that online tasks perform well in terms of accuracy and precision with regards to timing of visual stimuli and response capture (Bridges, Pitiot, MacAskill, & Peirce, 2020). Furthermore, our data are typical of many previous lab-based visuomotor adaptation studies, with comparable levels of final performance (Huberdeau et al., 2015; Morehead, Qasim, Crossley, & Ivry, 2015; Vaswani et al., 2015; Neville & Cressman, 2018; Weightman et al., 2020; Weightman, Brittain, Miall, & Jenkinson, 2021). With all of these results in mind, it is improbable that the failure to eliminate residual errors (and replicate results from Langsdorf et al., 2021) was a consequence of online data collection methods.

A further notable difference between the two studies is the apparatus used to complete the task. In the present study, participants either used a trackpad or a mouse to direct the cursor towards targets. We expect these movements demanded rotation of the wrist with flexion/extension of the index finger (trackpad) and small movements about the elbow/shoulder joint (mouse). The sensory and biomechanical control of these movements likely differ from those of Langsdorf et al. (2021), where a digitising tablet was used to make small point-to-point reaching movements while holding a stylus and may have contributed to some discrepancy in results between the two studies (De Rugy, Hinder, Woolley, & Carson, 2009; Yin, Wang, Wei, & Körding, 2019). However, as we found no differences between the mouse and trackpad conditions, which themselves entail very different biomechanical demands, we believe our results generalise across methodologies. Moreover, in contrast to Langsdorf et al. (2021), we

did not ask participants to cover or block vision of their upper-limb during the task. As a result, there may have been some differences in the explicit awareness of the cursor rotation and thus performance during adaptation (Wong et al., 2019).

An additional difference between the two studies, which may have had some bearing on the results, is the nature of response cueing used. We used a visual countdown sequence which enabled participants to accurately synchronise their movements with the go-signal and ensured a tight coupling between response times and the preparation time groupings. In contrast, Langsdorf et al. (2021) displayed the target and instructed participants to wait until they heard a tone before responding. This difference in protocol resulted in response times closer to 3 seconds. One may argue that more than 2.5 seconds are required to fully prepare for a 45° rotated reach. This is unlikely however, as we show that even a 30° angle was not fully compensated, and there was no evidence for a relationship with the preparation interval for those groups. Previous research has also shown that mental rotation and aiming towards angles up to 90° can be achieved in ∼1 second (McDougle & Taylor, 2019). There is perhaps an argument to suggest that attending to the countdown sequence may have interfered with mental rotation and other cognitive planning processes, by, for instance, vying for attentional resources and thus contributing to a consistent reach undershoot (Taylor & Thoroughman, 2007; Galea, Sami, Albert, & Miall, 2010). Nevertheless, prior studies using auditory response cueing have not cited attention to the timed-response sequence as a potential confound (Haith et al., 2015; Leow, Gunn, Marinovic, & Carroll, 2017; McDougle & Taylor, 2019).

Despite participants failing to eliminate residual errors during late adaptation, our data do include some hallmarks of a speed-accuracy trade-off. We found that motor adaptation was impaired in the 45° and 60° rotational groups, during both early and later stages, when planning time was restricted to 0.35 seconds. This result is in line with previous studies who report reduced error compensation when preparation times are limited (Fernandez-Ruiz et al., 2011; Leow, Gunn, et al., 2017; Leow, Marinovic, et

al., 2017; Albert et al., 2021) and may reflect the suppression of explicit re-aiming/cognitive strategies. Additionally, impaired adaptation associated with restricted preparation times was coupled with an increased retention during no-feedback trials, which is consistent with the idea that learning involved more implicit, procedural processes (Fernandez-Ruiz et al., 2011; Haith et al., 2015). The greatest retention was seen in the 0.35 seconds / 60° group, which implies that adaptation in this group may have been weighted more so towards implicit processes – also highlighted by the larger residual errors at the end of learning. This suggestion is reinforced by the equal retention seen for the 2.5 second condition, across all three rotation magnitudes. In this case, the residual errors are approximately equal, because the preparation time exceeded that required for mental rotation. However, these assumptions should be treated with some caution after recent commentary on how the dichotomy of implicit and explicit components of motor adaptation are inferred (Hadjiosif & Krakauer, 2021).

Although not statistically evident, a speed-accuracy trade-off may also be apparent in the 60° rotational group (Figure 5.2 & 5.3). On average, there was a linear increase in learning asymptote as preparation time increased, which may reflect how mental rotation of the intended movement angle increases the accuracy of reaches (McDougle & Taylor, 2019; Langsdorf et al., 2021). The addition of further adaptation trials might exaggerate these asymptotic differences, until statistically significant, yet data from our other rotational groups, modelling and previous literature would suggest that errors would still persist. To achieve full compensation, it is possible that explicit information about the nature of rotation and how to counter it ought to be provided (McDougle & Taylor, 2019) or strategies primed using methods such as verbal aiming reports (Bond & Taylor, 2015; Brudner, Kethidi, Graeupner, Ivry, & Taylor, 2016; Wilterson & Taylor, 2019; Albert et al., 2021; Langsdorf et al., 2021), which will inherently be coupled with increased reaction/plan times.

In summary, our data suggests that extending motor preparation and planning

periods alone is insufficient to eliminate residual errors during visuomotor adaptation, irrespective of the size of imposed cursor rotation. While increased preparation time may help to improve error reduction at larger rotation magnitudes, our results suggest there remains a limit at which learning saturates at asymptote, perhaps only overcome with priming of explicit strategies, further instruction or changes to experimental variables. We also provide further support of the use of online data collection methods in the study of motor control and learning. Understanding why the central nervous system fails to fully adapt movements in response to environmental changes may be key when aiming to optimise rehabilitation protocols following brain injury or disease.

