THE EFFECTS OF A VIRTUAL DISRUPTION ON MOTOR CONTROL AND MOTOR ADAPTATION STUDIED WITH TRANSCRANIAL MAGNETIC STIMULATION (TMS)

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Ph.D.

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PEGAH MOHAJER SHOJAII

A thesis submitted in partial fulfilment of the requirements of the University of East London for the degree of Doctor of Philosophy

September 2019

Abstract

The main aim of this thesis was to explore the neural and behavioural responses underpinning upper-limb motor control in a novel (force-field) robot-mediated reaching task using a non-invasive brain stimulation method known as transcranial magnetic stimulation (TMS). A new TMS-based network mapping technique was used to target different regions of the motor circuit (i.e. network nodes) using a 'virtual disruption' approach.

Seven cortical regions including the left and right primary motor cortex (M1), the supplementary motor area (SMA), the left and right posterior parietal cortex (PPC) and the left and right dorsal pre-motor cortex (PMC) were targeted with TMS at nine different time points during the preparation phase of upper-limb reaching towards a north-west target (i.e. reaching away from the body). Both neural mechanisms (corticospinal excitability with left M1 stimulation) and kinematic (behavioural) responses such as, movement onset, movement offset, maximum velocity, movement duration, summed error (reaching errors quantified by the calculating the difference between the subject's reaching trajectory and the ideal reaching trajectory) and maximum force were explored offline. When exploring the impact of TMS on each cortical region individually, the results demonstrated a behavioural effect on reaching responses because 1) TMS caused a significant disruption in reaching trajectories during motor adaptation compared to normal reaching (no force-field) at most time points and 2) TMS caused a significant delay in movement onset, particularly during motor adaptation. As well as exploring the effect of TMS on each region separately, it was important to determine the network of regions that may play a more functional role in novel reaching. Therefore a comparative analysis was performed between all stimulated regions for each kinematic parameter. The comparative analysis revealed a region specific relative influence on summed error. More specifically, the left M1 and left PPC were the principle structures that were involved in novel reaching because TMS to these structures resulted in significantly greater reaching trajectory errors. Based on this finding, it can be concluded that the left M1 and left PPC play a pivotal role in the preparation phase of upper-limb novel reaching compared to other regions in the motor network, including the right M1, SMA, left and right dPMC and right PPC.

Overall, the findings from this project can not only help 1) refine our understanding of the mechanistic elements that operate during reaching and 2) gain an insight into the

functional role of the different regions that are involved in novel reaching, but they also have a wide range of applications, ranging from brain machine interfaces (BMI) to neurocomputational models where data-based virtual lesions have been introduced into models of stroke patients.

Declaration

I declare that the work reported in this thesis was carried out in accordance with the regulations of the University of East London.

Pegah Mohajer Shojaii

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- **Shojaii, P**. and Turner, D. L. (2019) 'The posterior parietal cortex has a greater role than the supplementary motor area in novel motor behaviour: A TMS-based virtual disruption study', *Brain Stimulation: Brain, Translational, and Clinical Research in Neuromodulation*, 12(2), pp. 432 – 433. doi: 10.1016/j.brs.2018.12.402.

Abbreviations

ANOVA – Analysis of Variance

AP – Anterior Posterior

BB – Biceps Brachii

BMI – Brain Machine Interfaces

BOLD – Blood Oxygen Level Dependent

CED – Cambridge Electronic Design

CNS – Central Nervous System

CSE – Corticospinal Excitability

CSF – Cerebrospinal Fluid

CST – Corticospinal Tract

CT – Computed Tomography

DAI – Diffused Axonal Injury

DLPFC – Dorsolateral Prefrontal Cortex

dPMC – Dorsolateral premotor Cortex

DTI – Diffusion Tensor Imaging

ECR – Extensor Carpi Radialis

EEG – Electroencephalography

EMG – Electromyography

FAM – Familiarisation

FCR – Flexor Carpi Radialis

FDI – First Dorsal Interosseous

FF – Force-field

fMRI – Functional Magnetic Resonance Imaging

$GABA_A$ - gamma-aminobutyric acid A

$GABA_b$ - gamma-aminobutyric acid B

ICF – Intracortical Facilitation

IHI – Interhemispheric Inhibition

ISI – Interstimulus intervals

LICI – Long-interval Intracortical Inhibition

LIHI – Long Latency Interhemispheric Inhibition

LM – Lateral Medial

M1 – Primary Motor Cortex

MA – Motor Adaptation

MEP – Motor Evoked Potential

MEP – Motor Evoked Potential

MIT – Manus Interactive Motion Technologies

MNI – Montreal Neurological Institute

MRI – Magnetic Resonance Imaging

MRS – Magnetic Resonance Spectroscopy

MS – Multiple Sclerosis

mV – Millivolt

NFF – Null-field Reaching

NHS – National Health Service

PA – Posterior Anterior

PEG – Pneumoencephalography

PET – Positron Emission Tomography

PMC – Premotor Cortex

PPC – Posterior Parietal Cortex

PPR – Posterior Parietal Reach

PP-TMS – Paired Pulse TMS

rCBF – Regional Cerebral Blood Flow

RMANOVA – Repeated Measures Analysis of Variance

RMT – Resting Motor Threshold

rTMS – Repetitive Transcranial Magnetic Stimulation

SEF – Supplementary Eye-field

SEM – Standard Error of the Mean

SENIAM – Surface Electromyography for the Non-invasive Assessment of Muscles

SICF – Short Intracortical Facilitation

SICI – Short-interval Intracortical Inhibition

SIHI – Short Latency Interhemispheric Inhibition

SMA – Supplementary Motor Area

SP-TMS – Single Pulse TMS

SPSS – Statisical Package for Social Sciences

TB – Triceps Brachii

TBI – Traumatic Brain Injury

TMS - Transcranial Magnetic Stimulation

TTL – Transistor-Transistor Logic

VBM – Voxel Based Morphometry

vPMC – Ventral Premotor Cortex

WO – Washout

Acknowledgements:

I would like to take this opportunity to give my sincerest gratitude to all of the people who have helped me during my studies, in particular I would like to thank my supervisor Professor Duncan Turner for his valulable guidance, support, encouragement and advice throughout my PhD. I would also like to thank my second supervisors, Dr. Azmy Faisal and Dr. Arietta Spinou for their advice, time and help during my studies.

There are not enough words for me to express my graditude to my family. A huge thank you to my mum, dad, brother Pej and my aunty Lisa for their love and support, they raised me to never give up, provided me with the most valuable advice and comforted me in times of joy and stress! I would also like to thank my friends (for the lunch-breaks and gym-session breaks!), they have always kept an eye on me and provided me with words of encouragement when I needed it the most, and I thank you for your companionship along this journey.

A big thanks to all of the participants who kindly gave up their time to part-take in my research project, and the staff at the school of Health, Sport and Bioscience (University of East London) for their support and guidance throughout my studies.

Chapter 1: Introduction

1.1 Brief overview

The main aim of this thesis was to explore neural mechanisms and behaviours underpinning upper-limb motor control in a novel (force-field) robot-mediated reaching task using transcranial magnetic stimulation (TMS). A TMS-based network mapping technique was used to target different regions of the motor circuit (i.e. network nodes) using a 'virtual disruption' approach.

In order to study the neural mechanisms and behavioural responses of upper-limb reaching a laboratory-based set up was developed. A robot-mediated task was used for the reaching paradigm (i.e. to explore reaching performance), and a single-pulse TMS protocol was used to explore whether a disruption in neural activity can affect reaching performance. Generally, the neural mechanisms of reaching were investigated by acquiring electromyography (EMG) signals and the behavioural performance of reaching were investigated by acquiring kinematic data. The use of TMS and robotic reaching in an open-based environment in this project overcomes the general challenges when exploring reaching behaviours with other imaging modalities. For example, techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have been confined to exploring reaching-to-point tasks and reaching-to-grasp tasks (as explored further on in this thesis).

Overall, this project will aim to provide novel findings into the effects of single-pulse TMS during preparation for novel reaching, which can help; 1) refine our understanding of the mechanistic elements that operate during reaching, and 2) gain an insight into the functional role of the different regions that are involved in novel reaching (i.e. whether one region in the motor circuit plays a greater functional role in novel reaching compared to another region). Findings from this project have a wide range of applications, ranging brain machine interfaces (BMI) to neurocomputational models where data-based virtual lesions have been introduced into patient models.

Literature Review

1.2 History of neuroimaging

Neuroimaging has been defined as 'methods of brain imaging that help answer questions about brain structure and function' (Bandettini, 2009). Neuroimaging methods have developed over the last century from invasive methods such as ventriculography and pneumoencephalography (PEG) (Hoeffner *et al.,* 2012) to non-invasive methods, such as magnetic resonance imaging (functional [fMRI] and structural), magnetic

resonance spectroscopy (MRS), positron emission tomography (PET), electroencephalography (EEG) and transcranial magnetic stimulation (TMS - which was employed in this thesis).

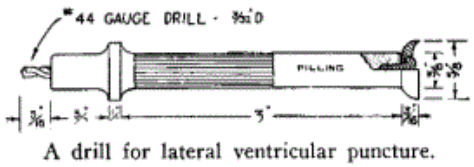
1.2.1 Invasive methods

1.2.1.2 Ventriculography and PEG

The discovery of X-rays by Roentgen in the mid 1890s (Sansare, Khanna and Karjodkar, 2011) which were first used to explore bone structure led to the development of invasive imaging methods, including ventriculography and pneumoencephalography (PEG) to explore brain structure (Tubiana, 1996; Hoeffner *et al*., 2012). Although X-rays successfully illustrate bone deterioration, as an imaging method it is poor in terms of demonstrating changes in intracranial tissue (Schuller, 1912). However, the invention of air ventriculography by Dandy during the 1910s enabled scientists to overcome this limitation. The technique was based on injecting air (via lumbar puncture) into the ventricles in order to outline intracranial pathologies on an X-ray image (Hoeffner *et al*., 2012) (figure 1.1A & B – Dandy, 1918). Although ventriculography methods increased the rate of tumour diagnosis, its invasiveness was associated with various after-effects, ranging from headaches to nausea (Hoeffner *et al*., 2012).

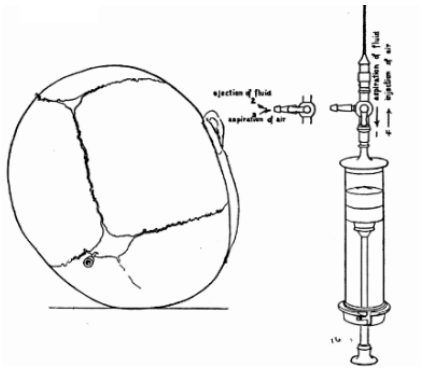
Similar to ventriculography in terms of its invasiveness, PEG was a method that drained cerebrospinal fluid (CSF) via lumbar puncture and replaced it with air for structural diagnostic purposes (Tondreau, 1985). The technique enabled an early diagnoses of hydrocephalous but could be fatal in terms of the various complications it could lead to (Bohn, 1937; Moseley, Loh and du Boulay, 1977; Tondreau, 1985). Figure 1.1C demonstrates the various types of symptoms that were reported in over 40 patients who had undergone PEG (White, Bell and Mellick, 1973). Although effective in terms of their diagnosis of structural pathology, the detrimental after-effects of ventriculography and PEG discouraged both patients and neurosurgeons and as a result both methods were abandoned. Nonetheless, its invasive nature helped improved radiographic techniques and build the foundations for non-invasive neuroimaging methods, including computerised tomography (CT).

A.



A drill for lateral ventricular puncture.

B.



C.

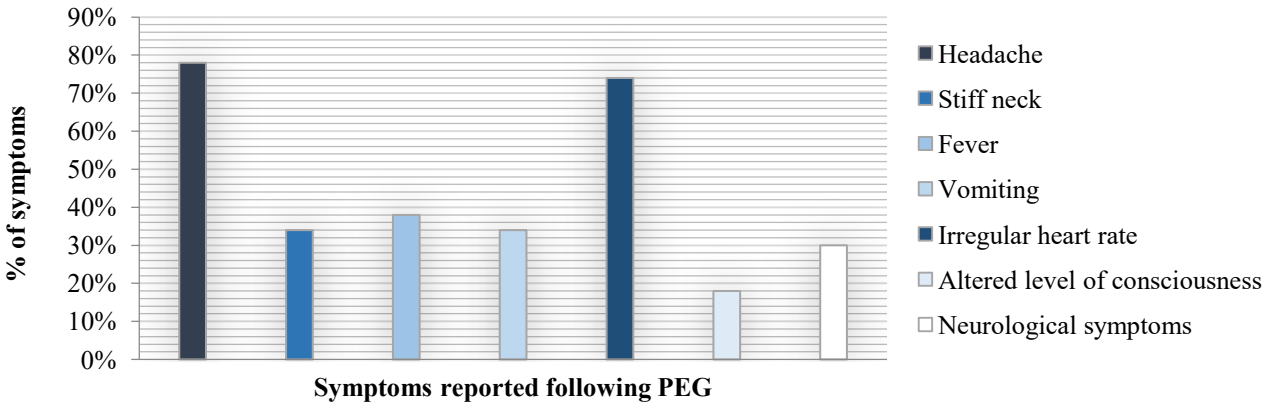


Figure 1.1: Previous imaging methods

(A) Drill used for puncture creation (Dandy, 1918), (B) Air ventriculography needle (Dandy, 1918) and (C) Symptoms reported following PEG procedures in over 40 patients (based on data from White, Bell and Mellick, 1973).

Ventriculogaphy includes:

(A) Lumbar puncture with a drill (Dandy, 1918)

(B) Followed by the use of a needle to remove CSF in the anterior fontanelle and replace it with air (Dandy, 1918).

(C) The various symptoms exhibited following PEG is demonstrated, whilst headaches and irregular heart rates were the most common symptoms reported, other symptoms included fevers, stiff neck, vomiting, neurological symptoms and changes in consciousness (based on data from White, Bell and Mellick, 1973).

1.2.2 Non-invasive methods

1.2.2.1 Computed tomography (CT) imaging

CT was developed by Hounsfield during the early 1970s, the method collects readings from the skull at multiple angles via a rotating X-ray tube (Hounsfield, 1973; Hounsfield 1980; Wellington and Vinegar, 1987; Kotwaliwale *et al*., 2011). Image slices of the cranium are then generated from these readings via a back-projection formula (Cunningham and Judy, 2000; Wellington and Vinegar, 1987). The main advantage of CT compared to conventional X-rays is its ability to explore anatomy through different angles as opposed to only one (conventional X-ray) (Wellington and Vinegar, 1987).

Despite CT scans being less physically invasive (compared to PEG) as no incisions are made during scanning, researchers have nonetheless argued that the method poses a radiation risk (Brenner and Hall, 2007; Berrington De Gonzalez *et al*., 2009). Berrington De Gonzalez *et al*., (2009) explored the adverse effects of CT radiation, including the risk of cancer and concluded that roughly 2% of future cancer diagnoses could be a result of radiation from CT scanning. Despite these concerns, it should be taken into account that such findings are general and not specific enough, i.e. they do not report the quantity of doses that can lead to the risk of cancer (McCollough, Guimarães and Fletcher, 2009). Additionally, radiographers as well as equipment manufacturers have employed different strategies, including ALARA (as low as reasonably achievable) to keep radiation doses low (McCollough, Guimarães and Fletcher, 2009; Mayo-Smith *et al*., 2014) and by following such principles, participant radiation exposure during CT scans can be reduced (Mayo-Smith *et al*., 2014).

The overall positive impact that CT scanning has had within the neuroimaging field has helped increase the rates of clinical diagnoses (McCollough, Guimarães and Fletcher, 2009). It has also helped pave the way for other imaging methods, including PET as both are usually combined (Townsend, 2008; Papathanasiou *et al*., 2011).

1.2.2.2 PET imaging

PET is a non-invasive imaging technique and was first used in humans during the mid-1970s to explore physiological functioning (Hoffman *et al*., 1976; Berger, 2003). The first stage of PET scanning involves the injection of radio-tracers into the participant's peripheral vein (Berger, 2003; National Health Service, 2018). The tracer that is used depends on what is being studied. For example, ^{18}F-fluorodeoxyglucose (FDG) is

commonly used to diagnose brain tumours (Kosaka *et al*., 2008). The pronounced glucose metabolism of tumor cells can result in an increase of FDG uptake during PET scanning and thus help diagnose and characterise tumours (Shukla and Kumar, 2006).

PET imaging studies have also helped demonstrate regions of the brain associated with upper-limb reaching. For example, during visually guided arm-reaching in non-human primates, Picard and Strick (2003) found significantly increased 2-deoxyglucose (2DG) uptake in the supplementary motor area (SMA) and the primary motor cortex (M1), but not in dorsal and ventral regions of the cingulate motor area. PET studies exploring the reaching preparation phase have revealed increased metabolic activity in the prefrontal cortex and areas of the parietal lobe (Decety *et al*., 1992). PET techniques during novel reaching (i.e. force-field paradigms) have also illustrated greater regional cerebral blood flow (an indicator of metabolic activity) in the cerebellum during the initial stages of reaching adaptation, however this was reduced following repeated reaching exposure (i.e. as reaching errors reduced, activity in the cerebellum also reduced; Nezafat, Shadmehr and Holcomb, 2001).

Despite PETs clinical efficacy and use in the research setting, there are some limitations to the technique. For instance, those who do undergo PET imaging should avoid contact with pregnant women as well as children as they can still remain radioactive for up to a couple of hours following scanning (National Health Service, 2018). The expensiveness of the technique also makes it difficult for some patients to have access to (Griffeth, 2005; Bateman, 2012; Akbari Sari *et al*., 2013). Nonetheless, PET remains to be effective in terms of 1) high quality imaging, 2) increasing the precision of diagnoses and 3) having shorter experimental protocols, thus making it a more patient friendly method (Bateman, 2012).

1.2.2.3 MRI imaging (structural and functional)

MRI brain imaging (both structural and functional [fMRI]) is a common non-invasive method used in both research and clinical fields. MRI functions by using the body's magnetic elements to create in depth images of organs, including the brain (Berger, 2002). MRI machines employ a magnetic field which can alter the ways in which the body's protons react (specifically hydrogen nuclei protons). The powerful MRI magnet leads to the alignment of protons, which in turn creates a magnetic vector along the axis of an MRI scanner (Berger, 2002). When additional radio-wave energy is added to the machine, the aligned magnetic vector gets deflected and the protons resonate, i.e. they

spin out of an equilibrium state. When the radiofrequency is turned off a signal is released and the protons return back to a resting state, MR images are then created from this emitted signal (Berger, 2002).

Structural MRIs have helped enhance the anatomical understanding of brain matter and regions and have been used as a form of clinical assessment among patients (Frisoni *et al*., 2010; Chen, Jiao and Herskovits, 2011). For example, diagnostic markers such as reduced hippocampal volume and medial-temporal atrophy have been consistently shown in structural MRIs and have been hypothesised to be the initial structural indicators of first stage Alzheimer's disease (AD) (Kantarci and Jack, 2003; de Leon *et al*., 2004; Devanand *et al*., 2012; Vijayakumar and Vijayakumar, 2013). Such imaging used for a clinical purpose can help delay the onset of diseases at an early stage, for example, through pharmacological interventions (e.g. balancing out the neurochemical disruption with drugs for AD; Yiannopoulou and Papageorgiuo, 2012).

As opposed to structural MRI, fMRI places greater emphasis on exploring brain function and activation patterns. Functional MRI methods have been used in cognitive, behavioural and motor and clinical studies (to observe changes in brain function in neurological diseases) (Glover, 2011). With regards to its clinical applications, surgeons have used the technique to map out and determine eloquent brain locations (e.g. lingual and motor regions) that may reside next to brain tumours or lesions in order to preserve their functions during neurosurgery (Beers and Federico, 2012; Mahdavi *et al*., 2015; Nadkarni *et al*., 2015).

When a brain region is activated by a particular task, it results in greater neuronal activity and blood flow to the region that is facilitating the activity (Buxton, 2013), and this can be demonstrated online and offline with fMRI. Therefore, fMRI methods are used to explore changes in blood oxygen level-dependent (BOLD) signals that occur when the brain state is altered e.g. from rest to a task (Gore, 2003; Glover, 2011). For example, in an fMRI motor observation task conducted by Buccino *et al*., (2001) participants were instructed to observe motor behaviours performed by other individuals, including arm reaching, hand grasping and mouth motions. Their findings revealed varied neural activity (i.e. cerebral blood blow) in different regions of the premotor cortex (PMC) depending on the movement that was performed. For instance, arm reaching and hand grasping movement led to greater neural activity in the dorsal regions of the PMC, whereas mouth actions resulted in increased neural activity in the

ventral PMC. Other activated regions during reaching includes the M1. For instance, in an fMRI reaching-outward task using non-ferromagnetic equipment, Eisenberg *et al*., (2011) reported increased BOLD related-activity in the M1. Increased M1 activity during reaching has been argued to be related to its functional role in encoding movement parameters, such as the direction of movement, arm position and movement speed (Ashe and Georgopoulous, 1994; Fu *et al*., 1995; Moran and Schwartz, 1999; Teka *et al*., 2017). fMRI studies have also helped identify cortical regions that are involved in other aspects of reaching, such as planning and preparing movements. For instance, Andersen and Buneo (2002) reported increased posterior parietal cortex (PPC) neural activity that was associated with movement planning of a reach during a memory-guided reaching task. Increased BOLD activity has also been noted in parietal regions during reaching: 1) observation, 2) imagery and 3) execution (Filimon *et al*., 2015).

Both fMRI and PET studies have illustrated that a large network of regions are involved in reaching preparation, planning and execution, with neural connections ranging from the parietal lobe (e.g. the PPC) to the frontal lobe (e.g. M1, PMC and SMA) (Rizzolatti and Luppino, 2001; Begliomini *et al*., 2014). Although fMRI and PET techniques have been useful in identifying cortical regions that are involved in reaching, there are limitations to consider. For instance, signal dropouts may occur during scanning which can affect the degree of BOLD signal found in fMRI studies (Glover, 2011). Furthermore, the confined parameters of an MRI scanner can cause set-backs in studying reaching behaviours, and can also result in movement artefacts (Culham, Cavina-Pratesi and Singhal, 2006). As a result, reaching fMRI and PET studies have mainly focused on 'point' reaching and 'grasp' reaching paradigms compared to arm-reaching paradigms (Culham, Cavina-Pratesi and Singhal, 2006). It can be argued that upper-limb reaching tasks may lead to novel findings in terms of identifying areas of cortex that are functionally related to reaching. This thesis will therefore introduce a new TMS mapping technique by targeting different regions of the motor circuit via a 'virtual disruption' approach during upper-limb reaching. The high temporal resolution of TMS and it use in disrupting regional functioning sets it apart from other non-invasive imaging methods, including fMRI and PET which are more correlation based and lack temporal resolution (Hallett, 2000).

In this thesis, TMS was used to explore neural behavioural responses during upper limb reaching. Section 1.3 below outlines the method in depth, in terms of: 1) its principles, 2) types of TMS coils, 3) types of TMS protocols, 4) how it has been used in both the clinical and research field, and 5) how it will be employed in this thesis.

1.3 TMS

1.3.1 Principles of TMS and its advantages of TMS compared to other imaging modalities

The non-invasive brain imaging method that this thesis is based on is TMS. TMS hardware includes a coil(s) which is connected to a stimulator. The stimulator contains; 1) capacitors that produce pulses, 2) voltage sources that produce the magnetic field, 3) switches to turn currents on and off, and 4) a pulse circuit to determine the type of TMS pulse shape that is administered (e.g. monophasic [employed in this thesis] or biphasic) (Wagner, Valero-Cabre and Pascual-Leone, 2007; Farzan *et al*., 2016) (these components are illustrated in Figure 1.2A - Farzan *et al*., 2016).

The key component of TMS is the coil that is used for stimulation, which operates on the principle of Faraday's law of electromagnetic induction (Eldaief, Press and Pascual-Leone 2013; Farzan *et al*., 2016).The principle is based on the notion that the pulse of the current which passes through copper wires in a TMS coil results in a magnetic field that is perpendicular to the plane of the coil and as a result this causes a secondary induced electrical current in cortical regions that are parallel to the orientation of the coil (Hallett, 2000; Hallett, 2007; Ridding and Rothwell, 2007; Bolognini and Ro, 2010; Eldaief, Press and Pascual-Leone, 2013; Farzan *et al*., 2016) (see figure 1.2B - Hallett 2000; Hallett, 2007). This induced TMS-current can briefly modulate neuronal activity in structures that generate action potentials and can result in either enhancing or inhibiting neural excitability (Kobayashi and Pascual-Leone, 2003; Eldaief, Press and Pascual-Leone, 2013; Farzan *et al*., 2016). Section 1.5.2.1 highlights specific details with regards to how TMS works and the cortical components activated during stimulation.

It should be noted that the effect of the induced secondary current does not only rely on the TMS coil and the stimulation intensity, but also other factors including cerebral matter (Hallett, 2000; Lefaucheur *et al*., 2014; Klomjai, Katz and Lackmy-Vallée, 2015). For example, it has been suggested that grey matter has greater levels of TMS resistance/impedance compared to white matter (Lefaucheur *et al*., 2014; Klomjai, Katz

and Lackmy-Vallée, 2015). Based on this notion, the electrical currents that are induced in grey matter structures are weaker and as a result TMS does not activate deep-cortical grey matter structures including the thalamus, but on the other hand activates superficial cerebral white matter layers of the cortex, such as the primary motor cortex (M1) (Lefaucheur *et al*., 2014; Klomjai, Katz and Lackmy-Vallée, 2015). There are also action at distance limitations to consider with TMS, which is based on the notion that the strength of the electrical field induced with TMS differs depending on the distance between the coil and the area being targeted (Deng, Lisanby and Peterchev, 2013). Action to distance limitations can however be overcome through the use of different coil types. For example, more recently designed TMS coils can be used to target deeper cortical structures. The round and figure-8 shaped coil (used in this thesis) provides a focal and localized current flow to explore regions on the surface of the cortex such as the M1. This coil has been used in different single pulse TMS protocols to investigate motor function in reaching (e.g. Hunter, Sacco and Turner, 2011; Orban de Xivry *et al*., 2013). The double cone coil on the other hand is able to penetrate into deeper cortical structures and has been used to target structures including the anterior cingulate, the cerebellum and the middle cingulate cortex (Ueno, Tashiro and Harada, 1988; Ugawa *et al*., 1995; Hallet, 2007; Deng, Lisanby and Peterchev, 2013; Hardwick, Lesage and Miall, 2014; D'Agata *et al*., 2015). Additional TMS coils includes the batwing coil. Due to its geometric features, it has been employed in a similar way to the double cone coil for the stimulation of areas deep within the cortex (Cai *et al*., 2011). Researchers have used this coil to target deeper muscle representations in Penfield's homunculus, such as lower limb areas including the leg (Roy and Gorassini, 2008). The H-coil has also been used in TMS experiments, namely repetitive (r) TMS (rTMS) protocols to stimulate areas that are deep within the temporal lobe (Gersner *et al*., 2016; Tendler *et al*., 2017). The “depth-focality trade off” described by Deng, Lisanby and Peterchev (2013) is a limitation that should be considered when using deeper coils to study neural responses. Deng, Lisanby and Peterchev (2013) argued that different coils have different electrical field features, and coils used to target deeper structures have limited focality. The figure-8 shaped coil, has greater focality and the electrical field induced with this coil is confined to targeting superficial areas (Deng, Lisanby and Peterchev, 2013). In this thesis, the depth-focality trade off is less of a concern considering that only superficial targets were explored with a figure-8 coil. The availability and development of various

TMS coils has helped researchers gain a deeper understanding into the depth-focality trade off, which has led to the design of novel coils to study human behaviour (Deng, Lisanby and Peterchev, 2013).

As well as the availability of various TMS coils, an additional advantage of TMS as method is based on its safety principles which has been noted in studies among healthy subjects. For example, Machii *et al*., (2006) applied rTMS to a range of cortical regions, such as the cerebellum, dorsolateral prefrontal cortex, the occipital lobe and areas of the parietal cortex in 200 healthy subjects. Their findings revealed that the most common negative effect of TMS included headaches, with the pain being very mild (as quantified by ratings on a questionnaire). Neck pains were also common, however this depended on the region that was stimulated (the cerebellum was associated with greater neck pain compared to areas such as the parietal cortex). In addition to this, they reported no siezures in the subjects that were tested (Machii *et al*., 2006). The thermal impact of TMS is also a factor to consider as some protocols may cause tissue heating (Rossi *et al*., 2009; Sabouni, Honrath and Khamechi, 2017). Tissue heating can become a cause for concern among individuals who have implanted electrodes (Roth *et al*., 1992; Rossi *et al*., 2009). It should be noted that in this thesis, only SP-TMS was delivered and studies have revealed that tissue heating with such protocols are minimal (Ruohonen and Ilmoniemi, 2002 cited in Pascual-Leone *et al*., 2002; Rossi *et al*., 2009). TMS has also been reported to be a pain-free method, particularly when compared to other stimulation methods, such as transcranial electric stimulation (TES) (Rossi *et al*., 2009). During TES the electrical charge projects to the scalp and flows through the skull (Rossi et al., 2009) and due to the the skull having low levels of conductivity, TES currents are commonly set to a high density level to stimulate neurons, which can therefore cause pain (Rossi *et al*., 2009). With TMS however, current density in the scalp to- current density brain is lower, which results in less pain during stimulation (Rossi *et al*., 2009).

Ethical and safety principles are consistently growing in the field of TMS research in order to identify the possible side effects of the method and factors to consider during stimulation, whether this be in healthy controls or clinical populations. Generally, the non-invasive nature of TMS compared to other methods such as TES, and its safety record has made it a popular technique to use in research and in the treatment of psychiatric conditions (Padberg *et al*., 2002; Rossi *et al*., 2009).

A. B.

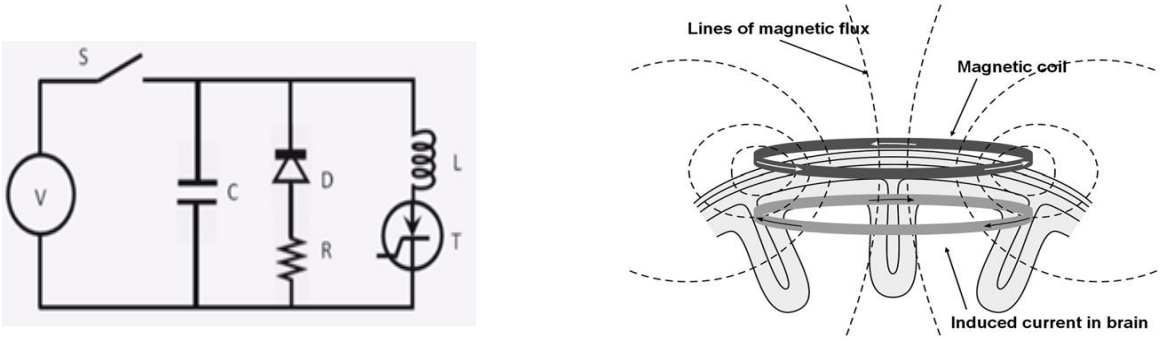


Figure 1.2: TMS components

(A) The different components in a stimulation unit includes; a coil (L), a voltage device (V) as well as a switch (S) and a capacitor (C). Other elements include a Thyristor (T) and a resistor (R) (figure from Farzan *et al*., 2016)

(B) During stimulation, a pulse is created in copper wires that are located in the magnetic coil, this produces a magnetic field with lines of a magnetic flux that pass perpendicularly to the coil. Following this, an electrical field is produced which is perpendicular to the magnetic field (figure from Hallett, 2000).

1.3.2 TMS protocols

When TMS is delivered to one hemisphere of the M1 (e.g. left), a corticospinal neural volley is elicited and this can be recorded as a motor evoked potential (MEPs) (Hallett, 2007) in muscles in the contralateral limb (e.g. right) (section 1.5.2.1 outlines the procedure in full – figure 1.6: Klomjai, Katz and Lackmy-Vallée, 2015). When MEPs are elicited by TMS, corticospinal excitability can be explored. Corticospinal excitability (CSE) is based on the affects that different excitatory and inhibitory mechanisms have on the corticospinal tract (CST) (Hallett, 2007; Cirillo, Todd and Semmler, 2011; Hunter, Sacco and Turner, 2011; Rossini *et al*., 2015). Such mechanisms include, short-interval intracortical inhibition (SICI), short intracortical facilitation (SICF) and IHI (interhemispheric inhibition [short latency - SIHI; and long latency LIHI]) and these can be studied with different TMS protocols. TMS protocols include single-pulse TMS (SP-TMS), paired-pulse TMS (PP-TMS) and repetitive TMS (rTMS). Whilst SP stimulation denotes a type of TMS that is not repetitive, during rTMS stimulation a train of single pulses are administered to a specific brain region at a specific frequency (Mishra *et al*., 2011). Low frequency rTMS stimulation inhibits neuronal firing, whereas high frequency rTMS stimulation facilitates neuronal firing (Mishra *et al*., 2011). rTMS protocols have been used in the treatment of psychiatric conditions, ranging from depression to schizophrenia (Padberg *et al*., 2002; Aleman, Sommer and Kahn, 2007; Rossi *et al*., 2009; Farzan *et al*., 2012; George, Taylor and Short, 2013).

PP-TMS can function either through the same coil at one cortical location or alternatively through two coils at two cerebral loci. PP-TMS protocols have enabled researchers to examine cortical networks in the brain, such as SICI, SICF and IHI (Rossini *et al*., 2015). There is a greater understanding of SICI, ICF and SIHI compared to LIHI. SICI suppresses cortical cell firing in the M1 (i.e. cortical inhibition; Wagle-Shukla *et al*., 2009; Rossini *et al*., 2015) and has also been linked to neurotransmitters in the M1 such as gamma-aminobutyric acid-A *(*$GABA_A$) (Di Lazzaro *et al*., 2006). ICF on the other hand, is based on excitatory cortical processes and has been linked to glutamate receptors with excitatory functions (Noda *et al*., 2017). For example, increases in glutaminergic activity has been associated with an increase in SICF (Smith et al., 1999; Kapogiannis and Wassermann, 2009; Wagle-Shukla *et al*., 2009).

With regards to IHI, one hemisphere of the brain suppresses the functioning of the other hemisphere (Ni *et al*., 2009) and this can also be studied with a PP-TMS protocol. Ferbert *et al*., (1992) were the first researchers to report IHI. They found that TMS applied to the ipsilateral M1, results in a reduced MEP in the contralateral M1 (i.e. inhibited). IHI has also been reported between different cortical regions. For instance, Mochizuki, Huang and Rothwell (2004) demonstrated that a conditioning pulse over the dorsal premotor cortex (dPMC) led to a reduced MEP response in the contralateral M1. This illustrates that IHI is not region specific, but rather a widely distributed phenomena found in different cortical structures (Ni *et al*., 2009). There are two IHI phases; short latency IHI (SIHI) and long latency IHI (LIHI), which occur when using different interstimulus intevals (ISIs). An ISI of approximately 10 milliseconds between the conditioning pulse and test pulse results in SIHI, whereas an ISI of 40-50 milliseconds between the conditioning pulse and the test pulse leads to LIHI (Ni *et al*., 2009). Although the mechanistic elements of SIHI are understood, for example, it has been reported to inhibit unwanted reflex actions, the role of LIHI is yet to be determined (Hubers, Orekhov and Ziemann, 2008; Morishita *et al*., 2014).

These neural mechanisms have also been studied with TMS during motor tasks, i.e. upper limb reaching and motor adaptation. Before considering how these mechanisms respond to motor tasks, it is important to define what is meant by motor reaching and motor adaptation.

1.4 Motor behaviours

1.4.1 Upper limb reaching

Motor behaviours fall into one of two categories; discrete or continuous. Upper limb reaching has been classed within the discrete category as it has a defined beginning and end point (Muratori *et al*., 2013). The concept of 'fine' and 'gross' motor skills should also be considered when defining reaching. While fine motor skills refer to actions that use small muscles (i.e. hands), gross motor skills are actions that use larger muscles (i.e. upper arm and the trunk of the body; Muratori *et al*., 2013). Motor reaching can involve both fine and gross motor skills. For instance, if someone is reaching for a cup whilst standing, both small (e.g. hand and fingers) and large muscles (e.g. torso and upper limb) will be used to carry out the action (Muratori *et al*., 2013). Carr and Shepherd (2000) noted that the environment in which motor skills are performed can be classed as

either open-based or closed-based. They defined skills in the closed-based category as actions that can begin and stop at any given time, whilst the environment remains constant. During open-based motor performance however, it is essential for the individual carrying out the task to adapt to the changes in their environment to be successful. Such skills can be seen when someone is catching a ball, i.e. they must adjust their body to the time at which the ball is arriving (Carr and Shephard, 2000; Muratori *et al*., 2013).

In this thesis, upper limb reaching will involve both gross and fine muscles as the hand will be used to grasp the joystick on the robotic manipulandum and upper limb muscles will be used to carry out the reaching motion. Also, the environment reflects open-based motor reaching, as the participant will have to adjust their reaching speed to avoid 'late' and 'early' reaching responses (see general methodology, section 3.4.1). The role of the corticospinal tract (CST) is vital during reaching. This has been shown in both human studies (such as stroke patients) and animal models, whereby damage to the CST resulted in impaired motor function and poor reaching accuracy (Martin and Ghez 199; Maraka *et al.,* 2014).

The act of upper limb reaching begins with preparatory neural activity within pre-motor and motor cortices before actual movement of the arm (Jones, 2012). These regions (i.e. M1 and premotor cortices) help regulate timing and outputs of motor behaviour (Halsband *et al*., 1993; Overduin, Richardson and Bizzi, 2009; Chang *et al*., 2015; Panouilleres *et al*., 2015). Motor output during reaching takes place due to neural communication between different brain regions (Figure 1.4B demonstrates the different projections and neural connections between regions of the motor circuitry - adapted from Briggs *et al*., 2018). The extent of projections from different motor areas to faciliciate motor functions were highlighted by Dum and Strick (1991). They reported that the M1 receives projections from 3 main regions: the SMA, the premotor cortices (specifically the arcuate sulcus) and the frontal lobe, particularly the cingulate motor areas. Different regional projections contribute to distinct motor behaviours and this has been shown in non-human primate lesion studies. For example, Pavlides, Miyashita and Asanuma (1993) noted that damage to somatosensory cortex in monkeys impaired the acquisition of novel motor skills but not previously learned motor skills. It was therefore concluded that cortical projections between the somatosensory cortex and the M1 facilitates the learning of a novel motor skill (Pavlides, Miyashita and Asanuma,

1993). As well as complex interactions and projections between different motor regions, there are also complex mechanisms that underlie motor responses elicited by SP-TMS during reaching, and these are explained below.

1.4.1.1 TMS during reaching preparation and reaching execution

TMS protocols have been used to explore whether changes in CST function occur during reaching. TMS motor responses during reaching have been consistently demonstrated with surface electrodes placed on the muscles of interest (Hunter, Sacco and Turner 2011; Groppa *et al*., 2012; Orban de Xivry *et al*., 2013). Responses investigated during the preparation phase and execution phase of motor reaching include both physiological changes (e.g. MEPs) as well as movement parameter changes (e.g. movement velocity and reaction time).

SP-TMS delivered to the M1 in reaching paradigms have shown changes in MEP amplitude. For example, during the preparation phase of right-arm reaching (towards the body*),* Hunter, Sacco and Turner (2011) revealed that the biceps brachii (BB) exhibited larger MEP responses compared to the triceps brachii (TB). However, reaching away from the body resulted in no differences in MEP amplitude between the BB and TB. Time specific differences related to MEP amplitude have also been found. For example, MEP responses in the BB was larger compared to the TB when TMS was delivered closer to movement onset. PP-TMS studies have also shown changes in physiological responses during preparation for reaching, including a reduction in SICI and an increase in ICF prior to movement onset (Floeter and Rothwell, 1999; Reynolds and Ashby, 1999; Nikolova *et al*., 2006; Koch, *et al*., 2008a; Hunter, Sacco and Turner, 2011). Therefore, changes in the balance of SICI and ICF mechanisms in the M1 can occur before the onset of movement, even if the MEP amplitude appears not to significantly change. rTMS protocols targeting the left and right M1 during motor preparation have also demonstrated increased motor cortical excitability and decreased inhibition at approximately 140ms before movement execution (Gilio *et al*., 2008; Massie *et al*., 2014).

Other physiological changes that have been explored with TMS protocols during reaching preparation includes the cortical silent-period. As previously mentioned, TMS to the M1 results in muscle contraction and MEPs occur (Klomjai, Katz and Lackmy-Vallée, 2015). However it should be noted that following the MEP there is a pause in EMG activity which is known as the cortical silent-period (Ahonen *et al*., 1998).

Therefore, whilst MEPs are based on excitatory responses, the cortical silent-period is based on inhibitory responses facilitated by GABAb interneurons synapsing on pyramidal neurons (Inghilleri *et al*., 1996; Ahonen *et al*., 1998; Poston *et al*., 2012). Studies have shown that TMS delivered during cue presentation in reaction time tasks can delay contralateral arm responses (Day *et al*., 1989; Hannah *et al*., 2018). Additionally, Ibanez *et al*., (2018) reported that TMS delivered 30ms, 60ms and 200ms before a subject's average movement led to a delayed response, and researchers have attributed such delays to the silent-period phenomenon (Day *et al*., 1989; Hannah *et al*., 2018; Ibanez *et al*., 2018). Based on such findings, it can be argued that TMS can cause a disruption to movement preparation in the studies conducted in this thesis by generating the cortical silent-period.

Whilst the physiological changes associated with upper-limb reaching have mainly focused on motor preparation responses, behavioural changes have focused on execution of motor responses involving reaction time, peak velocity and errors made during reaching (e.g. trajectory errors). Reaction time has been reported to be affected with TMS stimulation delivered during movement preparation. For example, Busan *et al*., (2012) found that TMS to the parietal lobe led to an increase in reaction time when TMS was delivered at the starting phase of reaching preparation, but a decrease in reaction time when TMS was delivered mid-way through the preparation phase of a reach. Similar findings have been noted when stimulating parietal regions near the intraparietal sulcus. For instance, Busan *et al*., (2009) found a decrease in reaction time when TMS was administered at approximately half of the mean reaction time among subjects. With regards to motor execution, Hunter, Sacco and Turner (2011) found that TMS to the M1 during reaching towards different targets (135° and 270° on a visually displayed "dart-board") did not lead to any significant changes in normal reaching trajectories. Studies that have targeted other regions with TMS have also demonstrated similar results. For example, Della-Maggiore *et al*., (2004) revealed no significant changes in reaching trajectories during normal reaching when TMS was delivered to both the posterior parietal cortex (PPC) and the occipital lobe following movement onset. However, it is not known if using TMS to target other regions of the wider motor network during reaching preparation and execution may lead to different behavioural findings.

1.4.2 Motor adaptation

TMS protocols have been used in both motor skill learning and motor adaptation studies. However, before exploring this it is important to consider the differences between 'motor skill learning' and 'motor adaptation' because the two often fall under the general term 'motor learning', and this project concerns motor adaptation only.

Motor adaptation is based on modifying a motor skill through an error driven process (Martin *et al*., 1996; Malone, Vasudevan and Bastian, 2011) compared to motor skill learning which is based on learning new information to acquire a new motor skill (Luft and Buitrago, 2005). Motor adaptation is also studied with force-field paradigms where individuals gradually learn to adjust their motor behaviours towards forces administered by a robotic device (Stockinger, Focke and Stein, 2014). On the other hand, motor skill learning has been investigated with motor sequence paradigms, which are tasks associated with learning motor information in a particular arrangement (Morin *et al*., 2008; Weiermann, Cock and Meier, 2010). During motor adaptation, behaviour can be unlearned (i.e. disappears when the perturbation disappears) and therefore has short-term effects (Reisman, Block and Bastian, 2005; Krakauer and Mazzoni, 2011) whereas motor skill learning has long term-effects (Luft and Buitrago, 2005).

1.4.2.1 TMS during motor adaptation

Corticospinal excitability has been investigated with TMS protocols (SP and PP) in motor adaptation paradigms. Studies have mainly explored differences in MEP amplitude in force-field reaching compared to normal reaching. For example, the BB muscle has been found to exhibit larger MEP responses during motor adaptation compared to normal reaching (Hunter, Sacco and Turner, 2011). Similarly, Orban de Xivry *et al*., (2013) revealed significant increases in peak-to-peak MEP amplitudes during force-field reaching in the BB compared to the TB.

The direction of a reach in force-field paradigms has also been shown to have an impact on physiological responses in different muscles. For example, the results from Orban de Xivry *et al*., (2013) concluded that reaching towards a south-east direction led to increased MEPs in BB, whereas reaching towards a north-west direction (135° target) increased activity in the TB and deltoid muscles. Therefore, there is direction-specific tuning of the corticospinal excitability (Orban de Xivry *et al*., 2013). PP-TMS paradigms of motor adaptation have also illustrated changes in physiological mechanisms. For example, SICI has been found to be reduced in the BB and TB nearer

to movement onset following motor adaptation (Hunter, Sacco and Turner, 2011). This finding suggests that SICI focuses the excitatory drive to specific muscles before movement in the force. SICI and ICF have also been found to be modified with regards to the factor of time. For instance, following motor adaptation in a north-west direction (135° target) a significant reduction in SICI was found at 190ms, whereas ICF was significantly increased at 160ms during reaching preparation (Hunter, Sacco and Turner, 2011).

Behavioural changes have also been noted during motor adaptation. For example, errors during reaching are increased during the initial stages of motor adaptation, however this gradually reduces trial by trial following additional blocks of force-field reaching (Hunter, Sacco and Turner, 2011; Pizzamiglio *et al*., 2017a; Pizzamiglio *et al*., 2017b). Errors made in motor adaptation when TMS has been delivered to regions of the motor network have also been studied. For example, Della-Maggiore *et al*., (2004) found significant errors in reaching trajectories during motor adaptation when SP-TMS was delivered to the left posterior parietal cortex (PPC). They also reported no errors in reaching trajectories when an area of the visual cortex was stimulated during motor adaptation. This was important as it suggested that the PPC had a specific role in motor adaptation but not in normal un-perturbed reaching (see earlier). Other kinematic measures such as movement onset and offset of reaching, movement velocity and movement duration have not been studied extensively with TMS paradigms.

A key aim of this thesis is to not only to explore neural mechanisms of reaching during motor adaptation, but to also investigate how TMS delivered to different cortical regions affects the kinematic behavioural responses of simple reaching and motor adaptation. Several cortical regions play a role in both reaching and motor adaptation. These regions include areas surrounding the M1 (e.g. the PPC, the SMA and the PMC) (Halsband *et al*., 1993; Krebs *et al*., 1998; Baizer, Kralj-Hans and Glickstein, 1999; Landi, Baguear, and Della-Maggiore, 2011; Shum *et al*., 2011; D'Angelo and Casali, 2012; Panouilleres *et al*., 2015; Borich *et al*., 2015; Chang *et al*., 2015). Other nodes in the motor network include associative cortical and subcortical regions (e.g. prefrontal cortex, basal ganglia and the cerebellum) (Goldman-Rakic 1987; Shima *et al*., 2007; Overduin, Richardson and Bizzi, 2009; D'Angelo and Casali, 2012). Before addressing the roles of specific cortical areas, it is important to outline the structure of the cortex (e.g. different cortical layers) and the ways in which the motor system governs motor

output. Section 1.5 therefore outlines the 1) human motor system, 2) other motor-related cortical regions that contribute to reaching behaviours, 3) the effects of TMS to these regions, and 4) the ways in which responses are altered when the motor network is impaired.

1.5 The human motor system

Numerous cortical regions make up the human motor system, including the posterior parietal cortices (PPC), the supplementary motor area (SMA), the pre-motor cortices (PMC), the cerebellum as well as the pre-frontal cortex, and regions of the basal ganglia (Dum, Levinthal and Strick, 2016). However, the key pivotal structure within the motor system is the primary motor cortex (M1) which is situated in the dorsal region of the frontal lobe (Miyachi *et al*., 2005). To move voluntarily, the M1 sends complex descending signals via the CST to motor neurons that innervate skeletal muscles (Drew, Prentice and Schepens, 2004). The corticospinal pathway crosses at the brainstem level of the neuraxis as it descends, so that the right side of our brain is responsible for moving the left side of our body and vice versa (Sun and Walsh, 2006) (figure 1.3 – adapted from Welniarz *et al.,* 2017).

The human cortex contains different cortical layers, including layer I (the molecular layer), II (the external granular layer), III (external pyramidal layer), IV (internal granular layer), V (internal pyramidal layer) and VI (multiform later) (figure 1.4A - figure adapted from Mitchell and Patterson 1954 cited in, Crossman and Neary, 2015). These layers contain different types of neurons that have different projections (e.g. afferent and efferent) and different functions (e.g. excitatory and inhibitory) (Briggs, 2010). Layer I is made up of axonal projections (from local regions), dendrites and fusiform cells. Layers II and III on the other hand contain pyramidal neurons (with the majority being found in layer III). Pyramidal neurons are glutamatergic, have an excitatory function, and communicate with other cortical structures via axonal projections (DeFelipe and Fariñas, 1992; Spruston, 2008; Tjia *et al*., 2017). Pyramidal neurons in layer II and III enable both local and distant communication between different cortical regions via long axonal projections (Fame, MacDonald and Macklis, 2010; Tjia *et al*., 2017). For example, it has been found that pyramidal neurons in layer III contain axons that project to regions such as the parietal cortices and the temporal gyrus (Goldman-Rakic, 1987; Pierri *et al*., 2001). Axonal projections in layer III end at the thalamic nucleus. It has been suggested that the thalamic nucleus facilitates the

excitatory functions of pyramidal neurons in layer III (Giguere and Goldman-Rakic, 1998; Pierri *et al*., 2001). Axons from regions such as the somatosensory and premotor areas also contribute to CST functions, more specifically their projections facilitate different phases of motor behaviours (Ueno *et al*., 2018). For example, Ueno *et al*., (2018) reported that both sensory and motor responses are combined to enable grasping and retrieving during reaching, as outlined in section 1.4.1 and figure 1.4B (adapted from Briggs *et al*., 2018).

Layer IV contains pyramidal and stellate cells (stellate cells are also excitatory) which are similarly distributed within the layer (Meyer *et al*., 1992; Schubert *et al*., 2003). The two cells do however have different properties with regards to their connecting pathways (Alonso and Klink, 1993; Alexander and Hasselmo, 2018). For example, stellate cells have been reported to have direct connections with various sub-hippocampal regions, however the same has not been noted regarding pyramidal cells (Alexander and Hasselmo, 2018). Studies have also revealed that while the excitatory functions of stellate neurons rely on monosynaptic excitatory inputs within the same layer, pyramidal neurons receive further excitatory inputs from other layers of the cortex (Schubert *et al*., 2003). Layer V contains large pyramidal neurons and the most extending axonal projections to different cortical regions, including the pons (Harris and Shepherd, 2015; Tjia *et al*., 2017). Studies have revealed that pyramidal neuronal dendrites in layer V extend to the pia matter, however this is not the case for pyramidal neurons in other layers, such as II and III (Spruston, 2008; Tjia *et al*., 2017). The pyramidal neurons in layer V also have higher action potential firing thresholds compared to other layers of the cortex and obtain strong monosynaptic inputs from stellate neurons in layer IV (Feldmeyer, Roth and Sakmann, 2005; Petersen and Crochet, 2013; Tjia *et al*., 2017).

Layer VI contains pyramidal neurons and non-pyramidal neurons, including stellate cells and fusiform neurons (Briggs, 2010). These neurons play different roles in receiving and transmitting signals, for instance pyramidal neurons project to other layers of the cortex (e.g. layer IV and V), whereas non-pyramidal neurons such as stellate and fusiform cells mainly have local projections that are confined to layer IV (Briggs, 2010). Inhibitory cells are present in layer VI, and these are also found in layer IV. The neurons found in layer VI have distinct functions, all of which play an

important role in regulating and enabling cortical processing between different structures (Briggs, 2010).

In the M1, cortical layers differ in terms of 1) cell distribution, and 2) axonal projections (see section 1.5.1 below). As this thesis is concerned with the motor network, it is important to highlight the ways in which the different cortical layers of the M1 enable motor output (specifically reaching) to take place.

1.5.1 Cortical layers of the M1

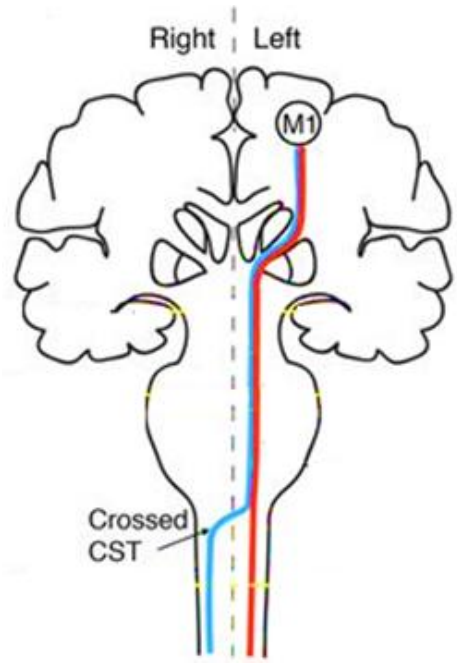
Excitatory responses in the M1 are a result of pyramidal neurons that project onto various cortical structures which enable the processing of 1) sensori-motor information (via cortico-cortical projections), 2) cerebellar information (via thalamo-cortical projections) and 3) modulatory information (via neuro-modulatory projections) (Donoghue and Wise, 1982; Weiler *et al*., 2008). Cortical layers in the M1 have varied cell distribution levels (Weiler *et al*., 2008; Castro-Alamancos, 2013; Harris and Shepherd, 2015; Tjia *et al*., 2017). Layer I of the M1 does not contain many pyramidal neurons, however it does have a horizontal axonal system which has resulted in the formation of dense synapses within its layer (Douglas and Martin, 2004; Harms *et al.,* 2008; Weiler *et al*., 2008). The connecting inputs from other regions into layer I facilitates neural communication between different cortical regions, and also aids the learning process (Cauller, 1995; Sanes and Donoghue, 2000; Harms *et al*., 2008). For example, Harms *et al*., (2008) found that 7 days of repetitive motor learning in rats resulted in significantly greater synaptic strength in layer I of the forelimb motor cortex representation, as measured by slice recordings (Harms *et al*., 2008). Synaptic connections in the M1 rely on descending pathways in layers II and III, which converge onto both corticospinal neurons and pyramidal neurons in layer V (Kaneko *et al*., 2000; Weiler *et al*., 2008).