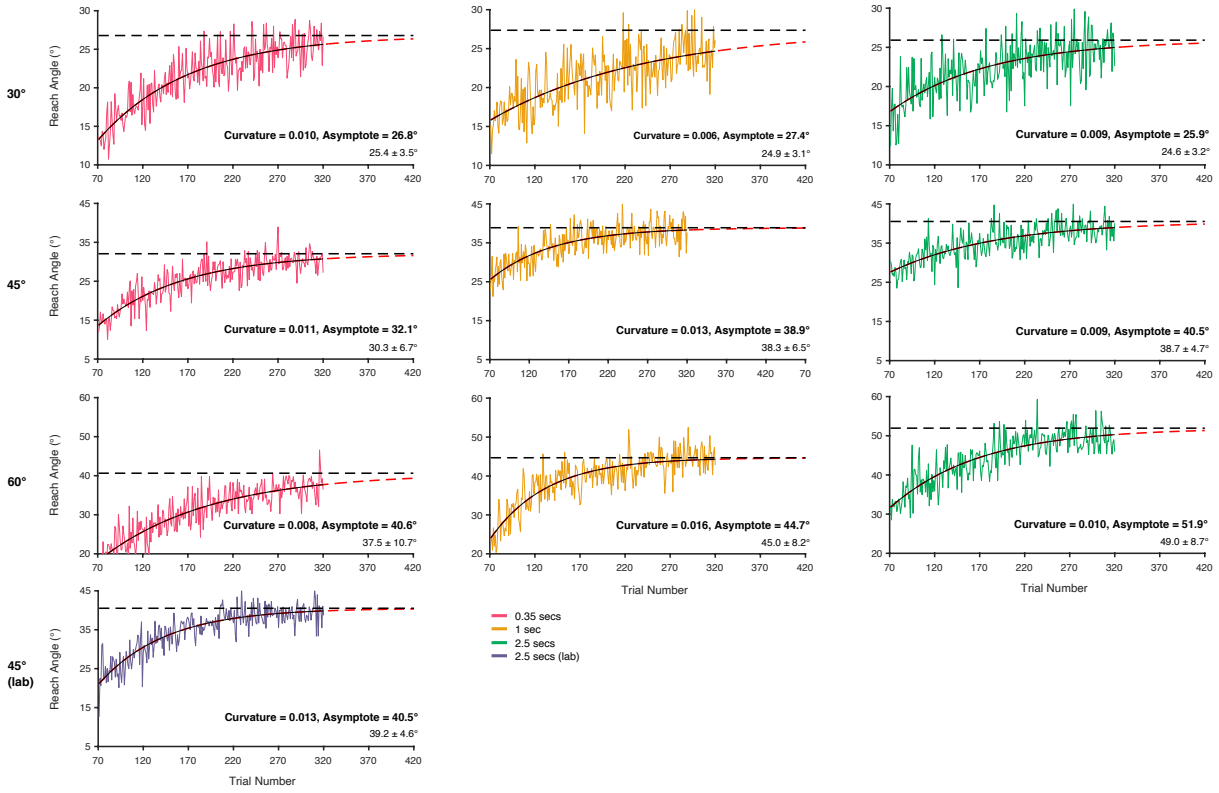


Figure 5.7: *Estimated asymptotic levels of adaptation modelled from existing mean reach angle data for each group* $(intercept + asymptote * (1 - exp(-curvature * TrialNumber)))$. *Mean data is plotted from trial 70 (the 30th trial of the adaptation phase) and continues until the end of adaptation (250 trials total). The model is fitted to the mean data (thin black line) and is extrapolated for a further 100 trials (dashed red line). The estimated asymptote is depicted by a horizontal dashed black line and is reported in bold along with the curvature of the data. The asymptote calculated from our analysis (average of the last 40 adaptation trials;* $\pm SD$*) is also reported underneath.*

Chapter 6

General discussion

6.1 Summary of experimental chapters

In recent years, there has been an exponential growth in research investigating the effects of transcranial direct current stimulation (TDCS) on central nervous system (CNS) function. TDCS has garnered much interest with regards to its potential for therapeutic application - especially as it is relatively cheap, portable and inexpensive compared to other non-invasive brain stimulation (NIBS) techniques. However, despite initial promise in a number of different fields e.g., psychiatry, cognition and rehabilitation post-stroke etc., there has been growing criticism regarding the efficacy, replicability and thus potential clinical translation of TDCS. This thesis therefore sought to investigate ways in which TDCS can be more optimally applied in order to modulate behaviour.

Firstly, using both anodal and cathodal stimulation, an effector-specific framework of TDCS effects was tested by applying stimulation to either the motor cortex (M1) or cerebellum during tasks which demanded either fine hand and finger or gross whole arm reaching movements (chapters 2 and 3). Following this (chapter 4), the specificity of stimulation timing was investigated by applying TDCS in short epochs, and coincidentally with movement, during a motor adaptation task. Finally, and due to restrictions associated with the COVID-19 pandemic, chapter 5 departs from the general theme of the previous chapters and thesis as a whole. As all human participant research was halted, a continuation of our work with TDCS was not possible. Instead focus shifted to investigate why individuals are unable to achieve full compensation during motor adaptation tasks - a behaviour especially notable in chapters 2 and 3 and possible to examine using online behavioural testing.