Additionally, layers II and III in the M1 have both efferent and afferent projections which facilitate neural communication in the motor circuitry (Kim *et al*., 2016a). The existence of layer IV in the M1 has been questioned because staining methods have only illustrated small sets of neurons in its layer (García-Cabezas and Barbas, 2014). However, it has been suggested that densely packed neurons in layers III and V has resulted in the hidden visibility of layer IV (García-Cabezas and Barbas, 2014). Labelling neuronal tracers (via markers) in layers III and V in primates has provided

evidence for the existence of M1 layer IV (García-Cabezas and Barbas, 2014). Moreover, studies have shown that the connecting neural pathways from the thalamus (which facilitates thalamic motor output) extend to layer IV, and this has provided further evidence for its presence (McFarland and Haber, 2002; García-Cabezas and Barbas, 2014).

Furthermore, layer V in the M1 has been argued to contain normal pyramidal neurons, and Betz cells (large pyramidal neurons) that extend into layer I (Betz, 1874; Castro-Alamancos, 2013). Electrical stimulation studies have shown that M1 current flow oscillations are facilitated by cells in layer V, with the strongest oscillation propagations found in its cellular dendrites (Castro-Alamancos and Rigas, 2002; Castro-Alamancos 2013). Layer VI in the M1 contains efferent neurons (Swadlow, 1994; Beloozerova, Sirota and Swadlow, 2003) that project into the sub-regions of the thalamus and this aids different types of motor activity including locomotion (Beloozerova, Sirota and Swadlow, 2003; Marlinski *et al*., 2012). Overall, the neuronal differences between these layers have led to specialised M1 functions which facilitate motor output (Castro-Alamancos, 2013).

A.

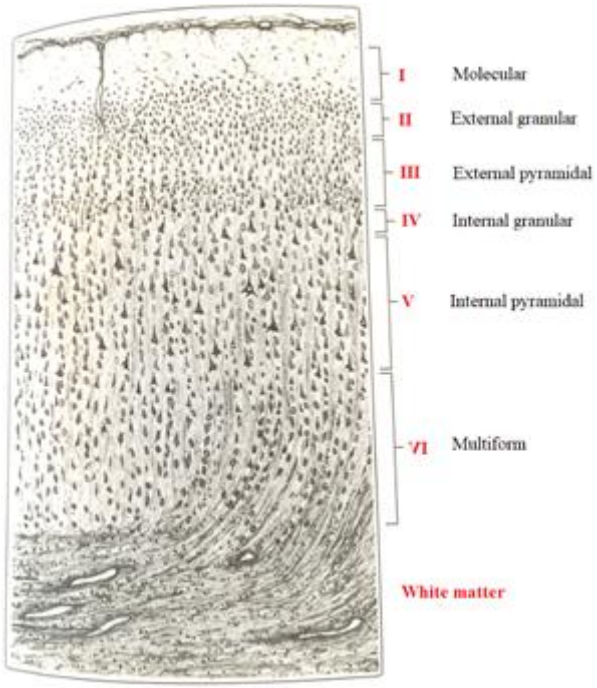


B.

Figure 1.3: The corticospinal tract

(A) A schematic presentation demonstrating the crossing of the corticospinal tract (as labelled in blue) in healthy controls which enables movement execution (i.e. the right-cortex controls left-sided motor execution, and the left-cortex controls right-sided motor execution) (figure adapted from Welniarz *et al.,* 2017).
(B) Diffusion MRI tractography illustrating the fibres of the corticospinal tract (figure adapted from Dalamagka *et al*., 2019).

A.



B.

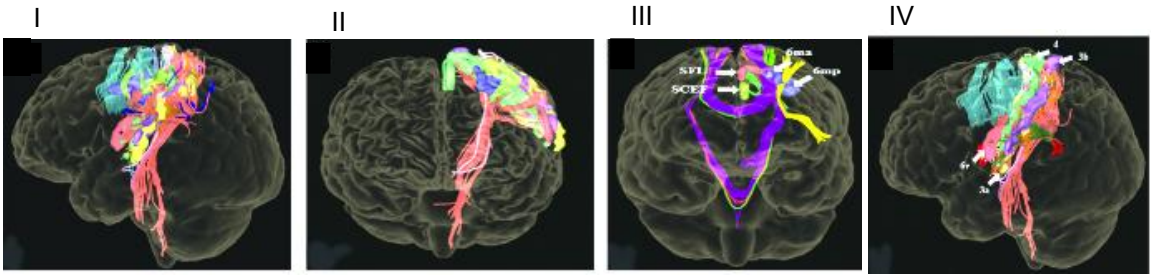


Figure 1.4: Layers of the cortex and motor network projections:

(A) The ways in which cells are presented within and across cortical layers (I, III, IV, V and VI) are shown (figure adapted from Mitchell and Patterson 1954 cited in, Crossman and Neary, 2014)

(B) Projections in the motor network are illustrated with diffusion tensor images - various interconnections can be seen between regions such as the M1, SMA, PMC, the insula, the anterior cingulate cortex as well as the middle frontal gyri (I [sagittal plane] and II [coronal plane]). Additional projections of sub-regions in the SMA (III) (e.g. the supplementary cingulate eyefield [SCEF], 6MA and 6MP) and ventral PMC (IV) (e.g. 3a, 3b, 4 and 6v) are also shown (figure adapted from Briggs *et al*., 2018).

1.5.2 The primary motor cortex (M1)

Cortical and electrical stimulation studies led to the discovery of the homunculus which is a map of the body's muscle representations that is contained in the M1 (Catani, 2017; Penfield and Rasmussen, 1950) (see figure 1.5B – Murphy *et al*., 2008). Penfield's homunculus has however been questioned because although studies have shown that muscles can be stimulated individually, they have also shown that muscle responses are not only restricted to the M1 (Purves *et al*., 2001; Catani, 2017). For example, responses have also been evoked in the postcentral and precentral gyrus (Catani, 2017). Stimulation studies have also found that muscle representations can overlap (see figure 1.5C – Catani, 2017; Penfield and Boldrey, 1937). Despite the controversies surrounding the homunculus, its discovery played a key role in the field of cortical stimulation and has aided surgical mapping procedures (Catani, 2017). TMS studies use specific coil positionings in order to target muscle(s) of interest and record their activity with surface electromyography (EMG) (figure 1.7B and 1.7C - Davidson, Bolic and Tremblay, 2016 and Abdalla, 2011). Recordings can therefore be visualised and quantified in order to accurately identify the muscle(s) (region of the homunculus) that has been stimulated.

As well as containing muscle representations, the main role of the M1 is to regulate the control and output of movements (Sanes and Donoghue 2000; Chang *et al*., 2015). It does this by directing movement signals (related to movement timing) towards the spinal cord which leads to an interaction with neuronal motor circuits, resulting in motor output (Alexander and Crutcher, 1990; Desmurget and Grafton, 2000; Scott, 2004; Teka *et al*., 2017). This is important in motor reaching paradigms that have time requirements to reach a specific target (Hunter, Sacco and Turner, 2011; Pizzamiglio *et al*., 2017a; Pizzamiglio, *et al*., 2017b) Therefore, simple movements already require a complex interaction between different systems including the nervous and musculoskeletal systems (Teka *et al.,* 2017). Furthermore, the role of the M1 in motor execution has been attributed to its connections to various motor related regions, including the SMA, PPC, PMC and the cerebellum (Tanji, 1994; Lotze *et al*., 1999; Whitlock, 2017). Different neural responses can be facilitated with M1 stimulation, and this is outlined below.

1.5.2.1 TMS delivered to the human M1

When TMS is delivered to the M1 of one hemisphere, a resulting corticospinal neural volley can be recorded as an MEP (Hallet, 2007) in muscles in the contralateral limb. The human motor cortex contains some of the largest pyramidal neurons which have numerous inputs and multiple functions (Kaas, 2000; Young, Collins and Kaas, 2013). Pyramidal neurons have excitatory functions in the cerebral cortex and are known as projection neurons (Bekkers, 2011). In layer V of the M1, these neurons transmit axons along the spinal cord for muscle function.

When TMS is delivered to the M1 (i.e. to a specific muscle representation in Penfield's Homunculus) it causes neuronal activity in a plane that is parallel to the coil and the surface area of the brain (Klomjai, Katz and Lackmy-Vallée, 2015). M1 TMS results in the transynaptic activation of pyramidal neurons, leading to the production of descending volleys (from pyramidal axons) which project onto the CST (Klomjai, Katz and Lackmy-Vallée, 2015). This causes an activation of motor neurons, leading to a contraction in the muscle of interest - i.e. an MEP is produced (Klomjai, Katz and Lackmy-Vallée, 2015). The MEP can be recorded using surface electromyographic (EMG) electrodes and corticospinal excitability can be quantified by measuring the peak-to-peak MEP amplitude (Summers, Chen, Kimberley, 2017). This process is graphically illustrated in figure 1.6 (Klomjai, Katz and Lackmy-Vallée, 2015). The degree of corticospinal excitability that one exhibits depends on a range of physiological factors. For example, glutamate transmittors have been argued to have an excitatory influence on connections between cortico-cortical axons and corticospinal neurons, and have been reported to play an important role in enabling rapid cortical synaptic transmission (Douglas and Martin 1998 cited in, Shepherd, 2004; Klomjai, Katz and Lackmy-Vallée, 2015). On the other hand, transmittors ranging from GABA and serotonin have been associated with inhibitory functions and have been found to reduce peak-to-peak MEP responses (Klomjai, Katz and Lackmy-Vallée, 2015).

The physiological activity evoked with TMS differs from TES activity (Klomjai, Katz and Lackmy-Vallée, 2015). TMS causes an indirect activation of corticospinal neurons via synaptic inputs. This has been illustrated by the different types of waves that are induced when a corticospinal volley is evoked with TMS, by which indirect waves (I-waves) as opposed to direct waves (D-waves) are first observed with stimulation (Di Lazzaro *et al*., 1998; Hallett, 2000). D-waves are based on direct responses from

stimulated axons, whereas I-waves occur due to stimulated corticospinal neurons (Rossini *et al*., 2015) and are more indicative of TMS evoked activity (Terao and Ugawa, 2002). Contrastingly with TES, the corticospinal volleys observed include D-waves, followed by late I-waves, and early I-waves. Based on this observation it has been argued that TES activates neurons in a plane vertical to the brains surface area, which differs from TMS which activates neurons in a plane that is parallel to the surface area (Klomjai, Katz and Lackmy-Vallée, 2015). Different factors can effect the types of waves that are recruited, for instance in some participants TMS at a high intensity can result in D-waves being observed prior to the I-waves (Klomjai, Katz and Lackmy-Vallée, 2015). However, in most participants, the I1 wave is recruited first, followed by the I2 and I3 wave (Klomjai, Katz and Lackmy-Vallée, 2015). Furthermore, there are various types of TMS coil orientations that can induce different electrical currents in the brain and can lead to different physiological mechanisms being observed (see figure 1.7C – Abdalla, 2011). For example, a lateral-medial (LM) induced current delivered to M1 results in late I-waves, whereas a posterior-anterior (PA) induced current first elicits an I1 wave, followed by late I-waves when stimulation intensity is increased (Di Lazzaro and Ziemann, 2013). On the other hand, an anterior-posterior (AP) induced current results in smaller and postponed I-waves (see figure 1.7A - Di Lazzaro and Ziemann, 2013). Figure 1.7A illustrates extrapyramidal recordings, although not usually elicited during surface EMG recording of MEPs, they have helped demonstrate the extent of indirect presynaptic activity and direct cortical axonal activity (i.e. I-waves and D-waves) (Di Lazzaro and Ziemann, 2013).

Differences in physiological responses such as the peak-to-peak MEP amplitude have also been observed with varying coil directionalities (Mills, Boniface and Schubert, 1992; Abdalla, 2011; Hallett, 2007). For example, Mills, Boniface and Schubert (1992) and Abdalla (2011) found that the largest MEP amplitude from the M1 (for the FDI muscle – Mills *et al.*, 1992, and for the BB muscle - Abdalla, 2001) was evoked with PA direction and the coil oriented 45° away from the midline (figure 1.7B – Figure adapted from Abdalla, 2011). Other cortical regions targeted with TMS do not have the same experimental output as the M1 (i.e. an MEP; Janssen, Oostendorp and Stegeman, 2015). Sections 4.1, 5.1 and 8.1 describe the neural mechanisms and behavioural responses that have been observed when TMS is delivered to the M1 (left and right) during both normal (experiment 1) and novel (experiment 2) reaching.

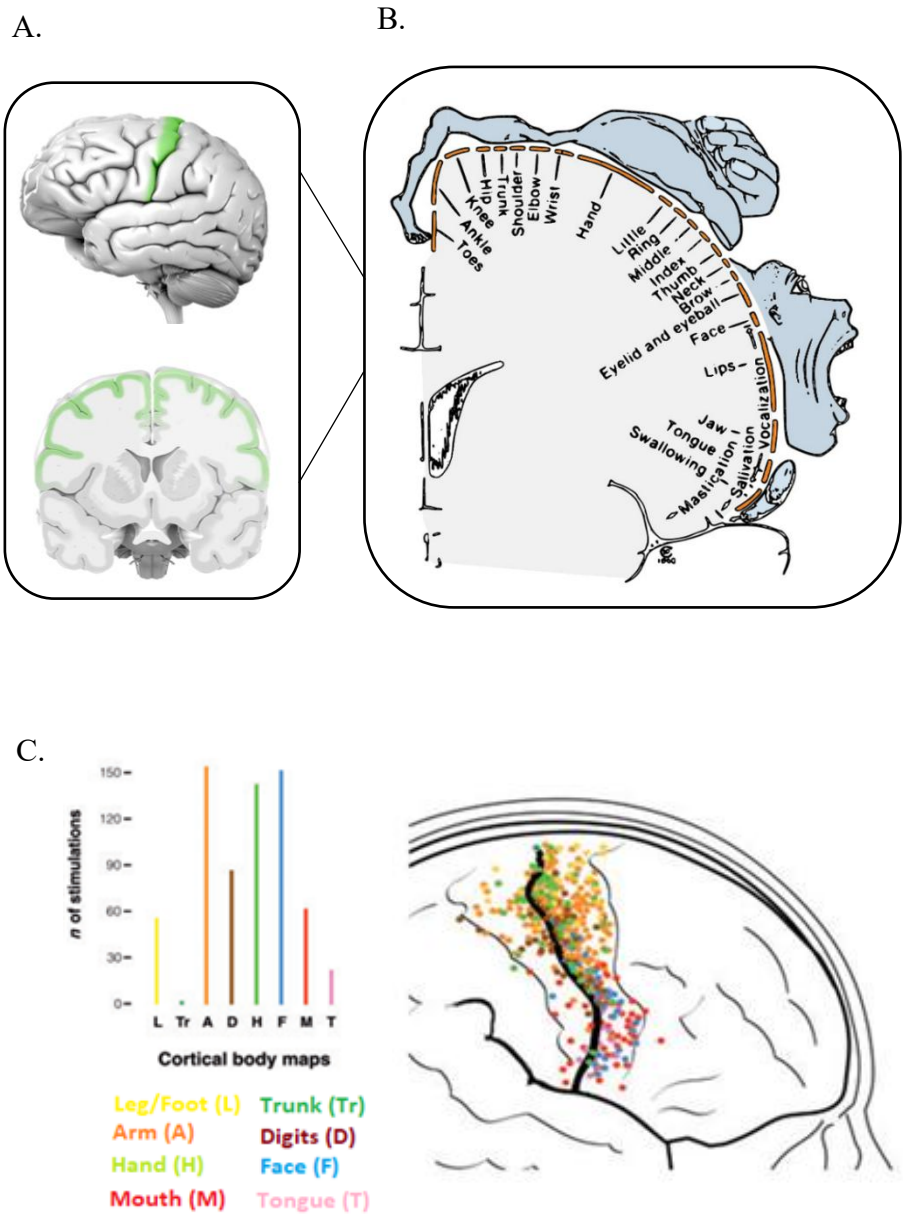


Figure 1.5: The primary motor cortex

(A) The first image in the panel is a canonical figure of the M1 and its location in the rostral segment of the frontal lobe (green) is demonstrated (figures adapted from the Florida Institute for Neurologic Rehabilitation, Inc: Atlas of Brain Injury and Anatomy: http://www.finr.net/).

(B) Penfield's homunculus is shown and the arrangement of the different muscles within the motor cortex can be seen ranging from the leg to the hip and trunk muscles (from Murphy *et al*., 2018).

(C) The motor responses elicited in different areas of the M1 are shown, demonstrating that muscle representations are not confined to one particular segment of the M1 (i.e. there are overlapping muscle representation responses during stimulation (data based on Penfield and Boldrey, 1937, figure adapted from Catani, 2017).

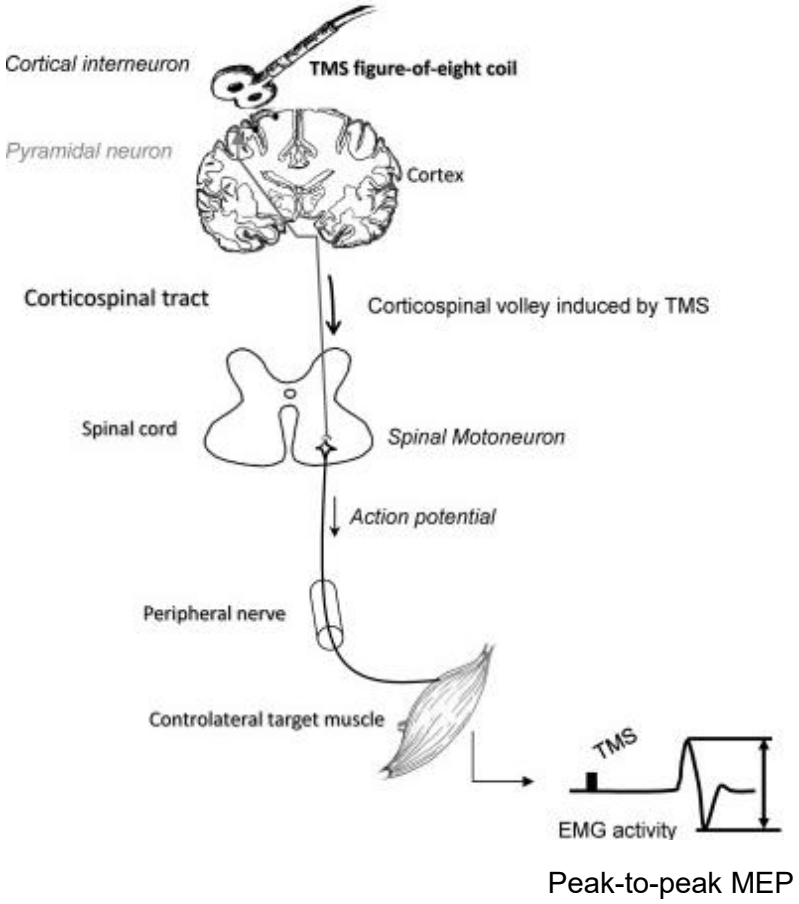


Figure 1.6: TMS to the human motor cortex

The mechanisms involved in producing MEPs with TMS to the human motor cortex is shown - when TMS is applied to the M1, pyramidal neurons are activated and this produces descending volleys that project onto the corticospinal tract. This activates motor neurons and leads to an MEP which can be quantified by measuring its peak-to-peak amplitude (figure adapted from Klomjai, Katz and Lackmy-Vallée, 2015).

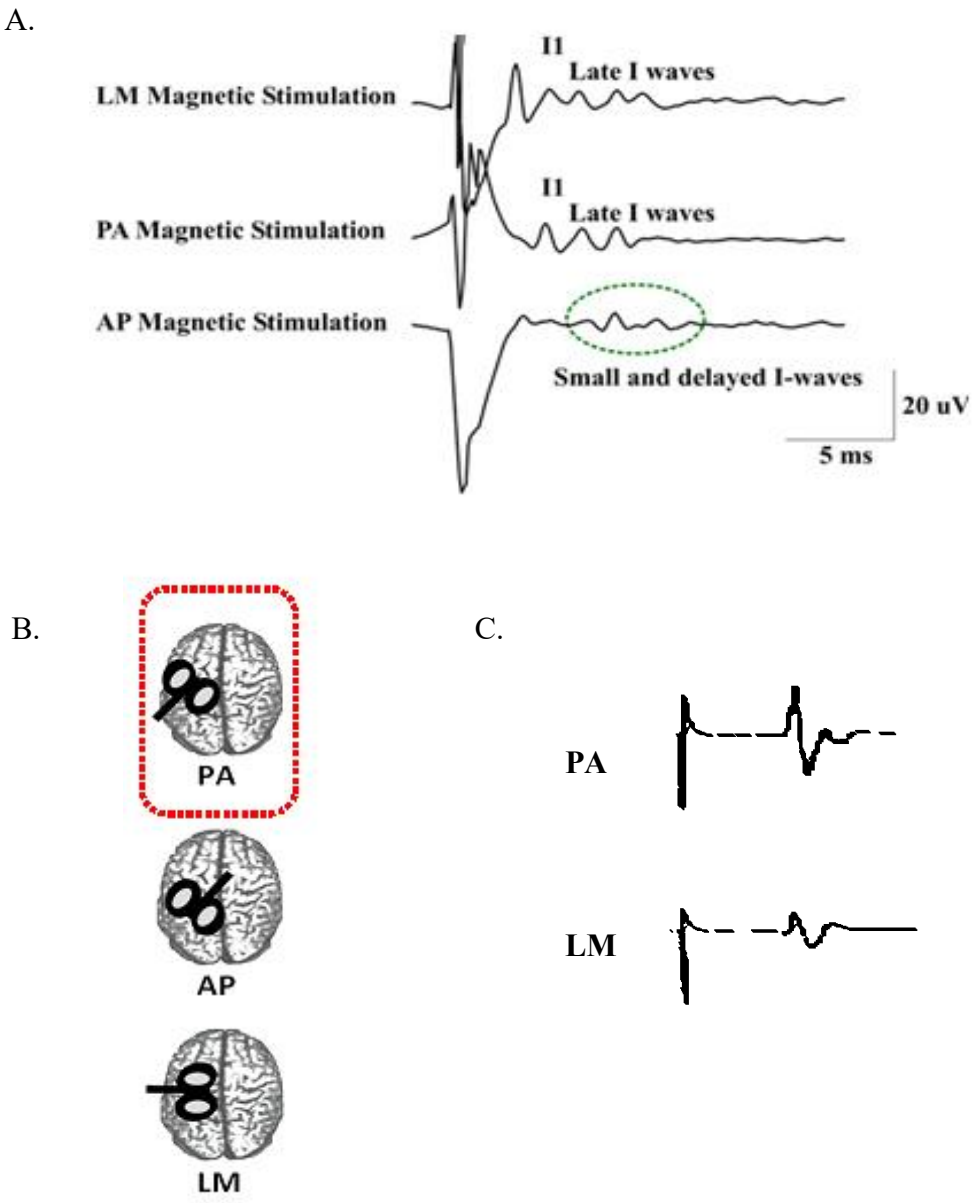


Figure 1.7: The effect of coil directionality on responses

(A) As previously mentioned in section 1.5.2.1, these extrapyramidal recordings demonstrate the different I-wave responses with varying coil orientations (figure adapted from Di Lazzaro and Ziemann, 2013). An LM induced current leads to late I-waves, compared to a PA current which can result in later I-waves when stimulation intensity is increased. The AP induced current on the other hand leads to both smaller and delayed I-waves (Di Lazzaro and Ziemann, 2013).

(B) Different types of coil orientations are demonstrated (figure adapted from Davidson, Bolic and Tremblay, 2016) (Canonical brain figures adapted from an MRIcron template – Rorden and Brett, 2000).

(C) Changes in the BB muscle MEP responses with different coil orientations are illustrated - the largest MEP from the BB was obtained with PA inducted current compared to an LM induced current, with the coil positioned 45° away from the midline (figure adapted from Abdalla, 2011).

1.5.2.2 Factors effecting MEP responses

There are different factors that can influence the output of MEP responses which are important to take into account. These include brain injury (either traumatic or caused by neurological impairments), age and gender (Chistyakov *et al*., 2001; McAllister, 2011; Prins *et al*., 2013).

1.5.2.2.1 Traumatic brain injury (TBI)

Brain injury can either be caused by external factors or by damage that has occurred due to neurological disease (McAllister, 2011; Prins *et al*., 2013). An example of brain injury caused by external factors includes traumatic brain injury (TBI) (McAllister, 2011). In cases of TBI, contact occurs between cortices and the bony ridges of the skull (McAllister, 2011). In severe cases, TBI can lead to permanent irreversible damage and its neurological impairments include white matter atrophy, demyelination and apoptosis (Newcombe *et al*., 2011; Stocchetti and Zanier, 2016).

Abnormal MEP responses have been reported among TBI patients. For example, researchers have demonstrated that TBI causes less excitatory MEP responses, particularly among patients with extreme brain trauma compared to minor head trauma (Chistyakov *et al*., 2001; Bernabeu *et al*., 2009). The reduced MEP amplitude has been suggested to be a result of neuronal and axonal damage which effects both motor excitability and motor conduction (Chistyakov *et al*., 2001). Changes in corticospinal excitability as a result of brain injury depend on the extent of the injury (Bernabeu *et al*., 2009). Although synaptic re-organisation can occur following TBI, this may not be the case for patients with extreme TBI because cortical damage can lead to impaired surrounding neural networks which can halt the recovery process (Blumbergs, Jones and North, 1989; Povlishock and Katz, 2005; Bernabeu *et al*., 2009; Castellanos *et al*., 2011). Figure 1.8A (Bernabeu *et al*., 2009) illustrates varying MEP amplitudes among TBI patients with different levels of diffused axonal injury (DAI). Other types of brain injury that can also impair physiological functioning and effect inhibitory and excitatory mechanisms, include those that arise from neurological conditions, such as multiple sclerosis (MS), and stroke.

1.5.2.2.2 Multiple sclerosis (MS)

MS is an inflammatory condition which effects the central nervous system (CNS) and results in de-myelinated plaques (Calabresi, 2004; Goldenberg, 2012). These plaques have been found in both white and grey matter and have been characterised by impaired

myelin sheaths and degenerated axons (Brück *et al*., 1996). The demyelination that occurs is caused by impaired immunological cellular responses, as well as glial cell death (glial cells are the primary cells responsible for myelin formation) (Brück *et al*., 1996; Ghasemi, Razavi and Nikzad, 2017). The condition results in slower impulse transmission between neural networks (Ghasemi, Razavi and Nikzad 2017). Researchers have demonstrated white matter structural impairments in MS patients, particularly in the corticospinal tract (Raz *et al*., 2010; Han *et al*., 2017).

MEP responses have been reported to be disrupted among MS patients. For example, Brum, Cabib and Valls-Solé (2016) noted that MS patients had a longer MEP duration at rest (FDI muscle) compared to healthy controls. Researchers have also reported a decrease in peak-to-peak MEP amplitude, whereas others have noted no MEP response during cortical stimulation in MS patients (see figure 1.8B - Fernandez *et al*., 2013) (Fernandez et al., 2013; Kale *et al*., 2014).

The different types of MEP responses that have been found in MS patients, have been suggested to correspond to the different types of disruption caused by MS. For instance decreased MEP amplitude has been associated with axonal damage, whereas increased MEP conduction time has been linked to de-myelination (Fernandez *et al*., 2013). Overall, the damage caused to white matter structures in MS detrimentally affects the corticospinal tract and its projections which facilitate healthy MEP responses (Diehl *et al*., 2004).

1.5.2.2.3 Stroke

Stroke patients demonstrate abnormal responses to cortical stimulation (Pennisi *et al*., 1999; Chae *et al*., 2002), however the degree of abnormality exhibited does depend on the nature of the lesion caused by the stroke. The main types of stroke include ischaemic stroke and haemorrhagic stroke (intracerebral or subarachnoid), with ischaemic stroke being the most common of the two (Musuka *et al*., 2015; Hui, Taddi and Patti, 2019). In an ischaemic stroke, there is a sudden reduced blood flow in the brain which causes destruction to various neurons and glial cells, resulting in focal damage and cellular death (Xing *et al*., 2012). The stages of a haemorrhagic stroke initially begin with clotted blood tissues, followed by oedema and cellular death (Kitago and Ratan, 2017). An intracerebral haemorrhagic stroke causes bleeding within the brain, whilst a subarachnoid haemorrhagic stroke causes bleeding between the pia mater and arachnoid space (Naidech, 2011). Physical impairments caused by a stroke include weakened

and/or loss of motor function (Tatemichi *et al*., 1994; Raghavan, 2015). Whishaw, Alaverdashvili and Kolb (2008) reported that limb dysfunction caused by a stroke can result in either; a) learned non-use of the limb, b) learned bad-use of the limb, whereby participants learn to use the paralysed limb in a non-typical way, which can result in poor movement accuracy, and c) failure to remember motor behaviours.

The damage caused to the motor network due to a stroke is vital when exploring cortical stimulation responses among stroke patients (Darling, Pizzimenti and Morecraft, 2011). The effects of lesions within surrounding motor regions can result in an inhibition in signal transmission from the M1 to the spinal cord which is involved in motor output behaviour (Raghavan, 2015). The impaired communication between the M1 and spinal cord can lead to delayed responses, which has been shown experimentally with cortical stimulation to the M1 (Pennisi *et al*., 1999; Chae *et al*., 2002). For example, Pennisi *et al*., (1999) investigated MEP responses in patients following an ischaemic stroke; 48 hours post-stroke, and 1 year post-stroke. Their findings revealed an absence in MEP responses after the 48 hour period, however the 1-year follow up did reveal MEP responses in patients, although the responses were both delayed and small in amplitude.

MEPs have been used as a measure of functional recovery post-stroke (Pennisi *et al*., 1999) (figure 1.8C – Stinear, 2017 based on data from Byblow *et al*., 2015). For instance, larger MEP amplitudes have been illustrated among patients with improved recovery post-stroke (Escudero *et al*., 1998; Kim *et al*., 2015; Kim *et al*., 2016b). Network re-organisation following a stroke can contribute to the recovery process, which can lead to improved MEP responses during cortical stimulation (Nudo and Friel, 1999; Byrnes *et al.,* 1999; Thickbroom, et al., 2002). More specifically, plasticity can occur in motor regions other than the motor cortex, ranging from the SMA to the PMC, which can facilitate corticospinal projection among patients and thus aid the rehabilitation process (Dum and Strick, 1991; Thickbroom *et al*., 2002; Thickbroom *et al*., 2004).

1.5.2.2.4 Age and gender

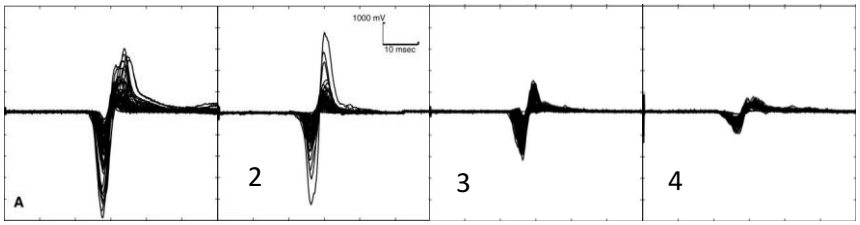
Demographic factors have an effect on physiological responses during stimulation. During healthy aging, atrophy occurs due to diminished synaptic development which leads to cell death (Scahill *et al*., 2003; Peters, 2006; Pascual-Leone *et al*., 2011). This can lead to a general decline in cognitive and physical functions, including poor motor skills (Buchman and Bennett, 2011). For example, in a go-task, Bedard *et al*., (2002)

found slower reaction times in older adults compared to younger adults. Similar results were obtained in a PEG-board task (a paradigm designed to assess fine motor control), whereby older-aged participants performed more slowly than middle-aged participants (Hamilton *et al*., 2017).

Paired pulse TMS protocols have been used to explore the impact of age on corticospinal excitability (McGinley *et al*., 2010; Opie and Semmler, 2014) For example, Opie and Semmler (2014) found that during muscle activation, short-interval intracortical inhibition (SICI) was reduced in older-aged subjects compared to younger subjects. They also found a decrease in long-interval intracortical inhibition (LICI) responses during rest among the older subjects. The decrease in LICI has been linked to age-related changes that occur in neurotransmitters (namely $GABA_b$) which can influence inhibition processes (Werhahn *et al.,* 1999). On the other hand, McGinley *et al*., (2010) noted an increase in LICI among older subjects compared to younger subjects. Therefore mixed findings have been noted, but this can be attributed to different factors, including the intervals used in the paired pulse TMS protocols and the muscles explored (Opie and Semmler, 2014). Individual subject differences could also be a reason for the inconsistency in findings (Opie and Semmler, 2014).

TMS studies exploring gender differences in MEP responses have also reported mixed findings between males and females. For example, Livingston, Goodkin and Ingersoll (2010) found that gender did not have an influence on three key MEP features; motor threshold, peak-to-peak amplitude and motor conduction time. On the other hand, Tobimatsu *et al*., (1998) reported a difference between males and females with regards to MEP latency and motor conduction time, but only in specific muscles (leg as opposed to hand). Surgical experiments which require motor cortex mapping have similarly demonstrated this difference - with females exhibiting shorter latencies than males (Picht, *et al*., 2012). These findings have been argued to be a result of physical differences between males and females, such as height (Säisänen *et al*., 2008; Sollmann *et al*., 2017). For example, Sollmann *et al*., (2017) found that matching physical features such as, height and upper limb length, led to no significant differences in MEP responses between males and females.

A.



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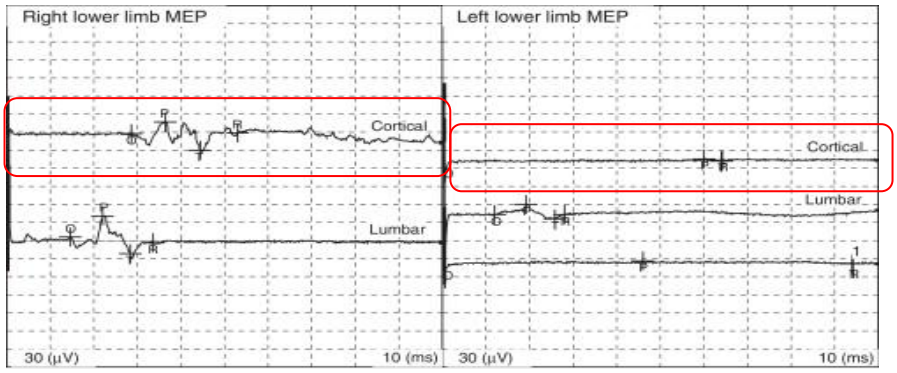

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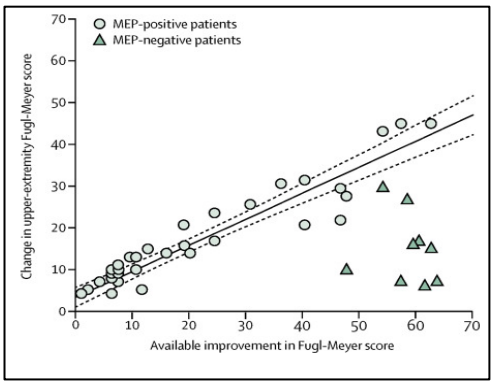


Figure 1.8: Patient MEP responses

(A) MEP responses from TBI patients with varying levels of DAI: 1) healthy controls, 2) patients with mild DAI, without motor function impairment, 3) patients with severe DAI without motor function impairment, and 4) patients with severe DAI with motor function impairment. The MEP responses are less excitatory in severe TBI cases (4), compared to mild and healthy cases - (figure adapted from Bernabeu *et al.,* 2009).

(B) Peak to peak MEPs responses from the lower limb in MS patients are shown (outlined in red). A smaller MEP amplitude was found in the right lower limb compared to the left lower limb whereby no MEP was elicited during stimulation (figure adapted from Fernandez, *et al*., 2013).

(C) The association between upper-limb recovery and MEP responses in patients 6 months following a stroke is shown. Recovery was quantified as 'change in upper-extremity Fugl-Meyer score'. A relationship was found between available improvement and actual improvement in MEP-positive patients, whereas this was not the case for MEP-negative patients. MEP responses therefore provide an important indication of the recovery process in stroke patients (figure from Stinear, 2017, based on data from Byblow *et al*., 2015).

1.6 The posterior parietal cortex (PPC)

The PPC resides posterior to the somatosensory cortex (figure 1.9A - figure adapted from the Florida Institute for Neurologic Rehabilitation, Inc: Atlas of Brain Injury and Anatomy: http://www.finr.net/), and throughout history it has evolved in terms of its structure and function. For example, studies in early placental mammals revealed that the PPC did not contain many multisensory segments, whereas studies in developed mammals have revealed that various PPC multi-sensory segments exist, which can be probed with TMS to elicit different behavioural responses, ranging from reaching to grasping (Kaas and Stepniewska, 2016). In human subjects compared to non-human primates (such as the macaque) the PPC differs in its morphology and functionality (Hill *et al*., 2010; Kaas and Stepniewska, 2016). For example, in humans the region is extended (i.e. morphology) and it has also been suggested to have additional functional areas related to gesturing behaviours (Frey 2008; Konen et al., 2013; Kaas and Stepniewska, 2016).

The various motor related functions of the PPC include novel reaching, movement planning, motor intent, navigation and spatial awareness (Batista *et al*., 1999; Connolly, Andersen and Goodale, 2003; Della-Maggiore *et al*., 2004; Kaas and Stepniewska, 2016; Whitlock, 2017). The PPC has a vast range of connections with other structures (such as the SMA, M1 and the pre-frontal cortex) and this has resulted in its multiple motor and cognitive functions (Kass and Stepniewska 2016; Whitlock, 2017). Kaas and Stepniewska (2016) suggested that the neural communication between the PPC and other motor related regions enables successful motor responses. This has been further supported in clinical studies among patients with PPC impairments. For example, patients with optic apraxia (caused by PPC lesions) have disrupted movement control during reaching and grasping (Andersen *et al.,* 2014). This has been argued to be due to the disruption of communication between the PPC and other motor related domains associated with movement control, such as the M1, PMC and the frontal cortex (Andersen *et al*., 2014). Figure 1.9B (Kaas and Stepniewska 2016) illustrates the neural communication between the PPC and other motor regions to facilitate motor output.

Further evidence for the role of the PPC in motor behaviour comes from neuroimaging studies. For example, fMRI research has revealed significantly increased neural activity in the PPC during different types of motor tasks, including motor execution (typing

task) (Gordon et al., 1998), motor planning (virtual driving task among taxi drivers) (Maguire, Woollett and Spiers, 2006) and spatial navigation and memory (navigation memory task in patients with PPC lesions) (Ciaramelli *et al*., 2010; Whitlock, 2017). Studies have also revealed the role of the PPC in motor reaching, for example evidence has illustrated that a posterior parietal reach (PPR) region exists in humans which is activated during pointing tasks (Batista *et al*., 1999; Connolly, Andersen and Goodale, 2003). Researchers have also found that the neurons located in the PPR region encode hand movement goals during a task, thus providing evidence for the functional role of the PPC with regards to motor intent (Batista *et al*., 1999; Whitlock, 2017).

Although studies have demonstrated that the left PPC is involved in motor adaptation there have been some controversies regarding its role. For example, researchers have argued that it is unclear as to whether it is the left or the right PPC that plays a more important role in learning (Bedard and Sanes, 2014). Bedard and Sanes (2014) explored bilateral activation patterns of parietal structures when participants were performing reaching outward movements using an MRI compatible joystick. Their findings concluded that during visuo-motor adaptation learning, both the right inferior parietal lobe and the left superior parietal lobe had similar levels of activation, therefore making it hard to decifer specific roles for different parietal structures. Perfetti *et al*., (2011) on the other hand concluded that learning during a visuo-motor task was accompanied with greater changes in the right compared to the left PPC, as quantified with EEG methods. However, Della-Maggiore *et al*., (2004) found greater changes in the left PPC during TMS whilst participants were performing a motor adaptation task. Based on these mixed findings it can be argued that the functional differences between the right and left PPC remain unclear. In addition to this, previous findings have not fully investigated the role of a number of regions during the different phases of motor adaptation (Bedard and Sanes, 2014). In this thesis, both the left and right PPC will be targeted and the findings will aim to elucidate the functional differences between the two hemispheres during preparation for motor reaching.

1.6.1 TMS to the PPC

Targeting other cortical regions, such as the PPC with TMS, does not have the same experimental output as the M1 (i.e. an elicited MEP; Janssen, Oostendorp and Stegeman 2015). However, comparable columnar arrangements exist across the cerebral cortex (Von Bonin and Mehler, 1971; Janssen, Oostendorp and Stegeman, 2015) and similar

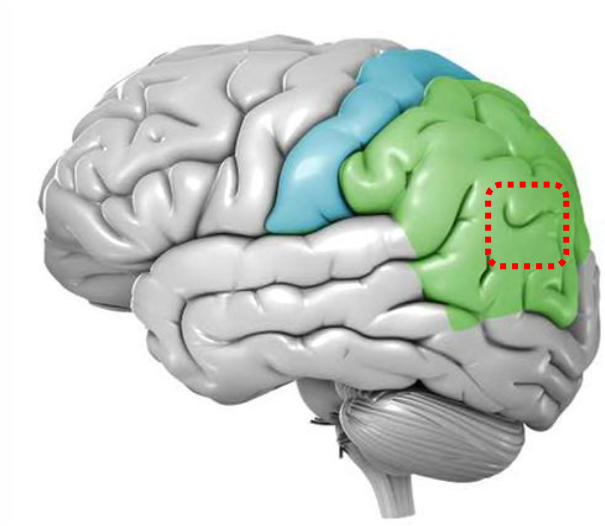
coil principles and models (to the M1) have been developed to determine the best orientation for stimulating other regions. Several imaging studies (e.g. PET) have been conducted to create new TMS protocols for stimulating areas such as the occipital lobe, pre-motor cortex, supplementary motor area, parietal cortices and inferior frontal gyrus (Janssen, Oostendorp and Stegeman, 2015; Cona, Marino and Semenza, 2017).

TMS protocols targeting the left and right PPC include single pulse, paired pulse and repetitive pulse paradigms (Della-Maggiore *et al*., 2004; Busan *et al*., 2009). Studies have demonstrated that the left PPC plays an important role in motor adaptation. For example, Della-Maggiore *et al*., (2004) TMS delivered to the left PPC following movement onset resulted in disrupted reaching trajectories, however this was not the case when TMS was delivered to a control region such as the occipital lobe. Repetitive TMS protocols targeting the left PPC was found to have an impact on motor synchronisation patterns in the right hand and also delayed responses during a finger tapping task, however this was not the case with right PPC rTMS (Krause *et al*., 2012). Based on these studies it can be argued the left PPC has important networking pathways with the M1, and TMS to the PPC could disrupt neural connections, resulting in delayed motor activity (Krause *et al*., 2012). Similarly Vesia *et al*., (2007) explored the role of the left and right PPC, however they employed a reaching and pointing task. They found that left PPC TMS disrupted the end-point of reaching whereas right PPC TMS caused a shift in movement trajectories and affected subject's gaze during the task. The left and right PPC therefore play separate roles in motor activity.

Paired pulse TMS studies have shown that TMS to the right PPC had impacted reaching only when targets were presented on the left-hand side rather than the right-hand side (Koch *et al*., 2008b). Most studies, have explored the effect of TMS on the PPC either 1) following the presentation of an auditory cue (Koch *et al*., 2008b) or 2) when movement onset had occurred (Della-Maggiore *et al*., 2004). Therefore, it is unknown whether TMS delivered a range of different time points during the preparation phase of motor adaptation results in the same findings. This will be addressed in this thesis when targeting regions such as the PPC. This paragraph aimed to briefly outline details regarding the action of TMS on the PPC during motor reaching. Sections 6.1 and 10.1 further describe the behavioural responses that have been observed when the PPC (left

and right) has been targeted with TMS protocols during both normal and novel reaching.

A.



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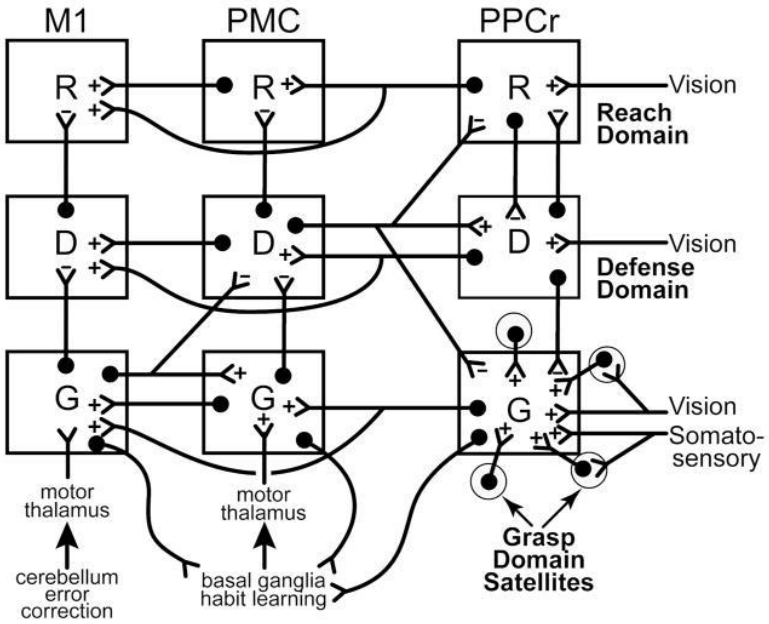


Figure 1.9: PPC location and a schematic presentation of neural pathways between motor regions and their contribution to motor behaviours

(A) The parietal lobe is shown in green, as is the PPC which is presented by the red dotted line (figure adapted from the Florida Institute for Neurologic Rehabilitation, Inc: Atlas of Brain Injury and Anatomy: http://www.finr.net/)

(B) The interaction between the M1, PMC and rostral region of the PPC (rPPC) is shown with regards to three types of domains: reaching, grasping and defence. The different domains of the rPPC become activated via commands that are received from different regions. For example, the reaching domain is activated due to 1) cerebellar and thalamus excitatory inputs (+) to the M1 and 2) basal ganglia excitatory inputs to the PMC. Overall, these connections facilitate specific rPPC domain activation (figure from Kaas and Stepniewska, 2016).

1.7 The supplementary motor area (SMA)

The SMA is located in the frontal cortex and lies between the prefrontal cortex and M1 cortices (Nachev et al., 2007) (figure 1.10A - figure adapted from the Florida Institute for Neurologic Rehabilitation, Inc: Atlas of Brain Injury and Anatomy: http://www.finr.net/). The functions of the SMA include; regulating posture, facilitating complex/demanding motor tasks, and also planning and executing movements (Goldberg, 1985; Tanji, 1994; Akkal, Dum and Strick, 2007; Hiroshima *et al*., 2014). Although previously thought of as one cortical structure, studies have shown that the SMA in fact consists of a different sub-regions (Akkal, Dum and Strick, 2007; Tanji, 1994). For example, the rostral part of the SMA is known as the pre-SMA, and the caudal part is known as the SMA proper, an additional part of the SMA forms what is known as the supplementary eye-field (SEF) (Akkal, Dum and Strick, 2007; Tanji, 1994).

Evidence for the SMA sub-regions has been illustrated in neuroimaging studies which have confirmed distinct functions of the pre-SMA and SMA-proper (Tanji, 1994; Akkal, Dum and Strick, 2007). For instance, in a motor sequence learning task (button pressing) using fMRI methods, Hikosaka *et al*., (1996) concluded that the pre-SMA had significantly greater neural activity only during the learning procedure but not when movements were performed. However, the SMA-proper was significantly active during movement performance but not during learning. Similarly, PET scanning techniques have revealed less activity in the pre-SMA compared to the SMA proper in tasks that involved movement control (Picard and Strick, 1996; Akkal, Dum and Strick, 2007). The pre-SMA has been associated with motor tasks such as, motor sequencing and retrieving motor memories, whereas the SMA-proper has been associated with movement execution (Halsband *et al*., 1993; He, Dum and Strick, 1995; Hikosaka *et al*., 1996; Alario *et al*., 2006). The SEF SMA sub-region plays a role in producing eye movements (Tehovnik *et al*., 2000; Fujii, Mushiake and Tanji, 2002; Nachev *et al*., 2007) and evidence for both its existence and function comes from patient models (Nachev *et al*., 2007; Husain *et al*., 2003). For example, Husain *et al*., (2003) reported a case study of a patient with a lesion to the SEF, who had impaired eye control movements.

The sub-regions communicate with each other and other areas of the motor circuit to facilitate motor output (Tanji, 1994). For example, the SMA-proper has direct

projections with the spinal cord (Tanji, 1994; Wang *et al*., 2001; Akkal, Dum and Strick, 2007). Furthermore, the pre-SMA is not densely connected with the M1, but rather with the prefrontal regions and the cerebellum which it receives input from (Wiesendanger and Wiesendanger, 1985; Tanji, 1994; Wang *et al*., 2001; Akkal, Dum and Strick, 2007). Furthermore, Akkal, Dum and Strick, (2007) revealed that the SMA-proper and pre-SMA inputs arise from separate regions in the globus pallidus which has resulted in the distinct motor functions of these two sub-regions. Despite studies demonstrating differences between SMA sub-regions during motor tasks (Picard and Strick, 1996; Akkal, Dum and Strick, 2007) there have been controversies surrounding pre-SMA and SMA proper functioning. For instance, researchers have found that the pre-SMA and SMA-proper are similarly activated in different types of motor states (Wang et al., 2010). With regards to movement control, Chen, Scangos and Stuphorn (2010) reported that the signals originating from the pre-SMA could have an impact on SMA proper activity (Wardak, 2011). Similarly, Vergani (2015) reported that SMA motor activity is influenced by the anatomical connectivity between the pre-SMA and SMA proper (Lima, Krishnan and Scott, 2016). Based on such findings it could be argued that the connectivity between the pre-SMA and SMA proper has made it difficult to determine the precise functional role of SMA subregions (Wardak, 2011; Lima, Krishnan and Scott, 2016). This thesis will both address and consider these findings by using specific coil orientations to target specific sub-regions of the SMA, and this is further outlined below in section 1.7.1.

1.7.1 TMS to the SMA

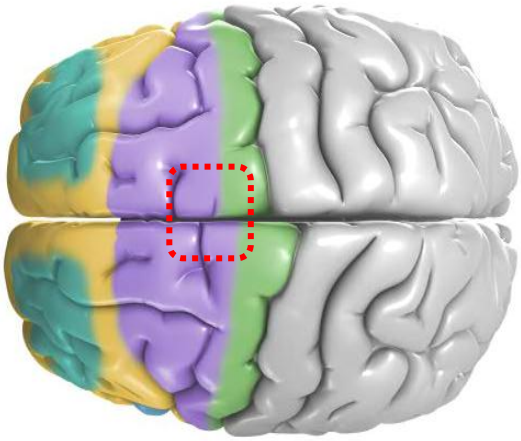
Different coil positions have been used to target different regions of the SMA. For example, a coil handle positioned to the right has previously been used to target the pre-SMA (Cona, Marino and Semenza, 2017), whereas a coil position which induces a posterior-anterior current has been used to target the SMA-proper (Terao *et al*., 2001).

Repetitive TMS paradigms have mainly been implemented to explore SMA activity during motor related tasks. For instance, Kim *et al*., (2014) applied rTMS to the M1 and the SMA during a motor sequence task and their results showed that rTMS to the SMA compared to the M1 caused a significant increase in movement time. The impact of SMA function on other regions has also been demonstrated. For example, Oliveri *et al*., (2003) found an increase in M1 excitability (quantified by MEPs) following pre-SMA stimulation (Chouinard and Paus, 2010). Matsunaga *et al*., (2005) similarly reported

heightened MEP responses after the SMA had been stimulated in an rTMS paradigm (Makoshi, Kroliczak and Van Donkelaar, 2011).

Differences have been found when comparing the results of pre-SMA stimulation to SMA-proper stimulation (Chouinard and Paus, 2010). While pre-SMA stimulation has been found to cause a greater disruption to tasks that have cognitive requirements ranging from switching to inhibition (Rushworth et al., 2002), SMA-proper stimulation has resulted in a disruption to 1) motor sequencing, 2) complex motor tasks and 3) bimanual tasks (Gerloff *et al*., 1997; Obhi *et al*., 2002; Steyvers *et al*., 2003) (Chouinard and Paus, 2010). Furthermore, Makoshi, Kroliczak and Van Donkelaar (2011) found that TMS to the SMA caused a disruption in movement onset responses in a load-holding task, whereas this was not the case when an area of the visual cortex was stimulated. This was also noted to be time-dependent (at approximately 400ms before motor activity). Makoshi, Kroliczak and Van Donkelaar (2011) therefore inferred that the SMA plays a key role in planning and predicting behaviours prior to the movement occurring. Studies exploring the role of the SMA during motor adaptation have primarily focused on non-human primate responses (Padoa-Schioppa, Li and Bizzi, 2004). In addition to this, SMA functioning has commonly been investigated using motor sequence paradigms compared to motor reaching paradigms (Gerloff et al., 1997; Kim *et al*., 2014). This thesis will address this by targeting the SMA using a novel reaching paradigm. Further details regarding the behavioural and neural responses that have been found with TMS delivered to the SMA during normal and novel reaching are described in section 7.1, as this section outlined experiment 4 whereby a virtual disruption approach was used to explore the role of the SMA in a motor control and motor reaching.

A.



B.

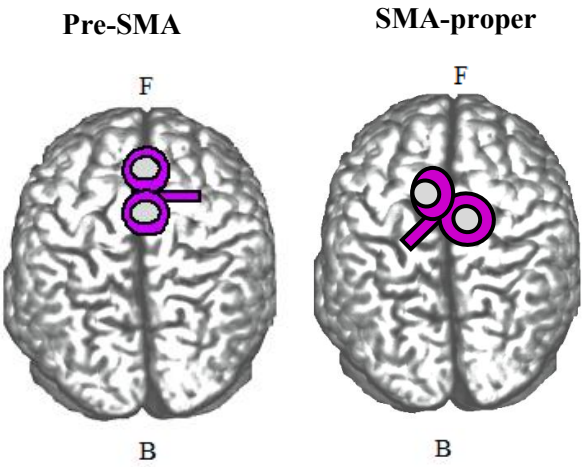


Figure 1.10: SMA location and coil position for targeting this region

(A) The red dotted line represents the location of the SMA (figure adapted from the Florida Institute for Neurologic Rehabilitation, Inc: Atlas of Brain Injury and Anatomy: http://www.finr.net/).

(B) Different coil positions have been used to target the sub-regions of the SMA. To target the pre-SMA, a coil position with the handle pointing to the right has been used (first image on panel B), however, to target the SMA-proper, a coil position inducing a posterior-anterior current has been used (second image on panel B) (positions based on Cona, Marino and Semenza, 2017; Terao *et al*., 2001) (canonical brain figures adapted from an MRIcron template – Rorden and Brett, 2000).

1.8 The Pre-Motor cortex

The Pre-Motor cortex (PMC) is located between the dorsolateral prefrontal cortex and the M1 (Kantak *et al*., 2012). The PMC has axonal signals that project to 1) the M1, 2) the corticobulbar pathway and 3) the corticospinal pathway, thus the region has a direct effect on motor-neurons in the brainstem and spinal cord (Purves *et al.,* 2001). The PMC is an important structure that forms part of the motor circuit and one of its key functions is to facilitate movement selection and preparation (Beck *et al*., 2009; Chang *et al*., 2010). Evidence for its role in movement selection comes from studies in non-human primates. For example, Kurata and Hoffman (1994) found that PMC lesions in monkeys resulted in significantly greater choice-selection errors during a reaction time task.