6.2 Main findings

In chapter 2 we demonstrated that stimulation applied to distinct neural substrates, which exert differing levels of control over dexterous hand or whole arm reaching

movements, can drive improved adaptation in tasks that share similar characteristics but isolate proximal and distal upper limb motor control. Specifically, anodal TDCS applied over the cerebellum enhanced adaptation of reaching but not of hand/finger movements, whereas M1 stimulation improved the adaptation of fine hand and finger but not whole arm reaching movements. This double dissociation was found in both a younger and older adult cohort and replicates effects found by both (Hardwick & Celnik, 2014; Panouillères et al., 2015).

The results from chapter 3 extended these effector-specific findings, as we found that cathodal TDCS over the cerebellum impaired the adaptation of reaching movements. Conversely and in opposition to our hypothesis, these stimulation parameters also resulted in enhanced adaptation of fine hand and finger movements. Cathodal TDCS applied to M1 had no significant effects on performance in either of the adaptation tasks, but a weak non-significant trend towards reduced adaptation in the hand movement task was observed.

Chapter 4 demonstrated that brief bouts of TDCS applied over the cerebellum simultaneously with a specific movement can selectively improve motor adaptation of that movement, while leaving adaptation of similar interleaved movements unaffected. We found no effects of M1 TDCS on context-dependent force-field adaptation, with participants performing similarly to a sham stimulation group. In the main experiment, these results were confined to a reduction in lateral deviation of movements and we found no stimulation-specific effects on force compensation. However, in an additional experimental group designed to replicate our original results, we found significant improvements in both lateral deviation and force compensation.

Finally, chapter 5 found that extending motor preparation periods is insufficient to eliminate residual errors during visuomotor adaptation, regardless of the size of imposed cursor rotation. We show that restricting planning time for moderate and larger rotations resulted in reduced final adaptation levels and greater implicit retention compared to those groups with more preparation time. All of our

experimental groups displayed final adaptation performance significantly lower than the imposed cursor rotation.

6.3 Discussion of results

6.3.1 Effector-specific framework

One of the main findings of this thesis is that TDCS can influence motor adaptation in an effector-specific manner. Historical research, distilled in Lawrence and Kuypers (1968a, 1968b) formed the foundations of this work, who in a series of experiments, showed a dissociated pattern of motor control recovery in rhesus monkeys, when the influence of differential descending pathways were abolished. Bilateral interruption of the pyramidal tracts initially left the animals with severe motor deficits, all of which were eventually recovered, barring the ability to fractionate movements of the hand and fingers. In contrast, when lesions were made to more medially descending pathways (including to the red nucleus) persisting deficits of trunk and proximal upper limb movements were observed. This evidence, along with comparable findings of upper limb recovery in humans post-stroke (Schambra et al., 2019) and an apparent discord between studies using TDCS to investigate motor adaptation (detailed in chapters 2 and 3: Galea, Vazquez, et al., 2010; Hardwick & Celnik, 2014 vs Panouillères et al., 2015), suggest that movements of the proximal and distal portions of the upper limb may be differentially modulated by targeting distinct regions of the brain.

Accordingly, we showed that TDCS targeted at the cerebellum or M1 specifically modulated motor adaptation in tasks that were dominated by proximal and distal upper limb movements respectively (chapters 2 and 3). In chapter 2 we found a double dissociated effect of M1 and cerebellar anodal TDCS on motor adaptation of the hand and arm. These results also replicate findings from similar TDCS/motor adaptation studies (Galea, Vazquez, et al., 2010; Block & Celnik, 2013; Hardwick &

Celnik, 2014; Panouillères et al., 2015) in both younger and older adult cohorts. A notable difference between these studies, other than the movements demanded by each of the tasks, was the degree of rotation applied to the cursor during adaptation (30° vs 60°). It could be argued that countering a larger rotation (as in chapter 2 and Panouillères et al., 2015) requires greater explicit strategies (Bond & Taylor, 2015), which are believed to be under greater cortical control (McDougle et al., 2015). Thus, stimulating M1 could have enhanced the cognitive processes involved in strategic re-aiming - especially as current flow is not focal. Along the same line of thinking, stimulating the cerebellum during smaller cursor rotations (Galea, Vazquez, et al., 2010; Block & Celnik, 2013; Hardwick & Celnik, 2014) may have facilitated the implicit learning system, which is cerebellar dependent and unconsciously drives the correction of small discrepancies between predicted and actual movement feedback (Smith et al., 2006; Tseng et al., 2007; Shadmehr et al., 2010). However, this reasoning cannot explain the enhanced adaption to a 60° rotation following cerebellar TDCS (and double dissociation) in chapter 2, therefore indicating that a modulation of differential learning processes unlikely contributed to the results.

One of the emerging theories regarding TDCS mechanisms of action is that stimulation targeted at different regions of the brain will preferentially modulate behaviour dependent on the function of that region and its activity during the stimulated period (Bikson & Rahman, 2013; Fertonani & Miniussi, 2017). This theory seems to align well with the present results, as TDCS enhanced adaptation only when applied to neural substrates that are most allied to the control of either proximal (cerebellum-brainstem) or distal (M1-corticospinal tract) upper limb movements. Consequently, and based upon the proposed bias in activity within the motor hierarchy for the control of reach versus fractionated hand movements, TDCS may have preferentially modulated neural circuits that were already activated by the constraints of each task - resulting the double dissociation we observed.

Results from chapter 3 go some way to support the suggested effector-specific

framework of TDCS effects. As hypothesised, we found cathodal cerebellar TDCS impaired adaptation of reaching movements, a reversal of the effect in chapter 2 with anodal stimulation. However, we failed to show a significant reduction in adaptive performance of hand/finger movements as a result of cathodal M1 stimulation. There are several potential reasons for this null finding; with floor effects and a zero-sum excitability model (details below) the most probable. Across both chapters 2 and 3, adaptation was more complete during the joystick version of the task. Hence, it is possible that there was a limit at which decreasing excitability of M1 could inhibit adaptation during the joystick tasks. This may partially explain the non-significant decrease in adaptive performance of hand and finger movements following cathodal M1 TDCS, a rationale that has previously been cited for possible masked effects of cathodal stimulation (Fregni et al., 2005; Horvath, Carter, & Forte, 2016). Moreover, there is some suggestion that increased activity/excitability of M1 due to adapting hand movements may have countered any depressive effect of cathodal TDCS and resulted in a net zero or attenuated stimulation effect (Reis & Fritsch, 2011). On the whole, there are fewer studies investigating the effects of cathodal TDCS on motor adaptation - quite possibly as decreasing neural activity seems counterintuitive from a rehab standpoint - which makes additional speculation regarding this result difficult.

A further result from chapter 3 provides indirect support effector-specificity, whilst also highlighting the importance of connectivity between brain regions when interpreting TDCS results. Results showed that fine hand and finger adaptation was enhanced by cathodal cerebellar TDCS, and we propose this is due to disinhibition of M1 via a reduction in cerebello-brain inhibition (CBI). Our conjecture is that cathodal cerebellar TDCS resulted in a decrease in Purkinje cell excitability, reducing the overall inhibitory tone of the cerebellum over the cortex (Galea et al., 2009), thus indirectly increasing the excitability of M1 and enhancing adaptation of fractionated hand movements. To the best of our knowledge this is the first study to link an alteration in CBI to motor behaviour using TDCS, with previous reports being confined to measures

of cortical excitability (see review Celnik, 2015) or behaviour in the cognitive domain (Pope & Miall, 2012, 2014). This result may also have important implications for the design of rehabilitation studies/protocols, especially when the direct application of electrical currents to an injured brain area may not be desirable. Given this line of prior reasoning, one might expect to observe a decreased level of adaptation following anodal TDCS over the cerebellum during the joystick task - as a result of increased CBI. However, this was not evident in our results. We suggest that floor effects may have played a role in this result, preventing a decrease in performance in this experimental group. Additionally, it is suggested that CBI decreases during adaptation (Jayaram et al., 2011) which may have countered any modulation in CBI via TDCS. Further research is required to provide more robust justification for this result.

In summary, data from chapters 2 and 3 present evidence to support an effector-specific framework of TDCS effects on motor adaptation. In line with the activity-selectivity model (Bikson & Rahman, 2013), our results suggest the function and activity during the prescribed task is important for behavioural effects. Further work is required to confirm these findings and ensure this framework generalises beyond sensorimotor adaptation.

6.3.2 Temporal specificity

There is a current discord between the foundational theories underpinning motor learning and how TDCS is generally applied: the former is dependent on tight coupling of events (Hebb, 1949; Shatz, 1992), while the latter is conducted with very low temporal resolution. Data from chapter 4 shows that when short duration stimulation (< 3 seconds) is yoked to movement, only reaching movements performed simultaneously with stimulation are enhanced. We posit that the low temporal resolution of TDCS application may be contributing to the growing number of mixed and null results in the literature. Previous research has shown that TDCS-based modulation of neural excitability and behaviour is dependent on the underlying state

of the network during stimulation (Li et al., 2019). Therefore, performing different behaviours associated with a particular task alongside the specific behaviour of interest and under the same stimulated period, may lead to non-specific alterations in neural excitability and result to conflicting findings.

Recent work in brain slices has shown that direct current stimulation (DCS) can enhance long-term potentiation (LTP) and boost Hebbian associativity (Kronberg et al., 2017, 2020). The authors found that the application of direct currents enhanced LTP, but only in pathways that were concurrently undergoing plastic changes. They suggest that these effects are mediated via a modulation of membrane potential dynamics and propose that TDCS in a human research setting should be applied during tasks that elicit similar plasticity mechanisms to improve outcomes (Kronberg et al., 2020). In theory these findings match our behavioural results from chapter 4, as only movements that were performed with concurrent event-related TDCS (er-TDCS) were potentiated. In agreement with this work, we propose that er-TDCS enhances learning by boosting Hebbian-like plasticity in circuits involved in, and activated by, a particular behaviour.

Given that specific behaviours can be precisely targeted with TDCS to achieve a more focal effect, this proof-of-principal study has clear potential impacts for rehabilitation protocols e.g., applying TDCS during specific movements or exercises in functional recovery tests. Also, considering the concerns associated with long continuous stimulation protocols causing a reversal or habituation of modulatory effects (Creutzfeldt et al., 1962; Kunori & Takashima, 2019; Asan et al., 2020; Hassanzahraee et al., 2020a), these results suggest TDCS can be applied more specifically and sparingly. However, the path to rehabilitation requires further work and clarification. In light of the scepticism regarding the effectiveness of TDCS, the current protocol could be repeated with stimulation delivered 'out of phase' e.g., during the preparation period or between movements, in order to further elucidate the underlying mechanisms and with a comparison to a 'standard' TDCS condition. This further work is especially important as consistent results were only found in one of our

outcome measures (lateral deviation), which may reflect a differential facilitation of feedback and feedforward processes. Additionally, these findings need to be extended beyond the controlled lab environment and into other motor control/learning settings to understand the potential impact. Finally, while we use timing-dependent plasticity to frame our hypothesis and interpretation of results, the rules associated with these mechanisms have a timescale of tens to hundreds of milliseconds (Feldman, 2012), rather than seconds over which TDCS was applied for during movements in chapter 4. Therefore, a greater focus on the specific timescale of behaviours may be necessary.