A key feature of the PMC is that it contains two structures, the dorsal PMC (dPMC) and the ventral PMC (vPMC) both of which have different functions. For example, the dPMC has been found to be involved in sequential motor learning, visually guided movements and also controlling kinematic responses (Johnson *et al*., 1996; Davare *et al*., 2015; Ohbayashi, Picard and Strick, 2016; Solopchuk, Alamia and Zénon, 2016). The functions of the ventral PMC range from speech control and production, to goal-directed behaviours (Binkofski and Buccino 2006; Meister *et al*., 2007). For example, neuronal firing in the vPMC was found to be increased during goal-directed behaviours, including grasping and holding (Sakata *et al*., 1995 Binkofski *et al*., 2000; Binkofski and Buccino, 2006). Imaging studies have also revealed additional functions of the vPMC including its role in motor imagery and its importance in motor tasks with increased levels of difficulty. For instance, Winstein, Grafton and Pohl (1997) found that the vPMC forms part of an important cortical loop in the motor circuit. They reported increased regional cerebral blood flow (rCBF) in the vPMC which was associated with greater levels of precision during motor performance.

Functional asymmetries exist between PMC sub-regions (Schluter *et al*., 1998; Schluter *et al*., 2001; Beck *et al*., 2009). For example, fMRI studies have revealed that the left dPMC has greater levels of neural activity when subjects performed motor tasks with both their right- and left-hand. However, the right dPMC was found to be more activated when subjects performed motor tasks with their left-hand (Schluter *et al*., 2001). Although researchers have illustrated that PMC subregions contribute to motor-related activity, Freund and Hummelsheim (1985) reported that uncertainties still exist

regarding the specific functional role of the PMC and they studied this notion through lesion studies. For example, Kennard, Viets and Fulton (1934) reported that PMC damage can result in skilled movement deficits, forced motions during grasping tasks and muscle stiffness (Freund and Hummelsheim, 1985). On the other hand, Derousne (1973) reported that PMC lesions were associated with a lost of rhythmic motion and uncoordinated movement (Freund and Hummelsheim, 1985). Therefore controversies exist with regards to specific PMC functions because different behavioural observations have been reported in lesion studies (Freund and Hummelsheim, 1985). In this thesis, motor control and adaptation will be explored, therefore specific PMC functions only related to this type of motor activity will be investigated. Additionally, participants will have similar age ranges and no history of neurological conditions that could effect PMC functioning and cause varied results. This thesis will thus help answer questions relating to the specific role of the PMC during preparation for motor control and novel motor reaching.

1.8.1 TMS to the PMC

TMS studies targeting the PMC have explored differences between its subregions (e.g. vPMC vs. dPMC) during motor tasks. For instance, paired pulse TMS protocols have revealed that the vPMC influences M1 activity during grasp-to-hold tasks (Buch *et al*., 2010). More specifically, Buch *et al*., (2010) reported that the impact of the vPMC on the M1 depended on the type of activity that was being performed. For example, their physiological measurements of corticospinal excitability revealed that during movement planning and execution the vPMC had a facilitatory effect on M1 activity compared to tasks in which movements had to be updated in which the vPMC had an inhibitory effect on M1 activity. Buch *et al*., (2010) also demonstrated behavioural effects of vPMC stimulation as their findings showed that subjects had a delay in adapting their grasping when their movements had to be updated (target switching from grasping a small cylinder to a large cylinder).

Furthermore, rTMS paradigms have been used in virtual lesion studies to provide a distinction between dPMC vs. vPMC functions. For example, Davare *et al*., (2006) applied rTMS to the left and right dPMC and vPMC during a grasp-lifting task. They found that: 1) rTMS to the left vPMC interrupted sequential hand movement activity, 2) rTMS to both the left and right vPMC similarly resulted in disrupted finger positioning during grasping and, 3) rTMS to the left dPMC interrupted the phase between grasping

and lifting, and thus caused a delay in motor related activity. Davare *et al*., (2006) therefore concluded that whilst the vPMC plays a role in finger positioning and grasping, the dPMC plays a role in managing the timing of sequential movements, e.g. from grasping to lifting, which is in line with studies in non-human primates (Murata *et al*., 1997; Marconi *et al*., 2001).

Furthermore, Schluter *et al*., (1998) explored functional hemispheric differences with regards to the role of the dPMC, and found that targeting the left dPMC with TMS protocols led to greater motor performance disruptions during bilateral tasks, whereas right dPMC TMS only affected motor tasks performed with the left-hand. As well as grasping tasks, PMC activity during reaching have also been investigated. For example, Ma *et al*., (2017) found that neural activity in the dPMC differed depending on the type of reaching being performed. They reported that whilst some neurons were only modulated by the location of the reaching target, other neurons in the dPMC were heightened and modulated during path switching of reaching trials. It should be noted that most studies exploring the role of the dPMC have implemented rTMS and paired-pulse TMS compared to SP-TMS paradigms and have mainly used grip/grasping and visuo-motor adaptation tasks as opposed to novel motor reaching tasks (Davare *et al*., 2006; Lee and Van Donkelaar, 2006; Buch *et al*., 2010). Chapter 9 and 11 therefore aim to provide novel findings regarding left and right dPMC functioning during preparation for normal and novel reaching with SP-TMS (virtual disruption approach). Sections 9.1 and 11.1 further describe the behavioural responses that have been observed with TMS protocols that have targeted the dPMC (left and right).

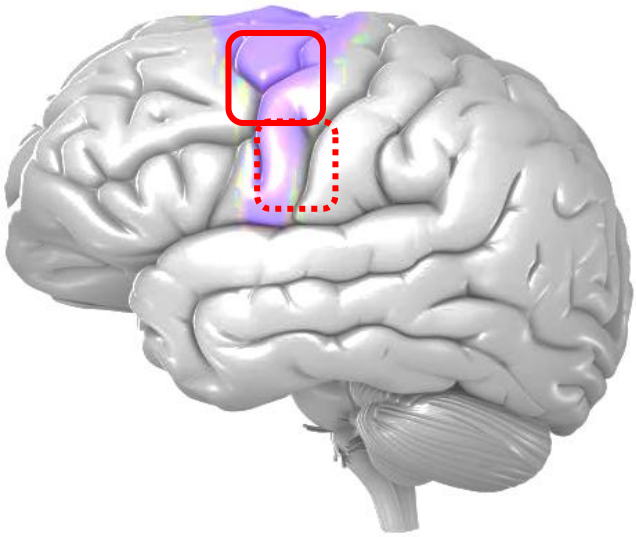


Figure 1.11: PMC location

The location of the PMC is demonstrated (purple) as are its two key structures: the dPMC (solid red line) and the vPMC (dotted red line) (figure adapted from the Florida Institute for Neurologic Rehabilitation, Inc: Atlas of Brain Injury and Anatomy: http://www.finr.net/).

1.9 Other regions of the motor network (the prefrontal cortex [dorsolateral] and the cerebellum) targeted with TMS

The prefrontal cortex has various neural connections with different regions of the motor network and therefore has a direct impact on motor behaviour (Goldman-Rakic, 1987). The functions of the prefrontal cortex range from executive functioning to organisation and planning (Tanji and Hoshi, 2001; Curtis and D'Esposito, 2003; Ball *et al*., 2011). An area of the prefrontal cortex involved in both movement control and motor output behaviour is the dorsolateral prefrontal cortex (DLPFC) (Hasan *et al*., 2012) (figure 1.12A - figure adapted from the Florida Institute for Neurologic Rehabilitation, Inc: Atlas of Brain Injury and Anatomy: http://www.finr.net). The DLPFC contains representations of motor sequences which is important in tasks where repetitive rhythmic motions are required (Shima *et al*., 2007). The DLPFC is also fundamental for motor learning due to its role in spatial attention, storing memories of sensory information and selecting appropriate motor responses (Badoud *et al*., 2017). Neuroimaging studies provide support for the role of the DLPFC in movement selection. For example, fMRI studies have found greater activity in the DLPFC when subjects were instructed to carry out an action selection task (Rowe *et al*., 2005). Similar findings have been illustrated with PET imaging techniques (Deiber *et al*.,1996). The DLPFC also plays a role in directing motor attention in a task which enables learning to take place (Shallice, 1982). This notion has been supported with repetitive TMS (rTMS) protocols. For example, Kantak *et al*., (2010) revealed that suppressing neuronal activity of the DLPFC with an rTMS paradigm during motor-skill learning had a detrimental effect on the motor learning process. Similarly, Robertson *et al*., (2001) found that rTMS delivered to the DLPFC disrupted spatial-sequential learning in a reaction time task.

The cerebellum is also a key structure in the motor network that is vital for motor control (Manto *et al*., 2012) (see figure 1.12B - figure adapted from the Florida Institute for Neurologic Rehabilitation, Inc: Atlas of Brain Injury and Anatomy: http://www.finr.net). Research has found that this region regulates the timings of movements, assists in accurate motor output (particularly during reaching) and it is involved in motor learning and motor memory (Albus, 1971; Attwell, Cooke and Yeo *et al*., 2002; D'Angelo and Casali, 2012; Koziol *et al*., 2014). During motor adaptation (i.e. force-field [FF] learning), the cerebellum encodes the kinematic elements of movement

and stores them as motor memories (Overduin, Richardson and Bizzi, 2009). This can explain the overshooting phenomena that occurs in normal reaching trajectories (i.e. no FF) after motor adaptation has occurred (Hunter *et al*., 2009; Hunter, Sacco and Turner, 2011; Pizzamiglio *et al*., 2017b). The role of the cerebellum in motor functioning has been highlighted in patients with cerebellar damage, whereby poor performance has been reported (Landi, Baguear and Della-Maggiore, 2011). This is because the damage leads to patients no longer being able to store and recall the kinematic memories for motor adaptation (Criscimagna-Hemminger *et al*., 2010; Landi, Baguear, and Della-Maggiore, 2011). Similarly, Bastian (2011) reported that impairments to the cerebellum resulted in movement control deficits (measured by trajectory reaching errors), as patients were not able to sustain accurate kinematics of movement control.

Studies using TMS have helped investigate the connectivity between different cortical regions, and how a region with deficits could impair motor function and physiological responses (Spampinato, Block and Celnik, 2017). For instance, in patients with cerebellar deterioration, MEP responses elicited during pre-movement were reduced when TMS was delivered to the M1 (Nomura, Takeshima, Nakashima, 2001). TMS studies during motor tasks have further elucidated the functional role of the cerebellum in the motor network. For example, rTMS of the medial cerebellum in a tapping task significantly affected the variability of tapping intervals during performance, however this was not the case during sham stimulation and also when targeting other regions, such as the M1 (Théoret, Haque and Pascual-Leone, 2001).

In summary, a variety of regions are involved and contribute to both upper limb reaching and adaptation. These regions range from the M1 to the PPC (Day, Rothwell and Marsden, 1983; Meyer and Voss, 2000) and other areas include the pre-motor cortex, as well as specific structures within it, such as the dPMC (Kantak *et al*., 2012; Hardwick *et al*., 2015). The role of the SMA should also be considered when noting its role in the planning of motor movements (Padoa-Schioppa, Li and Bizzi, 2004). Most TMS studies targeting these regions have implemented different TMS protocols, such as rTMS (Overduin, Richardson, and Bizzi, 2009; Ma, *et al*., 2017). Therefore, the studies conducted within this thesis employed a standardised SP-TMS protocol to examine the role of several cortical regions during motor adaptation (MA). Additionally, very few studies have explored the effect of stimulation given at different preparatory time points on novel motor behaviour (i.e. during motor adaptation). Experiments in this thesis aim

to provide novel behavioural biomarkers of region-specific mechanisms operating during motor adaptation.

A.

B.

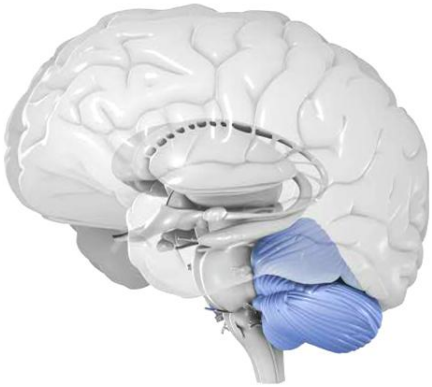


Figure 1.12: DLPFC and cerebellum location

The location of: (A) the DLPFC (green) and (B) the cerebellum (blue) is shown (figure adapted from the Florida Institute for Neurologic Rehabilitation, Inc: Atlas of Brain Injury and Anatomy: http://www.finr.net/).

Chapter 2

2 Purpose and aims of this thesis

2.1 Purpose and impact

This thesis aims to explore cortical region-specific mechanisms mediating functional reaching tasks using TMS. This knowledge could help bridge the gap between neural/cellular function and motor behaviour. Through exploring detailed limb kinematics, our understanding of how the brain interacts with muscles in a reaching task could be enhanced. Furthermore, by investigating how TMS induced disruption of cortical regions impacts on reaching behaviour we would gain an insight into how different cortical regions play a role in enabling us to learn new skills (i.e. notion of neuroplasticity) and how a change in neural activity can affect the ability to tackle new environmental demands.

The general questions that arise include:

- What neural cortical mechanisms are involved in both upper limb reaching and motor adaptation?
- Does delivering TMS at different times during the preparation of a reach alter MEP responses in different muscles?
- How does SP-TMS delivered at different times to different brain regions affect kinematics of reaching (i.e. behavioural responses) (in both normal reaching and motor adaptation)?
- How do MEP responses change in a novel motor reaching task (motor adaptation task vs. simple motor reaching task)?

The specific aims of the project are:

- To explore basic neural mechanisms of right arm reaching with single pulse TMS delivered to both the contralateral M1 and ipsilateral M1 (Experiment 1).
- To examine neural mechanisms (experiment 1 and 2) and behavioural responses (i.e. kinematics) (experiment 1 -8) during right arm reaching in a robot-mediated force-field with single pulse TMS delivered to the:

  1) Left primary motor cortex (experiment 2)

  2) Left posterior parietal cortex (experiment 3)

  3) Supplementary motor area (experiment 4)

4) Right primary motor cortex (experiment 5)

5) Left dorsal premotor cortex (experiment 6)

6) Right posterior parietal cortex (experiment 7)

7) Right dorsal premotor cortex (experiment 8)

- To compare region-specific roles in motor control and motor adaptation

2.2 Specific hypotheses

Experiment 1 – Exploration of 1) contralateral and 2) ipsilateral neural mechanisms of right arm reaching using single pulse TMS:

Hypothesis I: TMS pulses delivered in the preparation phase of a reach will have a significant disruptive impact on the kinematic behaviour of the subsequent reach. This is interesting because if true, the impact of disruption of M1 neurotransmission to the CST (i.e. by the TMS pulse) can be directly linked to disruption of motor behaviour. In other words, TMS is used as a tool for a virtual disruption in the M1/CST pathway.

Experiment 2 – Exploration of neural mechanisms of right arm reaching in a force field using single pulse TMS applied to the left M1:

Hypothesis I: There will be an increase in the MEP measured in the biceps brachii (BB) and flexor carpi radialis (FCR) (flexor) muscles because the force field is a clockwise velocity-dependent field, but not in the triceps brachii and extensor carpi radialis (extensor) muscles (see Pizzamiglio et al., [2017b] for comparisons of muscle responses to clockwise and counter clockwise force fields).

Hypothesis II. TMS will delay the movement onset by inhibiting a group of neurons in the brain (as previously demonstrated by Day, Rothwell and Marsden, 1983). The virtual disruption approach using TMS experimentally here can be compared to neurocomputational models where similar "data-based virtual lesions" are introduced into models of stroke (Small, Buccino and Solodkin, 2013).

Experiment 3 – Exploring the impact of SP-TMS to the left posterior parietal cortex (PPC) during right arm reaching in a motor adaptation protocol:

Hypothesis I. The disruption of PPC function using TMS will impair novel motor performance (as demonstrated by Della-Maggiore *et al*., 2004). This is because

the PPC feeds into other motor related cortical structures, signalling commands for successful motor output.

Hypothesis II. Different TMS timings will affect kinematic behaviour of the subsequent reach. These effects are not yet known and this is the first attempt to describe such behavioural data during motor adaptation.

Experiment 4 – Exploring the impact of SP-TMS to the supplementary motor area (SMA) during right arm reaching in a novel motor learning protocol:

Hypothesis I. TMS applied to the SMA would have a disruptive effect on novel motor performance. This is because the SMA is known to be involved in fast-learning which is required for motor adaptation to take place (King *et al*., 2013).

Hypothesis II. Different TMS timings will affect the kinematic behaviour of the subsequent reach, as the SMA is involved in motor planning and preparation (Padoa-Schioppa, Li and Bizzi, 2004).

Experiment 5 – The impact of SP-TMS to the right primary motor cortex (M1) during right arm reaching in a novel motor learning protocol

Hypothesis I. The ipsilateral motor cortex will be modulated during movement preparation, because it has been shown that the ipsilateral M1 can too undergo task-related modulations of activity (Van den Berg, Swinnen and Wenderoth, 2011).

Hypothesis II. TMS will delay the movement onset by inhibiting a group of neurons in the brain (Day, Rothwell and Marsden, 1983).

Experiment 6 – Exploring the impact of SP-TMS to the left dorsal pre-motor cortex (dPMC) during right arm reaching in a novel motor learning protocol:

Hypothesis I: TMS applied to the left dPMC during force-field reaching will have an effect on behavioural responses, demonstrating that this region is also actively involved in movement planning and preparation.

Hypothesis II: In simple reaching different TMS timings will have an effect on kinematic behaviours. This is because TMS can pre-activate the stimulated region before its typical activation begins, which as a result may speed up the onset of movements (Silvanto and Muggleton, 2008). It is unknown whether this is the case for motor adaptation, this will be therefore be explored.

Experiment 7 – Exploring the impact of SP-TMS to the right posterior parietal cortex (PPC) during right arm reaching in a novel motor learning protocol:

Hypothesis I: TMS applied to the right PPC during force-field reaching will have an effect on behavioural responses, demonstrating that this region is actively involved in movement preparation.

Hypothesis II: Although TMS may have an impact on reaching trajectories, the impact of TMS may not be detrimental at all time points of when TMS is delivered. This is because studies have shown that the right PPC is involved only in planning left handed, and not right handed reaching movements (Schluter *et al*., 2001; Oliveira *et al*., 2010).

Experiment 8 – Exploration of behavioural mechanisms of right arm reaching in a force field using single pulse TMS applied to the right dPMC:

Hypothesis I: TMS applied to the right dPMC during force-field reaching will have an effect on behavioural responses, because studies have shown that the region is densely connected to different structures in the motor circuitry (such as the prefrontal cortex and PPC) (Genon *et al*., 2017), and is therefore involved in motor reaching and planning. This study is the first attempt to describe the effect of TMS delivered to the right dPMC (at different time points) during preparation for novel reaching.

Experiment 9 – Comparing region-specific roles in the motor network during motor control and motor adaptation:

Hypothesis I: Statistical comparisons may reveal different levels of influence across different regions (quantified by summed error) thereby indicating the relative importance of specific regions in motor control and adaptation. This chapter builds a novel model for studying the motor network to demonstrate the different functional properties of cortical structures.

The general methodology implemented to study the aims and hypotheses' in this thesis are described in section 3.

Chapter 3

3 General methodology

This chapter describes the general procedures that were employed in this thesis and illustrates the apparatus used in each experiment. Although all studies employ similar apparatus (i.e. use of TMS, robotics and EMG), some experimental paradigms differ in terms of the task being carried out (e.g. force-field [FF] reaching vs. null FF reaching [FAM]) and the region of interest being stimulated with TMS. Each experimental chapter contains the methodological protocol that was specifically designed for the different tested hypotheses.

3.1 Ethics

All the procedures in this thesis were approved by the University Research Ethics Committee (UREC 1516_108, Appendix 1) and conducted according to the Declaration of Helsinki (World Medical Association, 2013). The approval of the research was issued to the researcher (Pegah Mohajer Shojaii), the principle investigator (Professor Duncan Turner) and the research site (University of East London - NeuroRehabilitation Unit). Before each experiment was conducted, participants were verbally instructed regarding the aims of the project.

In all experiments, the participants also received:

1) A participant information sheet outlining the details of the experimental protocol (Appendix 2)
2) A consent form to participate in a study involving the use of human participants (Appendix 2).
3) A medical questionnaire to complete – in order to ensure that TMS is a safe procedure for them to undergo (i.e. they do not have any metal or electrical implants) (Appendix 3).
4) The researchers' contact details, including an e-mail address – if they wish to obtain further details about the study, their performance, or their data/results (Appendix 1).

Participants were also made aware that they were free to withdraw from the experiment at any given time and were also welcome to discuss their thoughts and feelings with regards to their participation in the research.

3.2 Participants

Participant recruitment took place through online advertising (call for participants recruitment website – https://www.callforparticipants.com/), through emails and leaflets and 12-15 healthy young adults were recruited per experiment. The sample size selected was based on, 1) established methods used in the NeuroRehabilitation Unit, 2) similar studies that have been published (Hunter *et al*., 2009; Hunter, Sacco and Turner, 2011), 3) taking into account the variation of M1 excitability in healthy young adults, and 4) non-learning which can occur in motor adaptation paradigms (Pizzamiglio *et al*., 2017b). For example, we anticipated that one or two subjects per hypothesis will:

a) Not perform reaching correctly (i.e. their reaching movements would either be too fast or too slow)
b) They would not learn very well (i.e. more than 2 standard deviations away from the average learning rate)
c) They may not exhibit significant MEPs in the muscles of interest (biceps brachii).

Furthermore, only right handed participants were recruited and only the dominant hand was investigated. This is due to different brain responses in the dominant and non-dominant brain hemispheres (Haaland and Harington, 1996). The inclusion and exclusion criteria for participant recruitment are further illustrated in table 3.1.

Throughout this thesis TMS was used to target seven regions in the motor network, and the participant demographics with regards to each experiment is outlined in table 3.2. It should be noted that once all of the experiments were complete, the next experimental approach that was taken aimed to explore the importance and contribution of different cortical regions in motor control and motor adaptation. In order to investigate this, all of the experimental data (chapters 4 – 11) were pooled together and synthesised. This then formed the outline for chapter 12 in this thesis.

Table 3.1: Inclusion and exclusion criteria for participation

Category:	**Inclusion criteria:**	**Exclusion criteria:**
Participant health:	Healthy participants	History of neurological or psychiatric conditions Neuromuscular disease
Age range:	Young adults aged > 18	Aged <18 and >40
Handedness:	Right handed	Left handed
TMS safety guidelines:	No metal or electrical implants	Metal or electrical implants

Table 3.2: Participant demographics and experimental details for each region targeted in this thesis

	Experiment 1 (Chapter 4):	Experiment 2 (Chapter 5):	Experiment 3 (Chapter 6):	Experiment 4 (Chapter 7):	Experiment 5 (Chapter 8):	Experiment 6 (Chapter 9):	Experiment 7 (Chapter 10):	Experiment 8 (Chapter 11):	Chapter 12:
Ethical approval/ participants health:	Following ethical approval from the University of East London Research Ethics Committee (Appendix 1), all of the participants for each study met the inclusion criteria and had no personal or family history of neurological/psychiatric conditions, no neuromuscular disease and no metal/electrical implants (based on Appendix 3) and gave their written consent to participate (Appendix 2). All aspects of each study were conducted in accordance with the Declaration of Helsinki (World Medical Association, 2013).								
Age range (mean, +/- SEM):	21 - 32 (26, +/- 1)	18 – 37 (26, +/- 1)	20 – 32 (26, +/- 1)	20 – 32 (26, +/- 1)	18 – 32 (24, +/- 1)	18 – 32 (24, +/- 1)	18 – 32 (23, +/- 1)	18 – 32 (23, +/- 1)	18 – 37 (25, +/- 1)
Gender:	5 male; 8 female	Prior to data exclusion: 9 male: 7 female Following data exclusion: 8 male: 6 female	5 male: 9 female	5 male: 9 female	3 male: 10 female	3 male: 10 female	3 male: 10 female	3 male: 10 female	30 male: 64 female
Number of participants excluded and reasons for exclusion:	N/A (no participants were excluded)	Data from two subjects were excluded due to non-learning in the motor adaptation paradigm.	N/A (no participants were excluded)	N/A (no participants were excluded)	N/A (no participants were excluded)	N/A (no participants were excluded)	N/A (no participants were excluded)	N/A (no participants were excluded)	N/A (no participants were excluded)
Number of participants (N):	13	14 following data exclusion	14	14	13	13	13	13	94
Mean stimulus intensity (i.e. at 110% RMT)	56%	56%	57%	57%	56%	57%	55%	56%	

3.3 Transcranial magnetic stimulation

3.3.1 Electromyography (EMG) recordings for MEPs:

Overall electrical signal and activity that is generated from muscles can be recorded either invasively or non-invasively using EMG (Mills, 2005; Chowdhury *et al*., 2013). Invasive methods require the use of needle electrodes that are fit into the muscle(s) to capture the activity of muscle-fibres from a single unit (Chowdhury *et al*., 2013). Non-invasive methods on the other hand, employ the use of surface electrodes that are positioned onto the muscle(s) of interest and the signal recorded is based on overall motor-unit activity (Chowdhury *et al*., 2013). MEP responses in TMS research have commonly been recorded as a signal with surface EMG electrodes (Hunter, Sacco and Turner, 2011; Orban de Xivry *et al*., 2013; Summers, Chen, Kimberley, 2017).

The use of surface EMG to record MEPs have helped demonstrate patho-physiological responses in clinical populations, which have been found to differ when compared to responses from healthy controls. For example, Brum, Cabib and Valls-Sole (2015) recorded MEPs from the first dorsal interosseous (FDI) muscle with EMG surface electrodes in stroke patients and they found a significant decrease in peak-to-peak MEP amplitude among patients compared to healthy subjects. Additionally, MEPs from the FDI muscle in patients with multiple sclerosis (MS) were found to have a longer duration compared to a healthy control group (Kukowski, 1993; Brum, Cabib and Valls-Sole, 2015). Therefore, surface EMG recordings have been used to characterise differences in MEP responses and this has helped provide further information regarding patho-physiological mechanisms in different clinical populations (Chowdhury *et al*., 2013; Fernandez *et al*., 2013).

In this thesis, surface EMG was used to record MEP signals (EMG, mV) using Signal Software Version 6 (Cambridge Electronic Design LTD, Cambridge UK). For experiments 1 and 2, MEPs were only recorded as a signal for the duration of the experiment when TMS was delivered to the contralateral M1 in order to explore corticospinal excitability (CSE) responses during right arm reaching. For experiments 3 (left PPC TMS), 4 (SMA TMS), 6 (left dPMC TMS), 7 (right PPC TMS) and 8 (right dPMC TMS), MEPs were not elicited during stimulation. For experiment 5, MEPs were not collected as kinematics of right arm reaching was of interest. However, one of the

steps of the TMS protocol was to identify the participants resting motor threshold (RMT) (left M1) to deliver TMS to the region of interest at 110% of their RMT. Therefore, MEP responses were only acquired and recorded during the assessment of RMT for those studies. With regards to experiment 5, the right M1 was targeted to identify resting motor threshold (RMT) by measuring MEPs from the left arm. The TMS protocol for this experimental set-up was different compared to the other experiments within this thesis (except for experiment 1 and experiment 2) whereby the left M1 was targeted and MEPs were elicited from the right arm to identify RMT. Targeting the right M1 in experiment 5 helped ensure that an appropriate stimulation intensity was used for each participant during TMS when considering that motor thresholds can fluctuate and differences in RMT have been identified between the left M1 and right M1 (Alm *et al*., 2013; Karabanov, Raffin and Siebner, 2015). Paired-pulse TMS studies that have targeted both the right and left M1 have also used similar protocols to separately identify hemispheric motor thresholds between the two regions prior to stimulation (Morishita *et al*., 2014). Overall, the data for experiment 3 – 8 were based on kinematics only and not MEPs.