6.3.3 Residual errors in motor adaptation

During many forms of sensorimotor adaptation, performance reaches a point or limit at which learning saturates, despite the presence of residual errors. Recent research has suggested that these residual errors occur as a result of a speed-accuracy trade-off, whereby cognitive planning processes are interrupted by the onset of movement - even when time is not constrained (Langsdorf et al., 2021). Therefore, when forced to complete motor planning in a predetermined waiting period before movement initiation, individuals are able to fully compensate for visuomotor rotations. Contrary to these findings, we found no evidence to suggest that elongating motor preparation periods allows for the elimination of persistent errors at any magnitude of cursor rotation, with all experimental groups reaching a learning asymptote below that of the imposed cursor rotation.

These results seem to suggest that adaptive performance is not restricted by time to complete cognitive planning processes, such as mental rotation (McDougle & Taylor, 2019), but rather highlights that perhaps factors associated with the implicit learning system, not explicit strategies, limit adaptation. Previous research investigating the asymptotic limits of adaptation, supports this notion. In a series of experiments, Albert et al. (2021) showed that when reaction time was restricted so that learning relied in part, or solely, on implicit processes, residual errors occurred and were linked to the

variance of the environment and the consistency of previous errors. However, when explicit learning was isolated by delaying end-point feedback, residual errors were not present and individuals could achieve full compensation, with no effect of perturbation variance. Additionally, evidence from Vaswani et al. (2015) suggests error-dependent learning processes suppress alternative learning mechanisms that are capable of overcoming persistent errors in visuomotor adaptation. Together with our results, these findings point to limitations within the implicit learning system contributing to asymptotic levels of adaptation.

These results also provide support for the continued use of online research methodologies in the study of motor learning as we - like others (Tsay et al., 2021) - found close correspondence between in-lab and online data and replicated effects from numerous different studies (Fernandez-Ruiz et al., 2011; Haith et al., 2015; Leow, Marinovic, et al., 2017; Albert et al., 2021). Given the importance of motor learning in physical therapy practices (Leech, Roemmich, Gordon, Reisman, & Cherry-Allen, 2021), future work should continue to focus on understanding why the CNS fails to overcome persistent errors when adapting movements e.g., by extending learning periods and/or manipulating experimental conditions (akin to Albert et al.), in order to help improve rehabilitation protocols following disease or injury.

6.4 Directions for future research

While this thesis has proposed a number of different ways in which TDCS can be applied to modulate specific behaviours, there are still many outstanding questions that require further attention. An initial step would be to extend the findings of the present work into different motor control/rehabilitation settings, in an attempt to understand how functional and temporal targeting of TDCS to behaviour translates in other contexts. Combining some of the TDCS protocols/theories presented here directly into therapy sessions aimed to improve function after injury or disease and testing their effectiveness

using standard functional tests would help to inform efficacy. The generalisation of stimulation-based effects is key to determine the potential, and limitations, of TDCS as an adjunct therapy, with a lack of a clear path from controlled lab-based experiments to real-world application being a major critique of the technique over the years. Although studies conducted as part of this thesis have comparable if not greater sample sizes than the extant literature, a need for more higher powered studies is essential. As this thesis has highlighted, a more theoretical and hypothesis driven approach to stimulation protocols, particularly incorporating foundational concepts of learning and behaviour e.g., Hebbian-like plasticity, should be adopted to improve the application and outcomes of TDCS-based research.

It is clear that a multi-modal approach to brain stimulation is required to bridge gaps in mechanistic understanding. Imaging and neurophysiological methods will not only allow for more individualised electrode placements and tailored stimulation current/dosage parameters by providing a detailed anatomical map of each subject, but also help to unravel the complex interactions that drive behavioural modulations. To this end, a greater focus on electrical current modelling and computational neurostimulation may help to understand how current flow spreads through, and effects the targeted brain regions, as well as generate relevant predictions linking behavioural and physiological outcomes, which can then be tested against human data (Bestmann et al., 2015). However, the addition of these complex and expensive methods may ultimately detract from the initial appeal of TDCS, which was centred around its relative low cost and ease of application. Given the almost infinite parameter space of TDCS, there remains many avenues for further exploration and hurdles to be cleared before we have a full mechanistic picture of how stimulation contributes to complex behavioural modulations.

6.5 Final Remarks

Overall, this thesis has shed light on different ways in which TDCS can be applied to modulate sensorimotor adaptation. We have shown that stimulation of distinct motor areas can selectively improve adaptation of different movements dependent on their concurrent activity and functional specificity. Additionally, we have presented new ideas with respect to how stimulation protocols can be applied with greater temporal precision in order to target specific behaviours. On the whole, these findings lend support to existing theories aiming to elucidate mechanisms that can explain different stimulation effects. It is hoped that the results presented here can help to continue the development of TDCS-based research, open up new possibilities for its use in both experimental and clinical settings and ultimately maximise the potential outcomes.

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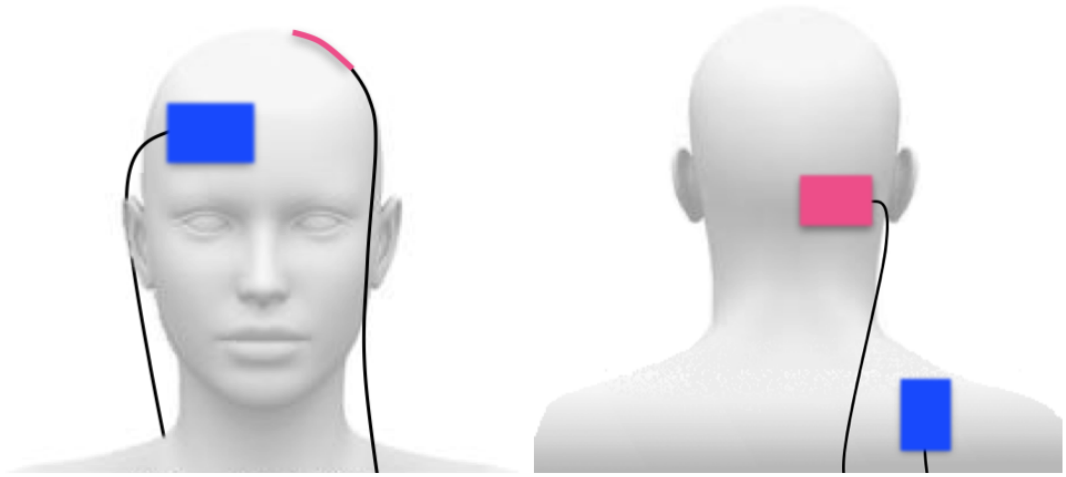
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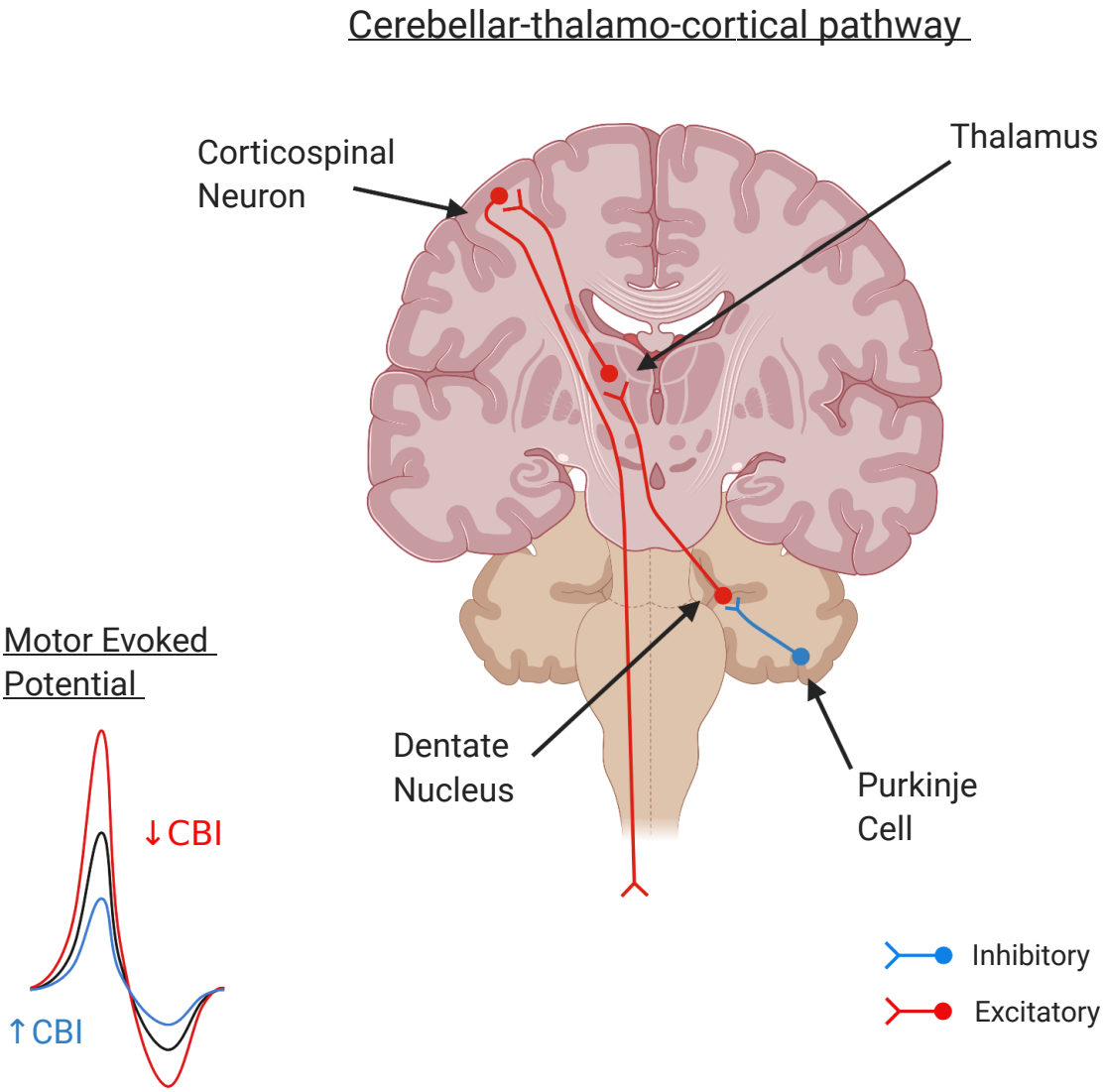
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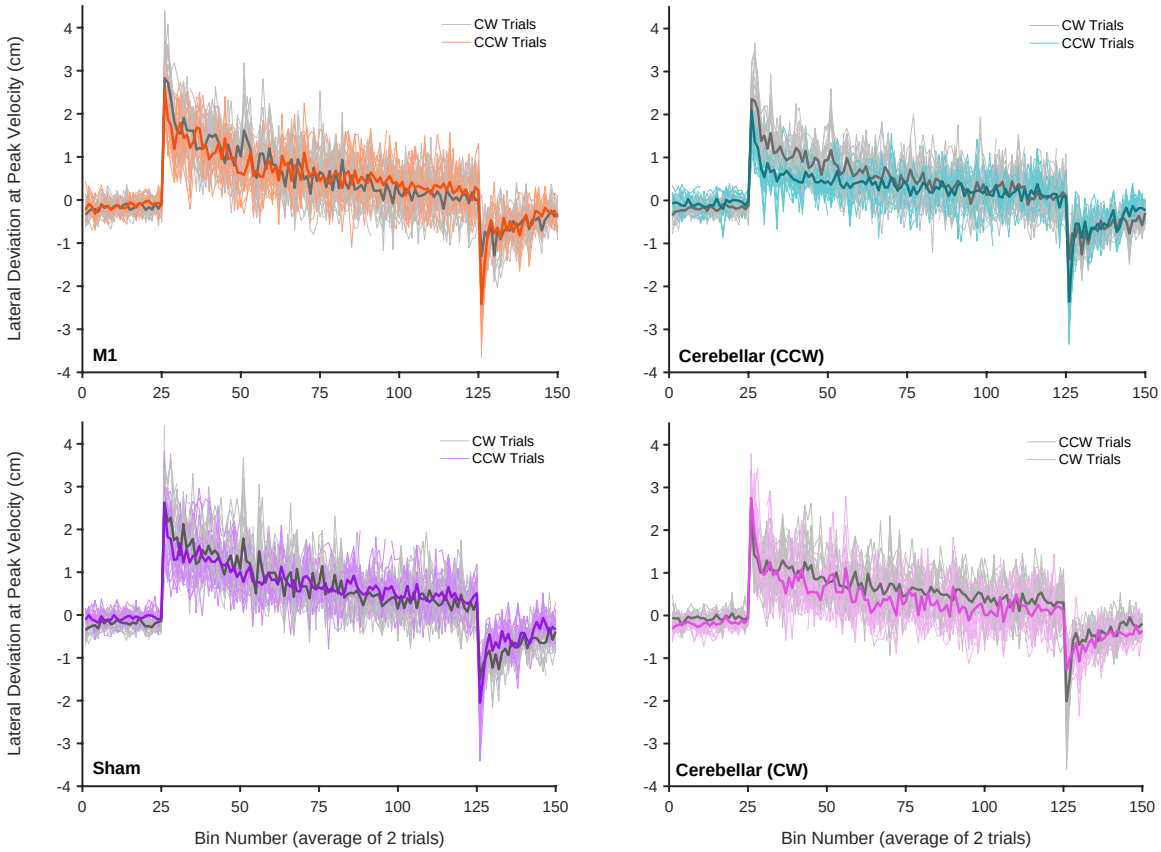
Appendix