Where MEPs were obtained, the EMG signal was amplified (1000x; 1902 amplifier; Power 1401, CED LTD, UK), band-pass filtered (45 Hz high pass, 1kHz low pass) and a notch filter was applied (50Hz). The data were digitised at 5kHz (Micro 1401; Cambridge Electronic Design LTD, Cambridge UK). MEPs were always recorded with two disposable solid gel surface electrodes (Unimed Electrode Supplies LTD, Surrey, UK) positioned 1.5 centimetres apart (SENIAM [Surface Electromyography for the Non-invasive Assessment of Muscles] guidelines; Hermens *et al*., 2000) along the muscle fibre direction of the right-sided biceps brachii (BB), triceps brachii (TB), extensor carpi radialis (ECR) and flexor carpi radialis (FCR) muscles. A ground electrode was also placed over the ulna styloid process bone (where the ulna joins the wrist) on the left arm.

These muscles have been studied in motor reaching paradigms, as they have been reported to be involved in horizontal planar reaching (Hunter, Sacco and Turner, 2011; Orban de Xivry *et al*., 2013). For example, the BB is not only a rotator of the forearm muscles, but it is also an elbow flexor (which is essential for reaching outwards) (de Bruin *et al*., 2011; Landin, Thompson and Jackson, 2017) and the TB is known to be involved in elbow extension and straightening the arm (O'Driscoll, 1992; Singh and

Pooley, 2002). The FCR plays a role in opposing a clockwise force (i.e. during motor adaptation) (Pizzamiglio *et al*., 2017b) and is a wrist flexor muscle, while the ECR is known to be a wrist extension muscle.

These muscles are graphically illustrated in figure 3.1 (figure adapted from Learn Muscles: https://learnmuscles.com/wp-content/uploads/2016/12/Wrist-Sp-St-Blog-Post-Photo-1.jpg).

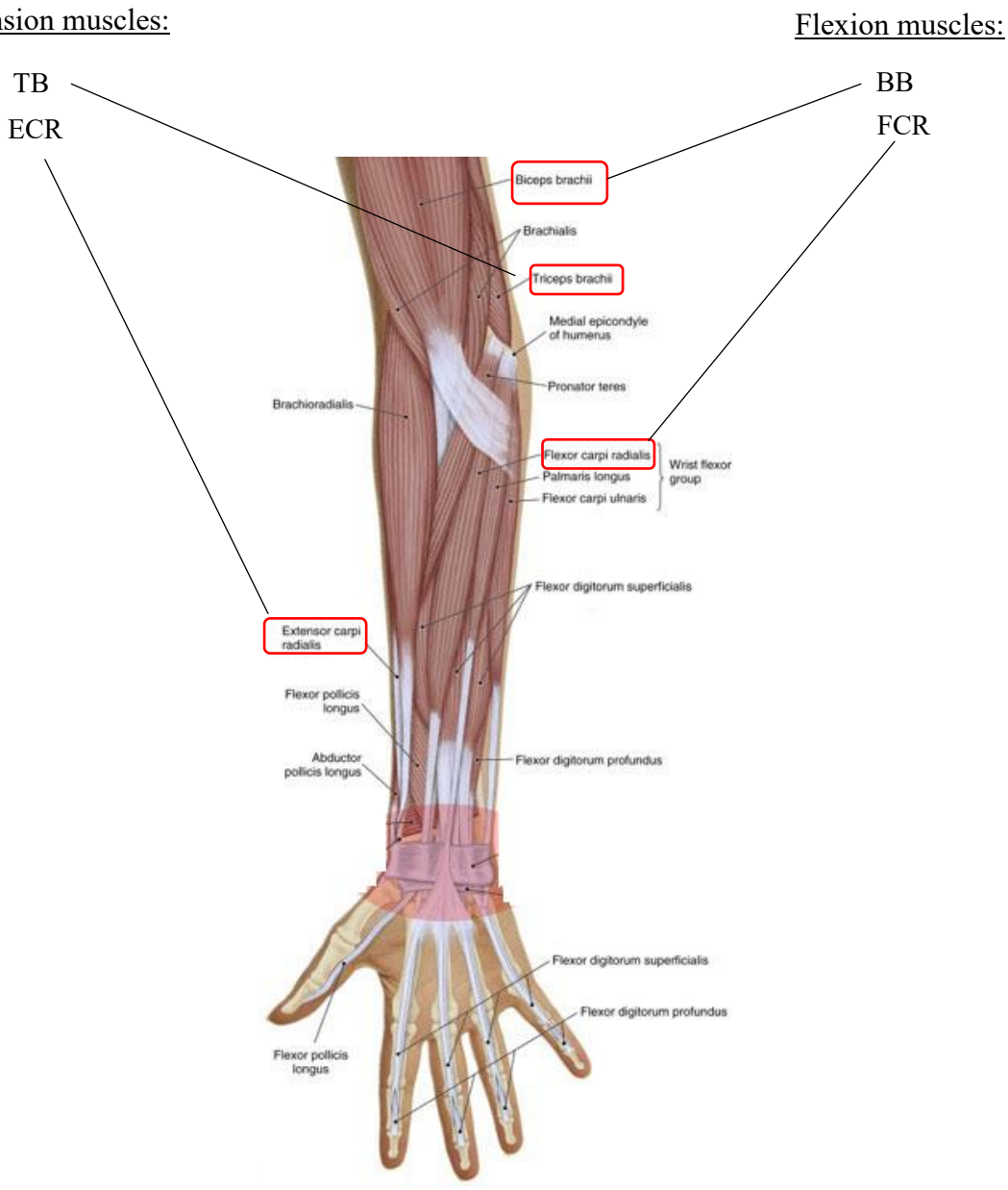


Figure 3.1: Muscles of interest chosen for electrode placement (outlined in red)

Muscles including those involved in extension (TB and ECR) and flexion (BB and FCR) are illustrated. The BB consists of a short head and long head within the shoulder region, which both connect at the elbow, the BB also connects to the ECR. The TB is comprised of different structures, including a long head and medial head which originate at the mid-section of the humerus (Watson and Wilson, 2007; Landin, Thompson and Jackson, 2017). These were the four muscles of interest in this thesis. Figure adapted from Learn Muscles: https://learnmuscles.com/wp-content/uploads/2016/12/Wrist-Sp-St-Blog-Post-Photo-1.jpg.

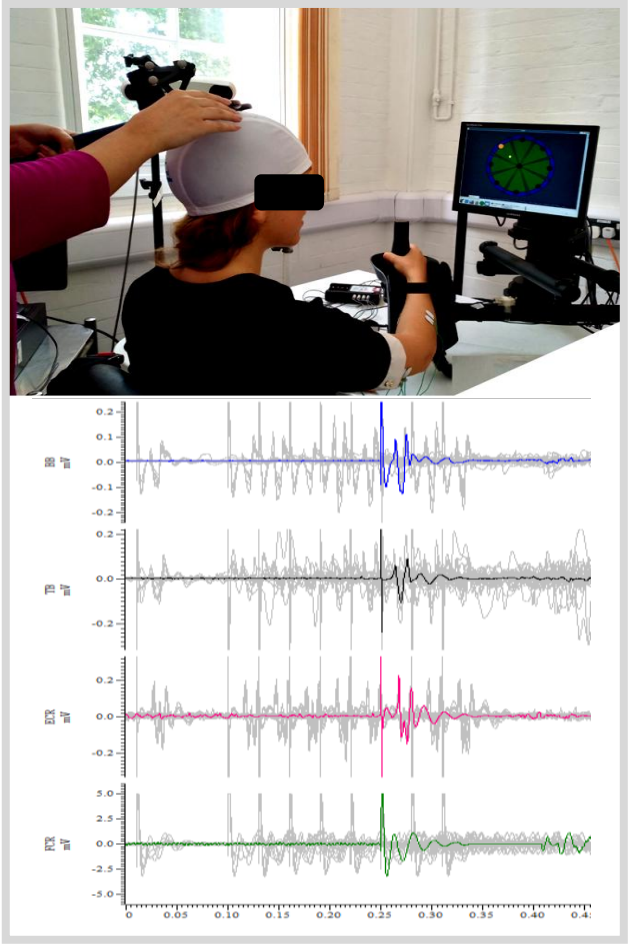


Figure 3.2: Visualisation of surface EMG recordings of MEPs

TMS applied to the left M1 during motor reaching (top panel) and data collected in Signal Version 6 and CED data acquisition software (Cambridge Electronic Design LTD, Cambridge UK) (second panel). Examples of MEP data from one specific TMS pulse time (250ms) are shown in the coloured traces. Each channel on the left-hand side of the bottom panel is associated with one muscle (blue for BB, black for TB, pink for ECR and green for FCR). The grey activity in the background represents overall EMG from each reaching trial and has been overlapped to illustrate the degree of muscle activity during a reaching trial. This raw data trace also illustrates the formal description of the preparation phase of reaching and the chosen timing at which TMS was delivered. Zero on X-axis represents the time (sec) of the visual cue to reach and the Y-axis represents elicited (by TMS) and ongoing muscle activity (mV) during the trial.

3.3.2 TMS Protocol:

In all experiments, TMS was delivered with a figure of eight coil connected to a Magstim Stimulator 200² (Magstim Company, Whitland, UK). The stimulator was triggered by a custom-built programme using Signal Version 6 and CED data acquisition software (Cambridge Electronic Design LTD, Cambridge, UK). Participants also wore a washable flat cap for the duration of the experiment, to mark the regions of interest that were stimulated, depending on the hypothesis being studied (left or right M1; left or right posterior parietal cortex, PPC; the supplementary motor area, SMA; left or right dorsolateral premotor cortex, PMC).

The TMS testing procedure always began with the coil being positioned above the scalp on the participant's left M1 to locate their motor 'hotspot' for the right-sided BB muscle. The area of the M1 stimulated for this was the upper arm representation which is approximately 4cm lateral to the top of head (vertex). To determine the optimal coil position for evoking MEPs in the right BB muscle, TMS was applied in 1cm steps around the upper limb region, with the coil handle positioned backwards and angled 45° away from the midsagittal line. The direction of the TMS induced current was posterior-anterior (PA). This coil position, and current flow has consistently been identified as the optimal position when targeting the BB, as well as other muscles, such as the first dorsal interossei (FDI) (Abdalla, 2011; Mills, Boniface and Schubert, 1992).

Once the hotspot was located and coil position was determined, it was marked with a washable pen on the participant's cap. This was to ensure consistent coil position for the duration of the experiment. In all experiments, resting motor threshold (RMT) was defined as the minimum intensity that induced MEPs ≥ to 50 μV peak to peak in the BB muscle (hotspot) in 5/10 trials (Hunter, Sacco and Turner, 2011; Rossi *et al*., 2009).

It should be noted that in all experiments, single pulse TMS (SP-TMS) was applied at 110% of RMT in all TMS reaching blocks (FAM, FF and WO) at a range of specific times after the visual cue (10ms, 100ms, 130ms, 160ms, 190ms, 220ms, 250ms, 280ms and 310ms) during the preparation phase of a reach - this is at a time after the visual cue to reach and before the actual onset of the physical reach. It should also be noted that for each experiment, 20 single pulses at rest (with the right arm relaxed in the robotic arm) was obtained from each participant before they began the motor reaching tasks. For all experiments, the time points at which a TMS pulse was delivered during a trial of

reaching was randomly selected through a custom built program using Signal Version 6 and CED data acquisition software (Cambridge Electronic Design LTD, Cambridge, UK).

3.3.2.1 Cortical targeting with TMS:

The participants in this experiment did not have individual structural MRI scans, therefore an electroencephalography (EEG) cap was used to locate the different regions that were targeted with TMS. An EEG cap contains various electrodes which correspond to different cortical regions (Herwig, Satrapi and Schönfeldt-Lecuona, 2003). The use of EEG to locate cortical regions for brain stimulation with TMS methods have consistently been employed (Herwig, Satrapi and Schönfeldt-Lecuona, 2003; Schutter and van Honk, 2006; Beam et al., 2009).

For the experiments in this thesis that had no physiological experimental output (i.e. an MEP) (experiment 3, 4, 6, 7 and 8) a 10-20 systems EEG cap (64 channels) (ANT Neuro, Enschede, Netherlands) was fitted on top of a washable flat cap that participants wore. Following cap placement two measurements were taken with the Cz electrode (which overlies the vertex) as the common reference point to locate the mid-sagittal plane of the skull. The first measurement that was marked was 50% of the distance between the nasion and the inion (this corresponded to the Cz electrode). A second measurement was then taken to confirm the location of the Cz electrode and this was taken from the left ear, to the right area (two pre-auricular points - 50% of the distance between the two). These landmark measurements individualised the electrode positions for each participant. The electrode position of interest (depending on the experiment that was being conducted at the time) was then marked with a pen through the EEG cap to the flat cap that the participants wore. The EEG cap was then removed and the inner markings of the electrode position for stimulation remained on the flat cap that the participants wore. It should be noted that when EEG cap was removed, the flat cap was not adjusted or shifted as it was tightly fitted on the subjects head and this helped further ensure the accuracy of cortical targeting during stimulation.

3.3.2.2 Cortical targeting of regions without an experimental output and coil positions employed:

Regions of interest that had no measured output (i.e. an MEP; left PPC, SMA, left dPMC, right PPC and left dPMC) were located using an EEG cap (10-20 system; ANT

Neuro, Enschede, Netherlands) once measurements were taken with the Cz electrode as the reference point for the mid-sagittal plane of the skull (section 3.3.2.1). It is also important to consider the different types of coil positions and orientations that can be used to assure that the behavioural responses that occur is due to the stimulation of the targeted area, rather than its surrounding cortical regions. It has been argued that employing one stimulation intensity across participants could result in differences in task responses, this is because the effects of stimulation could either be too much, or too little for each participant (Bolognini and Ro, 2010). Researchers have therefore reported that when targeting regions with no experimental output TMS intensity should be set individually for each participant through functional measures, such as resting motor threshold for an MEP obtained in left M1 (Bolognini and Ro, 2010). The following paragraphs below outline: 1) the electrode position selected for the different regions of interest and 2) the optimal TMS coil position that was used across stimulated sites.

3.3.2.2.1 Left PPC location and coil position:

For experiment 3, the P3 electrode location was used for left PPC stimulation. It has been reported that P3 corresponds to the left PPC with very little variation across participants (< 2cm) (Herwig, Satrapi and Schönfeldt-Lecuona, 2003). Various TMS studies that have employed EEG methods for location purposes have also used the P3 electrode for left PPC stimulation (Pourtois *et al*., 2001; Salatino *et al*., 2014; Parks *et al*., 2015). Additionally, the coil was positioned at an angle that was tangential and perpendicular to the midline, with the handle pointing sideways. Therefore, the current flow was in a lateral-medial direction. The coil position and orientation used for left PPC stimulation was based on the protocol of Della-Maggiore *et al*., (2004).

3.3.2.2.2 SMA location and coil position:

With regards to experiment 4, it has been reported that the SMA is located 3cm anterior to the vertex and 0.5cm to the left, which corresponds to the FCz EEG electrode (Cunnington *et al*., 1996; Oliveri *et al*., 2003). This area was therefore marked for stimulation and the coil was positioned tangentially to the skull with the handle pointing to the right (based on Cona et al., 2017 protocol for SMA stimulation).

3.3.2.2.3 Left dPMC location and coil position:

The left dPMC was targeted in experiment 6 and was located as 2cm anterior and 1cm medial to the left M1 motor hotspot with the coil angled at 45° with respect to the

interhemispheric fissure (handle backwards) as this has commonly been used in TMS paradigms (Fink et al., 1997; Münchau *et al*., 2002; Lee and Van Donkelaar, 2006; Zanon et al., 2013; Lega et al., 2016).

3.3.2.2.4 Right PPC location and coil position:

For experiment 7 in this thesis, the P4 electrode was marked for stimulation because it has been argued to correspond to the right PPC (Herwig, Satrapi and Schönfeldt-Lecuona, 2003; Prime, Versia and Crawford, 2008; Koch *et al*., 2009; Vernet, Yang and Kapoula, 2011). Additionally, the coil handle was positioned backwards (angled 45° to the midline) to induce a posterior-anterior current (Prime, Versia and Crawford, 2008; Koch *et al*., 2009; Vernet, Yang and Kapoula 2011; Salatino *et al*., 2014).

3.3.2.2.5 Right dPMC location and coil position:

The final experiment in this thesis was based on targeting the right dPMC, this region was located as 2 - 2.5cm anterior and 1cm medial to the motor hotspot and the coil was angled 45° from the midline (handle backwards and downwards) (Cincotta *et al*., 2004; Bestmann et al., 2005; Murase *et al*., 2005; Ruitenberg *et al*., 2014).

Figure 3.3 illustrates specific EEG locations for the stimulated regions and the different coil positions that were used (and electrical current that was induced) for each stimulated site (canonical brain figures adapted from an MRIcron template – Rorden and Brett, 2000).

3.3.2.3 Ensuring accurate targeting:

Researchers have reported the importance of accurate coil positioning during stimulation and different methods have been employed to ensure this, including TMS coil holders and neuronavigation (Chronicle, Pearson and Matthews, 2005; de Goede, Braack and van Putten, 2018). With regards to coil holders, Chronicle, Pearson and Matthews (2005) explored the precision, stability and durability of this method during M1 stimulation and their findings illustrated accuracy across different testing sessions. Automated robotic coil holders have also been used during stimulation and they have been argued to provide increased stability which has been reported to be particularly useful for longer experimental protocols and rTMS paradigms (Goetz *et al*., 2019). Coil apparatus for positioning purposes have also been useful during multimodal MRI-TMS imaging studies and have provided clinicians with a compatible way to accurately explore human behaviour (Navarro de Lara *et al*., 2015). On the other hand, there are

limitations to consider. For example, Goetz *et al*., (2019) reported the absence of manual adjustments, as well as the lack of coil pressure feedback during stimulation. Despite these shortfalls, coil holders have been reported to be both an effective and reliable method for improving TMS coil accuracy (Sparing *et al*., 2008; Rodseth, WashaBaugh and Krishnan 2017),

Neuronavigation methods have also been implemented in TMS protocols for: 1) marking anatomical regions and, 2) to ensure accurate coil positioning during stimulation. Neuronavigation functions via mapping out various physical landmarks on the subject, such as their cranium, ears and nasion. Following this, the system registers the TMS coil for the navigation of cortical structures (Sparing, Hesse and Fink, 2010). Neuronavigation methods take coil orientation in both space and time into account, which helps minimise any structural inaccuracies that may occur during stimulation (Sparing, Hesse and Fink, 2010). However, de Geode *et al*., (2018) argued that research is yet to confirm the significant impact of neuronavigation with regards to coil orientation for SP and PP TMS protocols.

For each experiment in this thesis, the coil was positioned and held manually on the region of interest on the participants scalp. This free-hand method does have limitations that should be considered, particularly when taking into account that increased accuracy has been reported with the use of coil positioning equipment, and that manual coil holding has been associated with operator fatigue (Goetz *et al.,* 2019). For location marking, an EEG 10/20 system method was used rather than neuronavigation and this is because the participants in each study did not have a structural MRI scan that could have been imported into the neuronavigation system. Furthermore, the use of neuronavigation for accurate coil positioning would have increased the duration of the reaching protocol (from 2 hours 30 minutes, to three hours) (this was tested in a pilot study) which could have been arduous for the participant during motor reaching. Despite coil position being determined manually, it should be considered that participant's head movements were minimised because the reaching protocol only required arm motions, additionally seatbelt straps were attached to the participants (section 3.4.1) to avoid trunk movements that may have occurred during reaching. Furthermore, there was manual control of the TMS coil, therefore, compensations for any head motions that did take place were taken into account. In addition to this, continuous attention was given to the coil position during the experimental protocol to

ensure precise coil placement and orientation, which has been argued to be important for TMS protocols that use manual methods for stimulation (Goetz *et al*., 2019). Nonetheless, the use of manual methods still remains a limitation that should be considered, and if this experiment was to be replicated it would be important to implement techniques that aid coil accuracy, including neuronavigation or automated coil holders (Sparing, Hesse and Fink, 2010; Goetz *et al*., 2019).

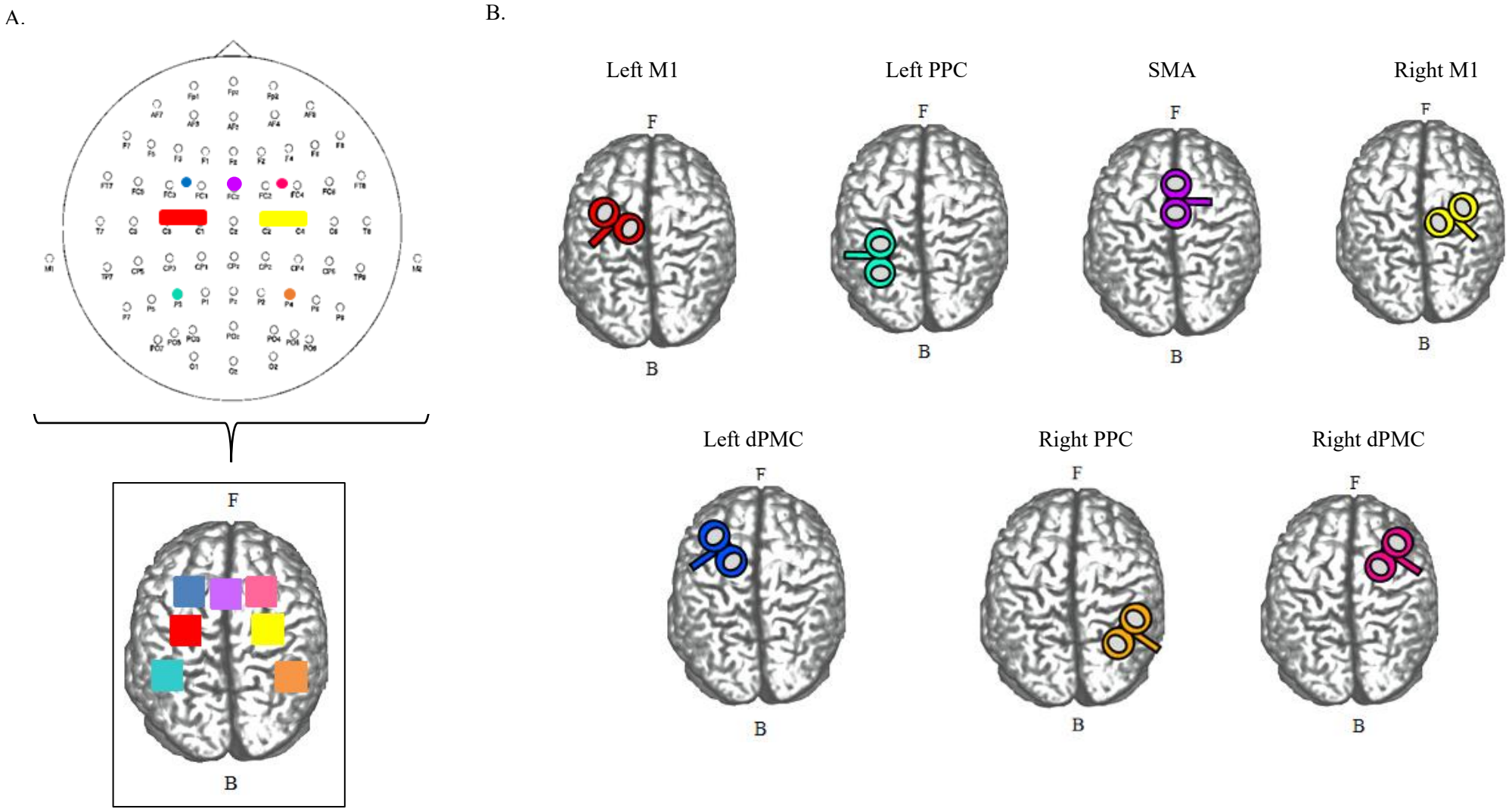


Figure 3.1: EEG locations for stimulated regions and optimal coil positions for the different locations targeted with TMS

(A) The different locations of the stimulated areas with reference to a 64-channel EEG cap is demonstrated (ANT Neuro, Entschede, Netherlands) (figure adapted from www.ant-neuro.com). The outlined figure below figure 3.3A illustrates a canonical model of all of the regions targeted with TMS (canonical brain figure adapted from an MRIcron template – Rorden and Brett, 2000).

(B) The coil positions for the various cortical regions targeted with TMS are illustrated. This includes an induced posterior-anterior current flow for the M1 and dPMC (both left and right hemispheres). For the left PPC, but not for right PPC stimulation, a lateral-medial current flow was induced. For SMA stimulation, the coil was positioned tangentially to the skull (handle to the right) (canonical brain figures adapted from an MRIcron template – Rorden and Brett, 2000).

3.4 Robotics

In all experiments, an interactive robot was used for motor reaching (MIT - Manus, Interactive Motion Technologies, Cambridge, MA, USA). The robot functioned via Linux software and also contained encoders which recorded different angular positions of the robotic manipulandum. There are different modes in which the robot could be used, this includes:

1. Assistive mode - this has been employed is rehabilitation programmes whereby the robot assists movements for motor output and different degrees of assistance can be provided (Patton *et al*., 2006).

2. Resistive mode - this has been used in motor adaptation paradigms, where subjects are required to counter a force-produced in order to perform a reach with an ideal trajectory (Pizzamiglio *et al*., 2017a; Pizzamiglio *et al*., 2017b).

3. Non-assistive mode - In this mode there is no assistance or resistance elicited by the robot during reaching.

The use of robotics in assistive and resistive forms has commonly been employed in motor reaching and adaptation in both healthy and clinical populations (Patton *et al*., 2006; Hunter, Sacco and Turner, 2011; Orban de Xivry *et al*., 2013). Clinically, Patton *et al*., (2006) noted that a resistive, rather than assistive mode led to enhanced therapeutic outcomes among stroke patients. They reported that in contrast to assistive reaching, reaching in a resistive mode, resulted in larger errors by which the patients were able to make significant improvements on. This demonstrates the importance of error-induced reaching through FF paradigms as a key model for motor recovery (Patton *et al*., 2006).

3.4.1 Reaching task: motor reaching and motor adaptation:

In this thesis the reaching task that subjects performed differed between experimental protocols:

1) Experiment 1 (chapter 3):

This motor task was performed in the non-assistive mode of robot operation as unperturbed (no force field present) reaching was explored. Therefore no robotic assistance or resistance was elicited during reaching. Participants were instructed to make outward arm reaching movements towards a north-west target (135°) from a

central starting position (15cm reach) within a target time of 1.0 - 1.2 seconds following the onset of a visual cue. Visual feedback for the timing of the reaches was shown on the screen (Section 3.4.2 describes further details regarding feedback). When participants reached towards the target and held their arm position, the robotic arm re-positioned the participants arm into the central starting point for the next reaching trial. The reaching protocol for this experiment contained two blocks of unperturbed reaching with no TMS (N = 24 trials per block), followed by 3 blocks of unperturbed reaching with TMS trials to the contralateral M1 (N = 48 x 3 trials total). Participants then had a break (5 minutes). The same protocol was then followed, however the ipsilateral M1 was stimulated. In all stimulation trials, SP-TMS was delivered at nine different time points (10 - 310ms) (randomly) during the preparation phase of motor reaching, at 110% resting motor threshold.