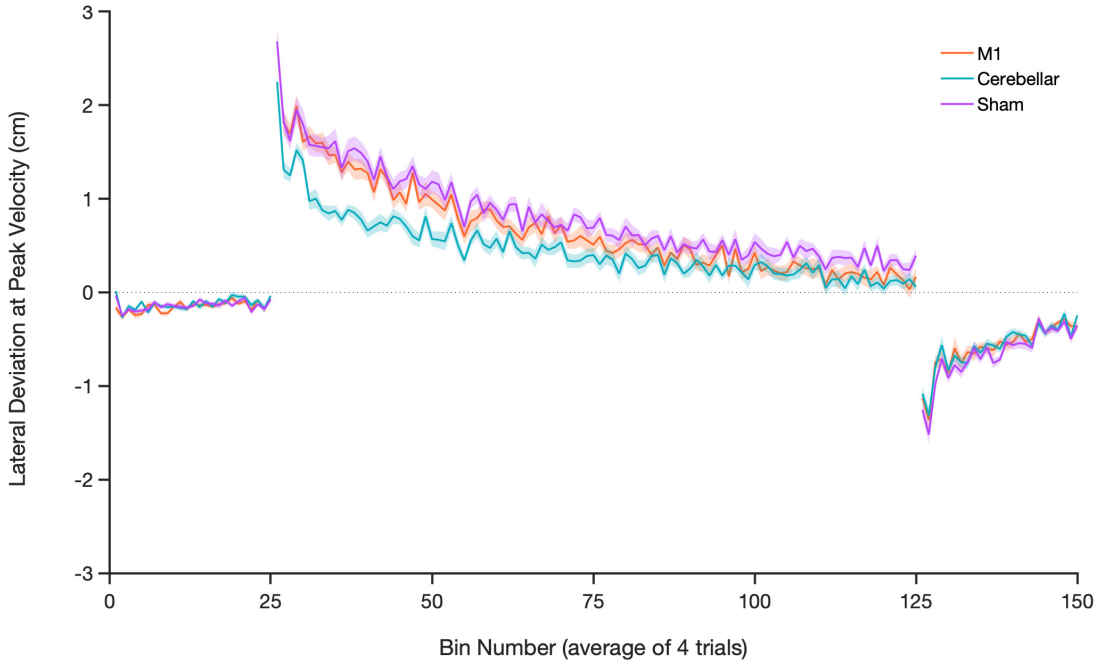
Appendix 1: Example TDCS montages used in experimental chapters for M1 (left) and cerebellar (right) stimulation.