A graphical illustration of the paradigm for experiment 1 is demonstrated in figure 3.4.

2) Experiments 2-8 (chapters 4 -11):

Motor adaptation was introduced into the reaching protocols for experiments 2-8 and the robot was used in a resistive mode. In these experiments familiarisation (FAM), force field (FF) and washout (WO) reaching conditions were explored. The robot was set to a non-assistive mode (i.e. unperturbed reaching) for FAM and WO reaching, and a resistive mode for FF reaching. During resistive FF reaching, the robot administered a velocity dependent clockwise force field (25 N ms^{-1}). In all reaching trials, participants were instructed to make outward arm reaching movements (away from the body) towards a north-west target (135°), from a central starting position (15cm reach) following the onset of a visual cue.

The experimental paradigm that was implemented for experiment 2 - 8 is shown in figure 3.5.

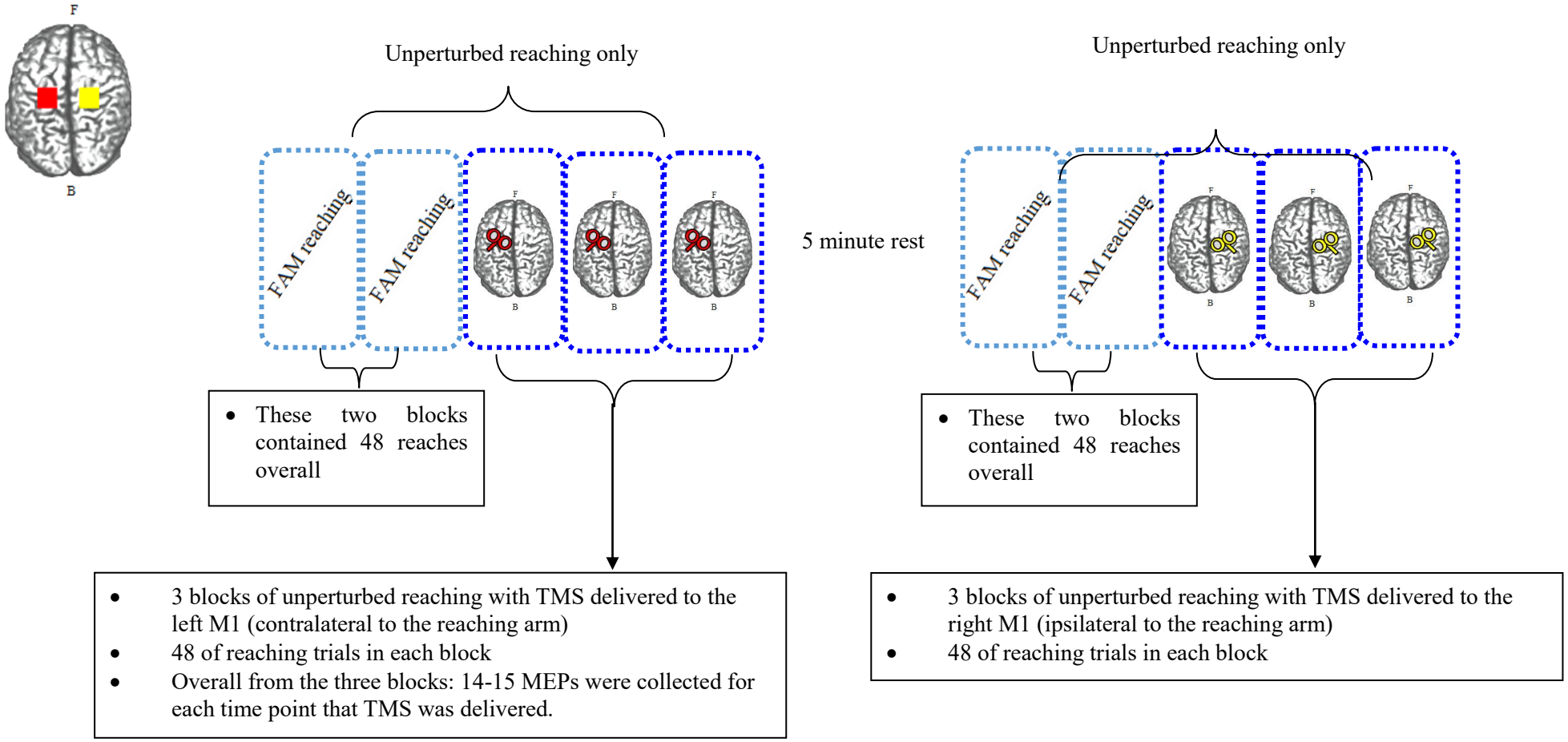


Figure 3.4: Graphical illustration of the paradigm implemented for experiment 1

The protocol for experiment 1 included two blocks of unperturbed reaching with no TMS, this was for the participants to familiarise themselves with the reaching task. TMS was then introduced (three blocks of unperturbed reaching) and single-pulses were delivered on the participant's left M1at a range of different times (10-310ms) to capture changes in M1 cortical excitability during the preparation of a reach. Following this, participants took a 5 minute break. The same protocol was undertaken, however with TMS delivered to the right M1 (canonical brain figures adapted from an MRIcron template – Rorden and Brett, 2000).

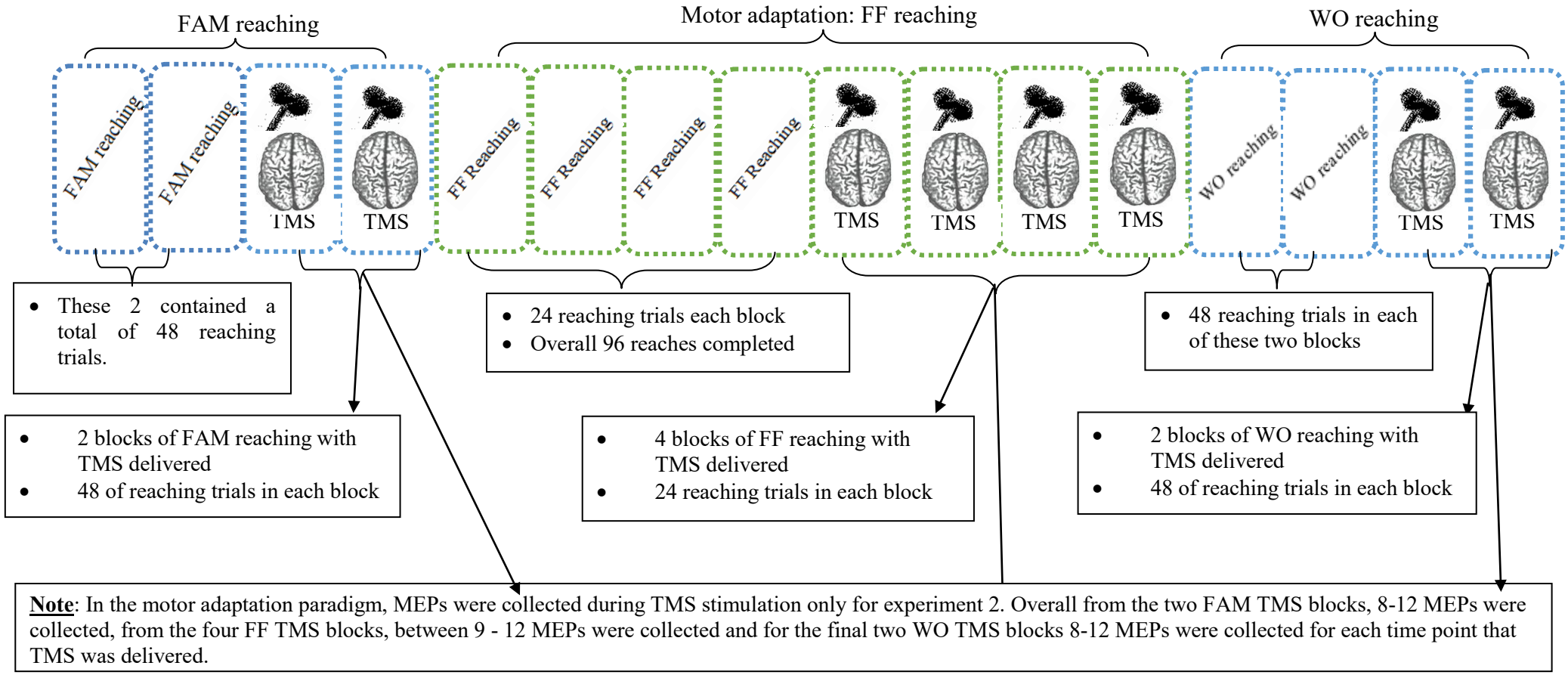


Figure 3.5: Graphical illustration of the reaching paradigm implemented for experiments 2 – 8:

The paradigm for experiments 2 – 8 included single-pulse TMS delivered to specific regions of the motor network. The area that was targeted with TMS depended on the experiment that was being conducted at the time (e.g. experiment 2, left m1 TMS; experiment 3, left PPC TMS; experiment 4, SMA TMS; experiment 5, right M1 TMS; experiment 6; left dPMC TMS; experiment 7; right PPC TMS and experiment 8, right dPMC TMS). TMS was delivered at a range of specific times to explore cortical excitability (specifically for experiment 2) and behavioural factors (for all experiments) during movement preparation. The motor paradigm consisted of different phases of reaching including, FAM reaching - firstly without TMS [2 blocks], and then with TMS delivery [2 blocks]. Following FAM blocks of reaching, motor adaptation was introduced, with FF blocks of reaching, firstly without TMS [4 blocks], and then with TMS [4 blocks]. The final 4 blocks at the end of the protocol acted as WO blocks, with 2 blocks of without TMS and a further 2 blocks with TMS (Canonical brain figures adapted from an MRIcron template – Rorden and Brett, 2000).

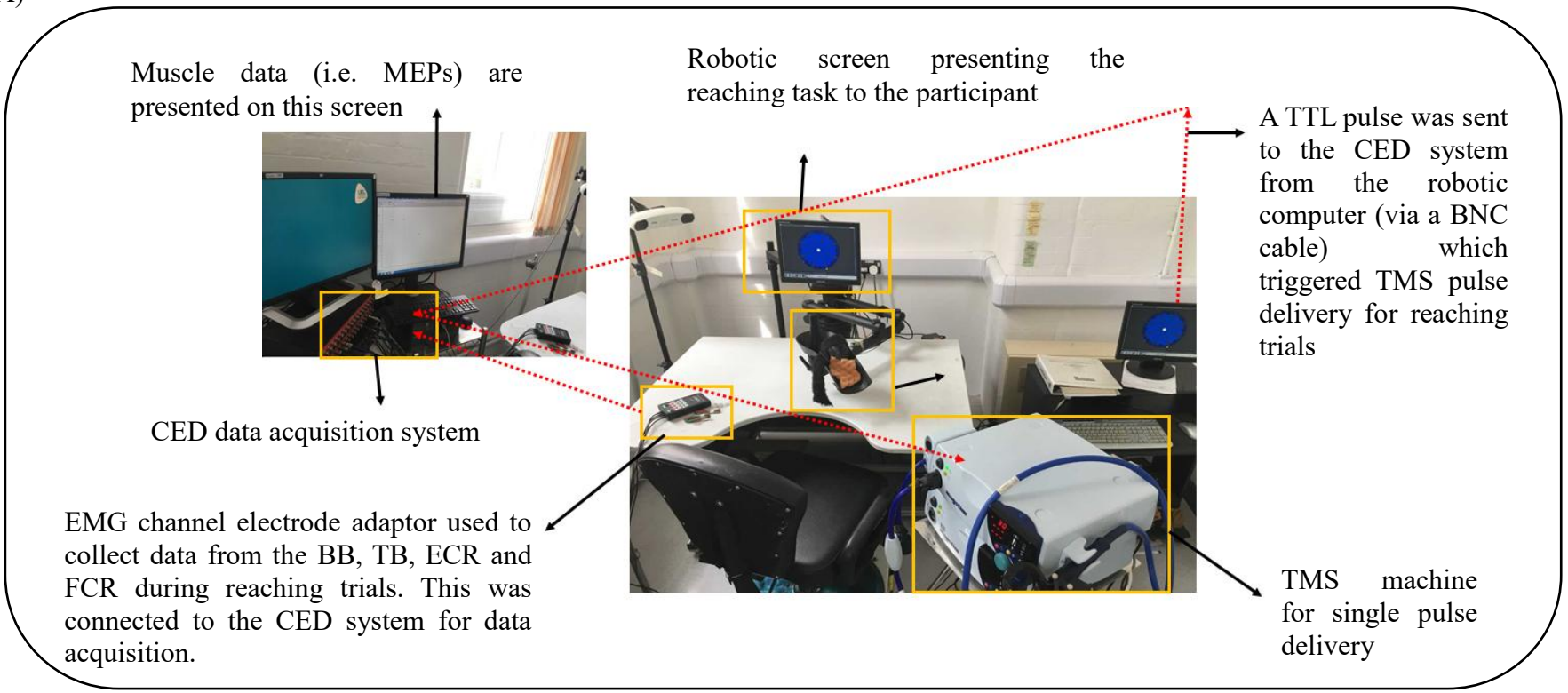
3.4.2 Reaching task set up and instructions:

Although experimental protocols differed for location of TMS (as outlined in section 3.3.2) the experimental set up was the same and instructions were only different when explaining the motor adaptation protocol. In all experiments, participants were seated in a customised chair in front of the robotic visual screen with their right arm rested in the robotic arm for support against gravity during reaching. The robotic arm contained an end-effector handle that the participants were asked to hold during reaching. Shoulder straps connected to the customised chair were attached to the participant to restrict trunk movement, particularly during motor adaptation (a common factor implemented in robotic motor adaptation paradigms - Hunter, Sacco and Turner, 2011; Pizzamiglio *et al*., 2017b).

A number of measurements were also made to ensure that the arm was semi-pronated at a 70° shoulder extension and with 120° elbow flexion (Hunter, Sacco and Turner, 2011). Additional measurements included making sure that the participants shoulder and end-effector handle were at an equal height. A vertical screen was attached to the robot and positioned at the participant's eye-level. This presented both: a) visual cues for the reach, and b) online feedback of their arm position during each reach (Pizzamiglio *et al*., 2017b). In all motor tasks, participants made outward arm reaching movements from the central starting point towards a north-west direction target (135°) within a 1.0 – 1.2 second time frame, following the onset of a visual cue (target was highlighted in an orange colour). After each single reaching trial, the robotic arm was automatically re-positioned into the central starting target, for the next reaching trial to take place.

A graphical illustration of the lab set up and robot reaching task is shown in figure 3.6A and 3.6B.

A)



B)

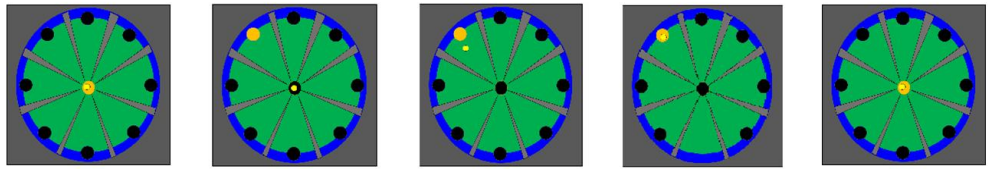


Figure 3.6: Experimental set up and reaching task

The experimental set up is demonstrated with the main equipment outlined in yellow (EMG channel electrode adaptor, CED data acquisition system, the TMS machine and the robotic system [screen and robotic arm]. The different connections between systems are shown in the red dotted line, including the links between the TMS machine, robotic computer and CED system, and the EMG adaptor box and the CED system. (B) The motor reaching task has a number of continuous components; B1. The reach begins at the central starting point; B2. An orange visual cue for a reach appears in the 135º NW target; B3. The participant reaches towards the NW target, and then remains in this target until the robotic arm automatically places their arm in the central starting position for the next reaching trial (B4-B5).

These were the oral instructions given to the participants before the start of the experiment:

1. I would like you to make linear “straight-line” reaching movements from the central starting position, to the north-west target (135º).
2. You will only have to make the reach when the target lights up in an orange colour.
3. You have a time frame of 1.0 -1.2 seconds to reach towards the target and will receive feedback for each reach you make from the screen, i.e. if you are too fast (> 1.2 seconds) or too slow (< 1.0 seconds). If you are on time (1.0 - 1.2 seconds), the feedback will be shown as "Good".
4. Once you have reached towards the north-west target, hold the position, until the robotic arm guides you back to the central starting position for the next reach to begin.
5. You may have short breaks after each reaching block if you wish to.
6. Are these instructions clear and are there any questions that you would like to ask before we begin.

When motor adaptation was introduced into the reaching paradigm, the additional instruction that the participant received was:

1. The robot will now administer a clock-wise force-field during each reaching trial. All other aspects of the reaching task will remain the same, as well as the target that you will be reaching towards (135º NW).

The reaching protocol implemented for the experiments included FAM, FF and WO blocks. When motor adaptation was not explored (experiment 1), only FAM and WO reaching was performed. However, when motor adaptation was introduced into the reaching protocol (experiments 2 – 8) a velocity dependent FF (25 N sm^{-1}) was applied during reaching. The aim of the FAM blocks was for the participants to become familiarised with the task, while the WO blocks intended to “wash-out” the effects of the FF. Each experimental chapter in this thesis describes the reaching blocks (FAM, FF and WO), and number of trials in each block for the different experiments that were undertaken.

3.5 Synchronisation

In all experiments, kinematics (from robotics) and physiological signals were synchronised via a BNC cable connected from the robot to the CED system. Before each reach (at the time of visual cue to reach at 0 seconds), the robot sent a TTL pulse to the CED system which triggered the start of a reaching trial in the Signal Software (Version 6, CED LTD, UK) for data acquisition.

3.6 Data acquisition and analysis

The data that was acquired and analysed in this thesis focused on the effects of TMS pulse administration timings (10ms, 100ms, 130ms, 160ms, 190ms, 220ms, 250ms, 280ms and 310ms) on kinematics of reaching and MEPS where expected (i.e. stimulating the left M1). Therefore the main outcome measures reported in this thesis included kinematics and MEPs.

3.6.1 Kinematics

Kinematics are different types of motion measurements that give an insight into the performance functions of limbs in different conditions (An and Chao, 1984). Kinematics of the upper limb emphasises the joint angles and position of the arm in relation to reaching in a specific direction (Soechting and Ross, 1984; Soechting, Lacquaniti and Terzuolo, 1986; Borghese, Bianchi and Lacquaniti, 1996). In this thesis, we used an end-effector robot which does not measure individual joint angles. Kinematic measures of the upper limb were investigated in this thesis to explore whether changes occurred in reaching movements during motor adaptation and also subsequent to TMS delivery.

Kinematic data was acquired by 16-bit encoders located in the robot armature (sampled at 200hz) which recorded the position of reaches made. Various kinematic parameters were measured during each reaching trial, including movement onset, movement offset, movement duration, maximum velocity, maximum force and summed error.

Kinematic parameters were all analysed offline in MatLab 2017b (The MathWorks Inc, Natick MA, USA), and were quantified as:

1. Movement onset (ms): This represents the starting time of movement and was quantified as a speed profile exceeding 0.03 ms^{-1}

2. Movement offset (ms): This represents the end movement time point and was quantified as a speed profile that was lower than 0.03 ms^{-1}

3. Movement duration (ms): This reflected the time-span of the movement (movement offset minus movement onset)

4. Maximum velocity ($m.s^{-1}$): The maximum velocity during each reach

5. Maximum force (N): The maximum amount of force produced in each reaching trial

6. Summed error: The cumulative perpendicular distance between the participant's reaching trajectory and the ideal reaching trajectory (Hunter, Sacco, Nitsche and Turner, 2009; Pizzamiglio *et al*., 2017a; Pizzamiglio *et al*., 2017b) (figure 3.7).

Summed error has been used as a measure of error in a number of motor reaching protocols (Hunter *et al*., 2009; Pizzamiglio *et al*., 2017a; Pizzamiglio *et al*., 2017b). In the reaching protocol there was an ideal linear reaching trajectory from the central starting point towards the north-west 135° target (figure 3.4). Summed error captured changes in reaching throughout the movement duration, i.e. from the start of the reach (onset) to the end of the reach (offset) (Pizzamiglio *et al*., 2017b). This measure was of particular interest in the final chapter of this thesis as the impact of TMS on different cortical regions (left and right M1, left and right PPC, the SMA, and left and right dPMC) during novel reaching was compared.

It should be noted that prior to statistical analysis, online data cleaning procedures took place automatically during reaching (via the robotic encoders). This was based on the kinematic criteria for movement onset and movement offset. For example, for single reaching trials, if movement onset values fell below 0.03 ms^{-1} and movement offset values exceeded 0.03 ms^{-1} this was noted as a missed trial. Additionally, if participants failed to reach the target this was also calculated as a missed trial. Following automated data cleaning, single trial-by-trial kinematic measures were collected and averaged for each participant in each TMS reaching block. This data was used in statistical analysis (see section 3.7) to explore whether: 1) TMS time pulses affected kinematic measures, and 2) whether the effects of TMS were condition specific.

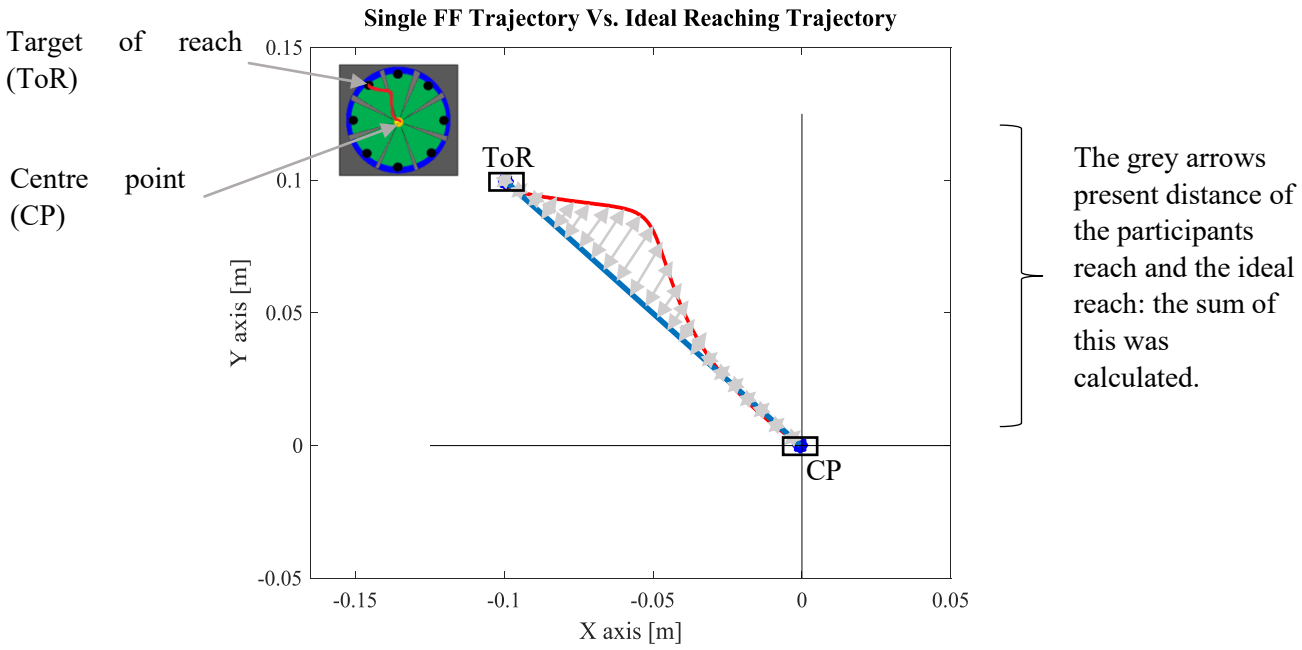


Figure 3.7: Calculation for summed error

The reach produced by one participant is shown (solid red line), as is the ideal linear reaching trajectory (solid blue line). The deviation between the two (i.e. ideal reach [blue] vs. participant's reach [red]) was calculated by summing the distance at each time point from movement onset to movement offset (Hunter et al., 2009; Pizzamiglio et al., 2017a; Pizzamiglio et al., 2017b).

3.6.2 MEPs

MEPs were obtained as a measure of corticospinal excitability (CSE) (Summers, Chen, and Kimberley, 2017) in experiment 1 and 2 (chapter 3 and 4) where TMS was delivered to the left M1. In these experiments, the MEPs evoked in muscles (BB, TB, ECR and FCR) during each reaching trial were recorded with EMG electrodes. It should be noted that quality control took place before the reaching protocol began to avoid the risk of artefacts during data collection. For example, prior to electrode placement, the muscles of interest were cleaned with alcohol wipes. This procedure has commonly been employed in TMS paradigms to reduce impendences that may arise during EMG/MEP recordings (Jubeau *et al*., 2014; Cantone et al., 2019).

Once MEPs were collected They were then quantified by calculating the peak-to-peak amplitude as this has been reported as the most common measure of CSE (Talelli, Greenwood and Rothwell 2006; Taube *et al*., 2006; Summers, Chen, Kimberley, 2017).

A custom built sampling configuration toolbox in Signal Version 6 and CED data acquisition software (Cambridge Electronic Design LTD, Cambridge, UK) was used to deliver TMS randomly at nine different time points (10ms, 100ms, 130ms, 160ms, 190ms, 220ms, 250ms, 280ms, and 310ms) during the preparation phase of reaching.

In the experiments were MEPs were elicited, a number of steps were taken to quantify the peak-to-peak amplitude. Firstly MEPs were assessed to ensure that they fell within the +15ms to +55ms time frame. The time window chosen for peak-to-peak analysis was +15ms to +55ms after the TMS pulse as this was when MEPs typically occurred (see figure 3.8). This time window has previously been used when measuring BB MEP amplitudes in motor reaching protocols (Harris-Love *et al*., 2011). If MEPs did not fall within this range, they were discarded from the analysis. Therefore, there was quality control against experimenter bias because the same protocol was used to discard data for participants. Following data cleaning procedures, an average waveform was firstly created for each time point (i.e. >5 separate MEPs from each time point were averaged to form one MEP waveform). The peak-to-peak MEP amplitude was then calculated from the resulting average waveform. All MEP analysis was performed in Signal Software version 6 (CED LTD, Cambridge, UK). The steps taken are visually presented in figure 3.8.

Individual subject differences in cortical physiology and structure can cause MEP amplitudes to vary (Kiers *et al*., 1993; Burke *et al*., 1995; Thickbroom, Byrnes and

Mastaglia, 1999; Darling, Wolf and Butler, 2013; Okamoto *et al*., 2015). Therefore, MEPs were normalised to adjust for the possible variability in peak-to-peak responses across participants. The MEPs of each TMS pulse time were normalised to the 10ms TMS pulse time. This was performed by dividing each averaged MEP at time x, by the 10ms MEP average. The 10ms pulse time was chosen as a baseline value for comparison, because it represents an active internal control for illustrating changes in MEP responses (from a fully relaxed state with arms resting on table during hotspot evaluation to a quiet resting state with the arm in the robot trough) and occurs at a time before any preparatory brain activity has been recorded (Klein-Flügge *et al*., 2013). MEPs ratios were represented as percentages rather than raw values.