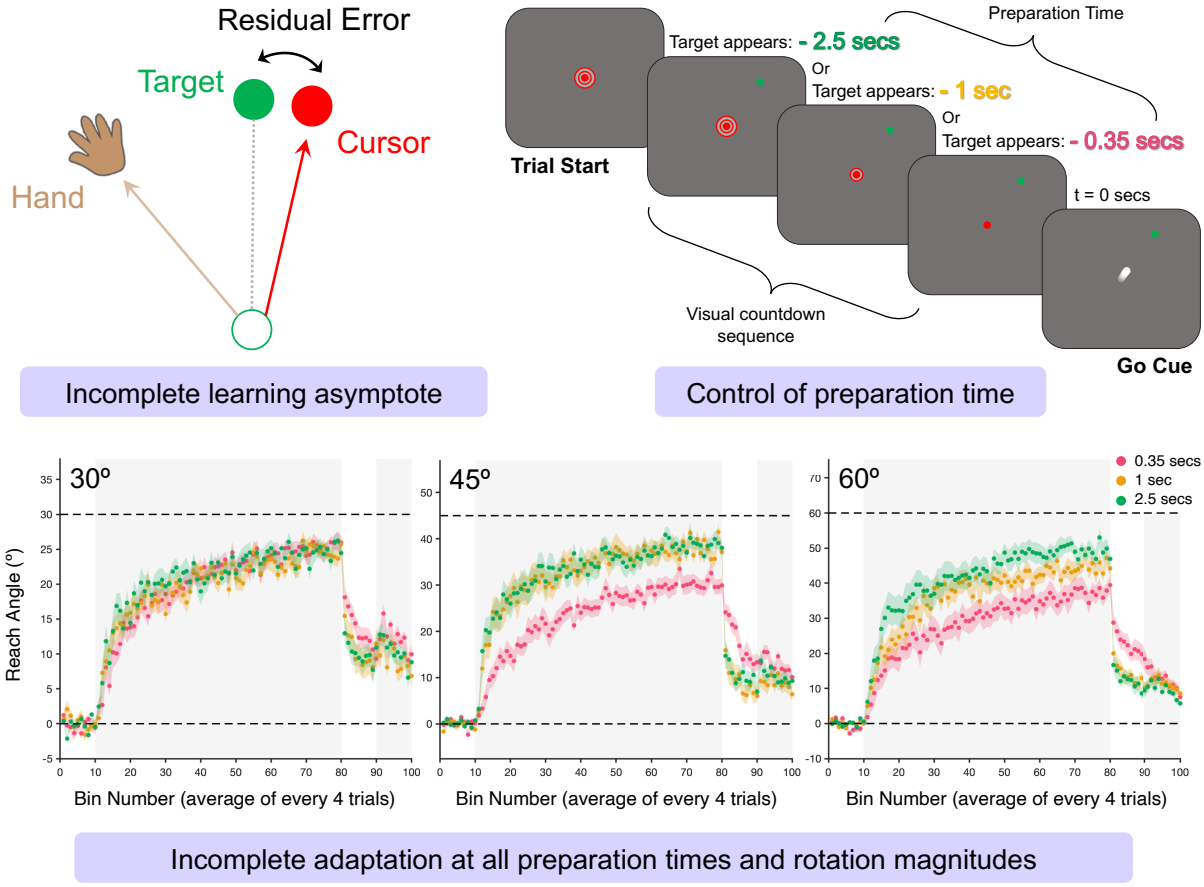
Appendix 2: Schematic of the cerebellar-thalamo-cortical pathway and how changes to cerebello-brain inhibition (CBI) affect cortical excitability measured via motor evoked potentials (MEPs).



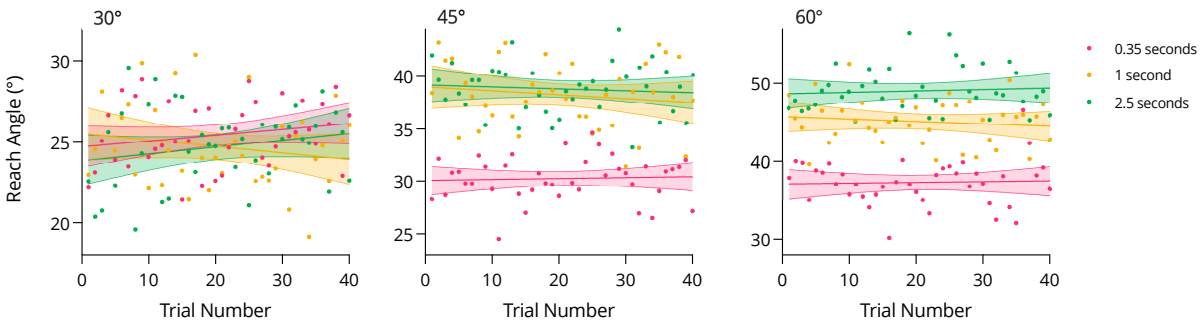
Appendix 3: Individual lateral deviation data traces plotted against the mean for both clockwise and counterclockwise force-fields in all experimental groups used in chapter 4.



Appendix 4: Sign adjusted mean lateral deviation to depict adaptation to both CW and CCW force-fields combined for all three stimulation groups in chapter 4.



Appendix 5: Graphical abstract used for manuscript submission of chapter 5; now published in The Journal of Neurophysiology.



Appendix 6: Visualisations of regression analyses from the learning asymptote for each rotational group used in chapter 5.