In experiments where cortical regions did not have a measured output (left and right PPC, left and right dPMC and the SMA) TMS intensity was always set individually for each participant through functional measures – i.e. left M1 TMS (hotspot for the right-sided BB muscle – at 110% RMT). Considering that all of the participants were right handed and performed a right hand reaching task, the left M1 rather than the right M1 was chosen for BB "hotspotting" because of the neural correlates of handedness (i.e. the contralateral (left) hemisphere controls the right hand) (Gut *et al*., 2007). Left M1 TMS as a functional measure ensured that stimulation intensity was individually set for each participant to avoid possible under- or over- stimulation of the targeted cortical regions. Similar functional measures have been used in TMS experiments (Della-Maggiore *et al*., 2004; Bolognini and Ro, 2010).

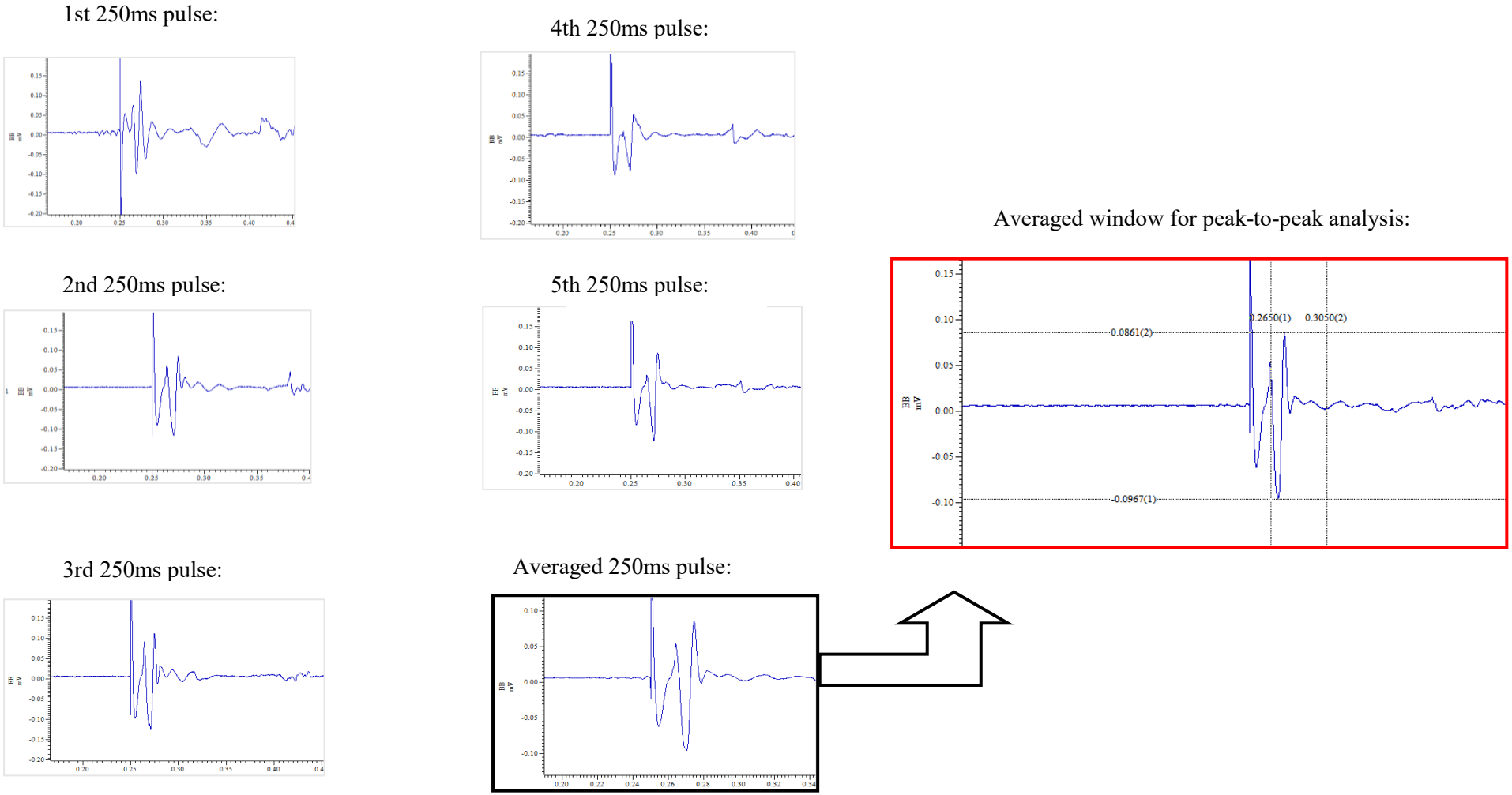


Figure 3.8: Protocol for MEP analysis

The MEP evoked in the BB for each TMS pulse for example delivered at 250ms after the visual cue to reach for one participant.
An average MEP waveform based on data from the five individual MEPs at 250ms is shown in the last window (black outline). In the red outlined box, the horizontal cursors display the peak-to-peak amplitude of the MEP trace, and the vertical cursors show the time that was chosen to quantify the peak-to-peak amplitude (0.265ms and 0.305ms - i.e. +15 to +55 ms after the TMS pulse).

3.7 Statistical analysis

Statistical analysis was performed in the Statistical Package for the Social Sciences (SPSS) 23 (IBM). Block by block statistics were gathered for all measures (kinematics and MEPs). Generally, the paradigm of all experiments carried out was designed to compare the results of whole reach kinematics (experiments 1 - 8) and MEPs (in experiments were MEPs were collected; experiments 1 and 2) at different TMS pulse times (time: 10ms, 100ms, 130ms, 160ms, 190ms, 220ms, 250ms, 280ms and 310ms). In each experimental chapter, a within-subjects analysis design was undertaken as all participants were exposed to the same conditions in reaching (i.e. same TMS pulse times, and same reaching conditions). Therefore, the analysis for the kinematic data, and MEP data was performed using well established tests and this is further described below.

3.7.1 Kinematic data (experiments 1-8):

Kinematic data were collected in all of the experiments carried out in this thesis. A number of steps were taken for the statistical testing of kinematic data. For example, in the first step of statistical testing, a two-way repeated measures analysis of variance (ANOVA) (repeated measures; RMANOVA) was performed using two factors:

1. Factor 1: TMS pulse time (10ms, 100ms, 130ms, 160ms, 190ms, 220ms, 250ms, 280ms and 310ms)
2. Factor 2: Condition (FAM, FF and WO)

Kinematic measures of movement onset, movement offset, movement duration, maximum velocity, maximum force and summed error were tested for statistical significance, with TIME and CONDITION as the main within subjects factors. The significance level for RMANOVA testing was set at $p < 0.05$. Interaction effects were also noted in the outputs (TIME*CONDITION). For RMANOVA testing, sphericity assumptions were tested for with Maulchy's Test of Sphericity. If sphericity was violated (i.e. $p < 0.05$), degrees of freedom were adjusted for using the Greenhouse Geisser correction, as this has been reported to reduce the risk of type 1 error rates by producing a more effective *F*-value (Winer, Brown and Michels 1991 cited in, Smith, 2017). Once sphericity assumptions were tested for and subsequent adjustments were made to the degrees of freedom, where statistical significance was found in the

RMANOVA (i.e. $p < 0.05$), post-hoc testing performed in order to confirm where the specific differences in results occurred. Post-hoc testing was conducted using paired Student's t-test and corrections for multiple comparisons for post-hoc testing were performed with the Bonferroni method, whereby the p value was set to 0.05/number of comparisons performed. For example, where TIME was found to be a significant factor in kinematic variables following RMANOVA testing, the 10ms pulse was taken as a baseline value for comparison in post-hoc statistical testing. Therefore, the significance value for was set as $p < 0.006$, as:

$$\frac{0.05}{8} = 0.006$$

For the factor of CONDITION where the RMANOVA revealed significance, 3 paired comparisons were made between the different conditions (i.e. FAM vs. FF, FAM vs. WO and FF vs. WO), with the p value set as < 0.016 as:

$$\frac{0.05}{3} = 0.016$$

The Bonferroni method used helps control for the family-wise error rate by avoiding false positives occurring in the results (Armstrong, 2014) and it has been implemented in previous motor adaptation protocols (Pizzamiglio *et al*., 2017a; Pizzamiglio *et al*., 2017b).

3.7.2 MEP data (experiment 1 and 2)

There were three factors to consider when exploring MEP data; TIME, MUSCLE and CONDITION. Therefore, each TMS pulse time, and individual muscle response was tested for statistical significance with an RMANOVA with TIME (10ms, 100ms, 130ms, 160ms, 190ms, 220ms, 250ms, 280ms, and 310ms), MUSCLE (BB, TB, ECR and FCR) and CONDITION (FAM, FF and WO) as the within-subject factors. Statistical outputs included main effects of TIME and CONDITION for muscles as well as interaction effects.

As with kinematic data, the RMANOVA significance value for MEP data was set as $p < 0.05$ and sphericity assumptions were tested for using Maulchy's Test of Sphericity. Greenhouse Geisser correction was used if sphericity assumptions were violated to adjust for the degrees of freedom. Following this, where main effects revealed significance, post-hoc testing performed (paired Student's t-test, with Bonferroni methods). If RMANOVA testing for the factor of TIME was found have a significant

effect on MEP responses in muscles, the p-value for post-hoc testing was set as $p < 0.006$. In post-hoc testing for the factor of CONDITION, significance was set as $p < 0.016$, and for the factor of MUSCLE significance was set as $p < 0.0125$.

All data in the results section for kinematics are presented as mean values ± the standard error mean (SEM).

3.7.3 Additional statistical testing:

TMS can have a disruptive effect on subsequent motor reaching, depending on the region that is stimulated. For example, stimulating the left PPC was found to result in greater disruption in novel learning compared to FAM reaching *(*Della-Maggiore *et al*., 2004). However, the effect of stimulating other regions have mainly been studied with repetitive TMS protocols and whilst observing non-human primates. Therefore, in the penultimate chapter of this thesis (chapter 12), there was an aim to explore the impact of TMS delivered to different cortical regions during 1) motor control and 2) motor adaptation. In order to investigate this, performance during TMS FAM, FF and WO reaching were compared between all of the cortical regions with a three-factorial mixed ANOVA. Therefore, analysis consisted of a between-subjects factor (cortical region stimulated - REGION) and within-subject factors (TIME and CONDITION). For each kinematic variable, statistical outputs included main effects for region, condition and time. Various interaction effects were also produced from the ANOVA including, REGION*CONDITION, REGION*TIME, CONDITION*TIME and TIME*REGION*CONDITION. Individual ANOVA tests were then carried out for the significant mixed ANOVA findings ($p < 0.05$). Where significance was revealed in the individual ANOVA tests ($p < 0.05$), post-hoc testing with Bonferroni methods to correct for multiple comparisons were performed (paired Student's t-test for CONDITION [FAM, FF and WO comparisons, p-value set at 0.016] and TIME [vs. T10, p value set at 0.006] comparisons, and Independent t-test for REGION comparisons [p value set at 0.002]).

Chapter 4

4 Experiment 1

The neural and behavioural mechanisms mediating right arm reaching probed with TMS delivered to the contralateral (left) and ipsilateral (right) primary motor cortex

4.1 Introduction

Motor behaviours fall into one of two categories; discrete or continuous. Reaching with the upper limb has been classed within the discrete category, because it is a motion that has a defined beginning and end point (Muratori *et al.,* 2013). The concept of 'fine' and 'gross' motor skills should also be considered when defining reaching. While fine motor skills refer to actions that use small muscles (i.e. hands), gross motor skills are actions that use larger muscles (i.e. upper arm and the trunk of the body; Muratori *et al*., 2013). In this experiment, reaching involved both gross and fine muscles. This is because the hand was used to grasp the joystick on the robotic arm, and the upper limb muscles were used to carry out the reaching motion. The role of the corticospinal tract (CST) is vital during reaching. This has been shown in both human studies (such as stroke patients) and animal models, whereby a damaged CST resulted in impaired motor function and poor reaching accuracy (Martin and Ghez 1991; Maraka *et al*., 2014).

The act of reaching begins with preparatory neural activity within pre-motor and motor cortices before actual movement of the arm (Jones, 2012). These regions help regulate timing and outputs of motor behaviour (Halsband *et al*., 1993; Overduin, Richardson, and Bizzi, 2009; Chang *et al*., 2015; Panouilleres *et al*., 2015). Reaching also involves complex information flows between different brain regions. For example, the dorsolateral prefrontal cortex (DLPFC) transmits organisation and planning information to the pre-motor cortex (PMC) to transfer to the primary motor cortex (M1). The PMC also receives information from the posterior parietal cortices (PPC) for preparation and spatial navigation of movements (Kantak et al., 2012). Section 1.5 provides further specific details with regards to how motor output occurs.

Although unilateral movements rely on recruiting contralateral brain regions for motor output, lateralisation exists between the contralateral and ipsilateral M1, therefore the two hemispheres may not exhibit the same functions (Hayashi *et al*., 2008; Barber *et al*.,

2011). For example, TMS and functional magnetic resonance imaging (fMRI) during thumb abduction and finger dexterity tasks illustrated that the contralateral (left) M1 in right handed participants showed a greater recruitment of activity in both right and left hand motor tasks compared to the ipsilateral (right) M1 which was only recruited during left hand motor tasks (Kim *et al*., 1993; Ghacibeh *et al*., 2007; Muellbacher *et al*., 2000). Therefore, exploring the role of both the contralateral and ipsilateral M1 can be important in investigating how these two regions differ with regards to their contribution to reaching behaviours.

TMS protocols have used surface electromyography (EMG) electrodes on different upper-limb arm muscles to capture physiological responses (e.g. motor evoked potentials [MEPs]) during the preparation and execution phases of reaching (Groppa *et al*., 2012; Hunter, Sacco and Turner, 2011; Orban de Xivry *et al*., 2013). Single-pulse TMS (SP-TMS) delivered to the M1 in reaching paradigms has shown dynamic changes in MEP amplitude. For example, during the preparation phase of right arm reaching towards the body (270° target on a visually presented dart-board), Hunter, Sacco and Turner (2011) found that the biceps brachii (BB) exhibited larger MEP responses than the triceps brachii (TB). However reaching away from the body (135° target) resulted in no differences in MEPs measured in the two muscles. Hunter, Sacco and Turner (2011) also demonstrated time-specific differences with regards to physiological responses between the BB and TB. For example, when TMS was delivered closer to movement onset (during 135° reaching*)* MEP amplitudes were significantly increased at 190ms and 220ms in the BB as opposed to the TB.

These physiological changes are important to consider because they show that there are complex mechanisms that underlie the time- and direction-tuning of an MEP. However, there is little literature on the time-dependent changes in MEPs comparing the contralateral and ipsilateral M1 and capturing the whole preparation phase of reaching. This new evidence might be important in revealing whether hemispheric-specific cortical excitability changes enable effective reaching.

As well as physiological changes being illustrated in both reaching preparation and reaching execution tasks, researchers have also explored how TMS affects behaviour. Behavioural changes as a consequence of TMS include errors made during reaching (e.g. trajectory errors) and altered maximum velocity and reaction time. With regards to errors made during reaching, Hunter, Sacco and Turner (2011) found that TMS to the

left M1 during reaching with the right hand towards different targets (135° and 270°) did not lead to any significant changes in trajectory errors made. However, *s*tudies have shown that TMS application to the contralateral M1 during movement preparation for unperturbed reaching delayed reaction time (Day, Rothwell and Marsden, 1983). Meyer and Voss (2000) also found similar results and reported a delay of up to 40ms during contralateral M1 stimulation during right-limb finger movement. Whether reaching errors and delays are affected by TMS delivered to the ipsilateral M1 during upper-limb robotic reaching are yet to be confirmed. Identifying differences between the two hemispheres is important in revealing whether there are specific reaching processes (determined by kinematics) that the contralateral M1 contributes to during right arm reaching, that the ipsilateral M1 does not, and vice versa. For example, the left hemisphere has been reported to be more specialised in motor sequence learning compared to the right hemisphere (Mutha, Haaland and Sainburg, 2012). This notion has support from studies on stroke patients with left-hemispheric lesions who performed poorly in sequential hand movement tasks (involving the ipsi-lesional arm and contra-lesional arm) compared to stroke patients with right-hemispheric lesions (Kimura, 1977). Motor planning, action and attention in finger and hand selection are also specific to functions of the left hemisphere (Schluter *et al*., 2001; Mutha, Haaland and Sainburg, 2012; Oliveira *et al*., 2010) and therefore the role of the contralateral hemisphere has been noted to have a greater prominence in motor tasks than the ipsilateral hemisphere.

This experiment set out to investigate whether TMS delivered at different time points, to either the contralateral or ipsilateral M1 during the preparation of a reach has an effect on distinct reaching kinematic parameters (movement onset, movement offset, maximum velocity, summed error and movement duration), and whether changes are common to stimulation of both hemispheres or selective to one hemisphere only. This is important in showing how reaching behaviours are modulated between hemispheres.

4.2 Methodology

Table 3.2 outlines participant's specific details for this experiment (e.g. N, age and gender). The ways in which the left and right M1 was located for this study is also described in section 3.3.2 and demonstrated in figure 3.3. The experimental paradigm

for this experiment is shown in figure 3.4. Section 3.41 and 3.4.2 outlines specific details regarding the instructions given to the participants in this experiment.

4.3 Data acquisition

4.3.1 MEPS recorded with EMG:

It should be noted that in this experiment MEPs were only recorded when TMS was delivered to the contralateral M1 to explore corticospinal excitability (CSE) responses during right arm reaching. The muscles that were explored and the filtering protocols used for signal acquisition are identified in section 3.3.1. Furthermore, section 3.6.2 describes the steps taken for MEP analysis (such as MEP normalisation) and figure 3.8 demonstrates the protocol for MEP quantification (i.e. calculating the peak to peak amplitude).

4.3.2 Kinematics recorded with the robot:

The kinematic variables that were recorded and the ways in which they were quantified and analysed (Matlab 2017b - The MathWorks Inc, Natick MA, USA) are explained in section 3.6.1.

4.4 Statistical analysis

Generally, the paradigm of this experiment was designed to compare the results of MEPs and kinematics during different TMS pulse times (TIME factor) and muscles (MUSCLE Factor for MEP data) and to compare contra-lateral and ipsi-lateral hemisphere stimulation (HEMISPHERE factor for kinematic data only).

4.4.1 MEPs:

Peak-to-peak MEP amplitudes for each TMS pulse time (TIME factor) and individual muscles (MUSCLE factor; BB, TB, ECR and FCR) were tested for significance with a two-way RMANOVA with TIME and MUSCLE as within-subjects factors in SPSS 23 (IBM). The ways in which sphericity assumptions were tested for are outlined in section 3.7.2. Post-hoc testing was performed (where significance was found (RMANOVA, $p < 0.05$) with a paired Student's t-test for TIME ($p < 0.006$) and MUSCLE ($p < 0.0125$; both corrected for multiple comparisons using Bonferroni methods).

4.4.2 Kinematics:

Kinematic responses for each TMS pulse time was calculated trial by trial and averaged across participants for each hemisphere. Overall, the aim of the analysis was to identify

significant differences for TIME and HEMISPHERE factors between the contralateral and ipsilateral M1 for kinematic variables. Section 3.6.1 describes the ways in which kinematic parameters were explored and analysed in SPSS 23 (IBM) (including how sphericity assumptions were tested and how post-hoc testing was carried out).

4.5 Results

4.5.1 MEP results: Contralateral M1 stimulation only:

The results of average peak-to-peak MEP amplitudes during reaching (values as ratio of TMS 10ms) are shown in table 4.1. TIME factor had a significant main effect on peak-to-peak MEP amplitude (RMANOVA $p < 0.05$). However, there was no significant effect of MUSCLE factor and no MUSCLE*TIME interaction was found (RMANOVA $p > 0.05$) (table 4.1).

4.5.2 Kinematics: contralateral and ipsilateral stimulation:

The results of the two-way RMANOVA revealed a significant difference for TIME for movement onset, offset and maximum velocity (all $F > 4.558$, all $p < 0.05$) (table 4.2), but not for maximum force, movement duration and summed error (all $F < 0.593$, all $p > 0.05$). Kinematic conditions were not significantly different between the contralateral and ipsilateral M1 (HEMISPHERE factor; all $F < 0.022$, all $p > 0.05$) (therefore post hoc testing was not performed for this factor). A significant interaction was only found for movement onset ($F = 3.61$, $p < 0.05$) (see table 4.2).

Post hoc testing for time with regards to movement onset revealed a significant increase in all pulse times during contralateral and ipsilateral M1 stimulation when compared to 10ms (all $p < 0.006$). This was also the case for movement offset (all $p < 0.006$) for contralateral M1 stimulation. During ipsilateral M1 stimulation however, TMS delivered at 100ms was not significantly different from 10ms ($p > 0.006$). Maximum velocity was significantly increased when TMS was delivered at 280ms and 310ms when compared to 10ms during contralateral reaching ($p < 0.006$), whereas maximum velocity responses did not differ between 10ms and all other time points of TMS delivery during ipsilateral stimulation ($p > 0.006$). Table 4.3 and figure 4.1 further demonstrates post-hoc testing results.

Table 4.1: Average peak-to-peak MEP amplitudes during FAM reaching at different time points, and results of RMANOVA testing:

	TMS Pulse Time								
	10ms Mean [SE]	100ms Mean [SE]	130ms Mean [SE]	160ms Mean [SE]	190ms Mean [SE]	220ms Mean [SE]	250ms Mean [SE]	280ms Mean [SE]	310ms Mean [SE]
Biceps brachii (BB)	1.00 [0.00]	1.05 [0.13]	1.32 [0.17]	1.20 [0.08]	1.29 [0.13]	1.31 [0.10]	1.42 [0.17]	1.31 [0.17]	1.40 [0.18]
Triceps brachii (TB)	1.00 [0.00]	1.17 [0.17]	1.32 [0.25]	1.20 [0.12]	1.22 [0.11]	1.33 [0.14]	1.30 [0.11]	1.25 [0.09]	1.30 [0.11]
Extensor carpi radialis (ECR)	1.00 [0.00]	0.89 [0.06]	1.13 [0.06]	1.06 [0.06]	1.01 [0.05]	1.03 [0.07]	1.02 [0.09]	0.96 [0.05]	0.99 [0.05]
Flexor carpi radialis (FCR)	1.00 [0.00]	0.91[0.08]	0.99 [0.07]	0.93 [0.06]	1.02 [0.07]	1.05 [0.06]	1.07 [0.08]	1.02 [0.07]	1.12[0.09]
ANOVA TESTING									
	Time (10-310ms)			Muscle (BB, TB, ECR, FCR)			Time*Muscle		
Statistical output	*Df (Errors)*	F	Sig	*Df (Errors)*	F	Sig	*Df (Errors)*	F	Sig
Results:	3.7 (44.2)	3.631	**0.014**	1.6 (18.1)	2.737	0.103	24 *288)	0.899	0.604

Table 4.2. Two-way RMANOVA results for kinematic variables during contralateral and ipsilateral M1 stimulation

	Two-way ANOVA								
	TIME factor: 10ms - 310ms			HEMISPHERE factor (Contralateral and Ipsilateral M1)			Interaction effects TIME * HEMISPHERE		
	df(Error)	F	Sig.	*df*(Error)	F	Sig.	*df*(Error)	F	Sig.
Movement Onset (ms)	2.9[34.5]	76.65	**< 0.001**	1 [12]	0.547	0.474	3.3 [39.4]	3.608	**0.019**
Movement Offset (ms)	8[96]	23.27	**< 0.001**	1 [12]	0.461	0.510	8 [96]	1.928	0.064
Maximum Velocity ($m.s^{-1}$)	8[96]	4.558	**< 0.001**	1 [12]	0.022	0.883	8 [96]	1.554	0.149
Duration (ms)	8[96]	1.935	0.063	1 [12]	2.231	0.154	8 [96]	1.346	0.230
Summed Error (distance: cm)	8[96]	1.457	0.183	1 [12]	0.976	0.343	8 [96]	0.734	0.661
Maximum Force (*N*)	8[96]	0.593	0.781	1 [12]	0.208	0.656	8 [96]	0.874	0.541

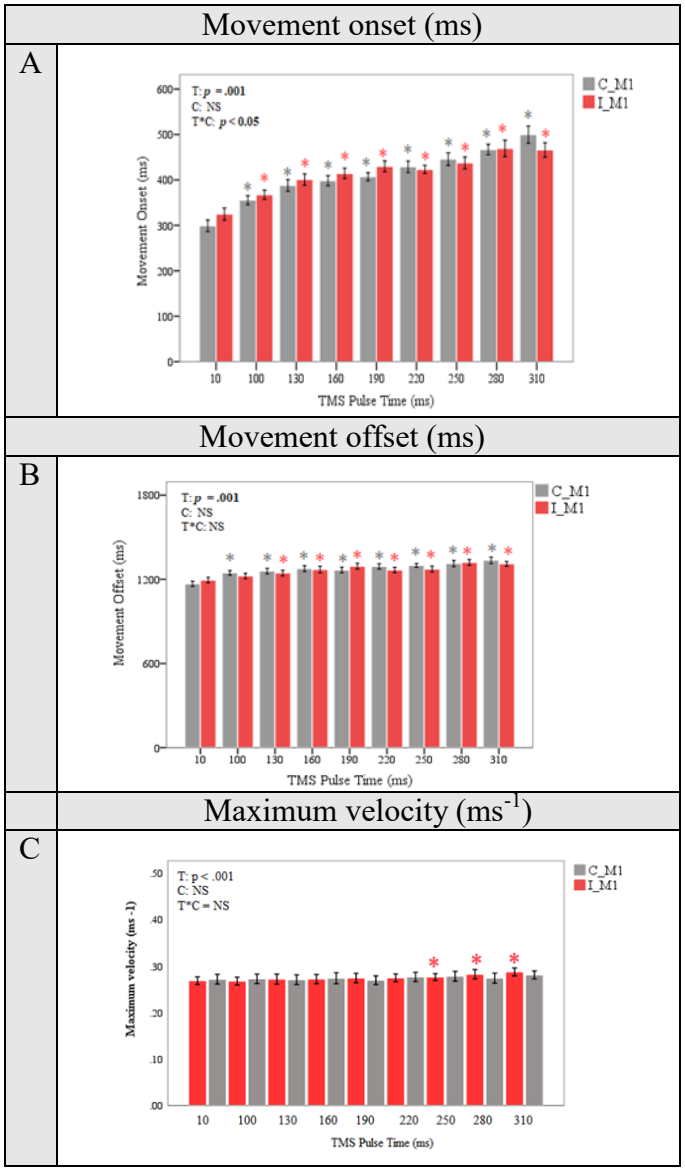
Table 4.3. Post-hoc testing following significant RMANOVA findings:

	TIME								
	10ms Mean [SEM]	100ms Mean [SEM]	130ms Mean [SEM]	160ms Mean [SEM]	190ms Mean [SEM]	220ms Mean [SEM]	250ms Mean [SEM]	280ms Mean [SEM]	310ms Mean [SEM]
	Contralateral M1								
Movement Onset (ms)	298 [12]	351 [10] *	386 [12]*	395 [11]*	403 [9]*	428 [12]*	440 [12]*	433 [12]*	494 [18]*
Movement Offset (ms)	1167 [18]	1242 [16]*	1244 [24]*	1265 [22]*	1258 [21]*	1282 [21]*	1282 [22]*	1303 [23]*	1323 [26]*
Maximum Velocity ($m.s^{-1}$)	0.27 [0.01]	0.27 [0.01]	0.28 [0.01]	0.28 [0.01]	0.28 [0.01]	0.28 [0.01]	0.28 [0.01]*	0.29 [0.01]*	0.29 [0.01]*
Duration (ms)	868 [17]	827 [62]	856 [23]	823 [65]	856 [23]	854 [19]	841 [19]	842 [19]	843 [21]
Summed Error (distance: cm)	2.51 [0.23]	2.50 [0.24]	2.31[0.18]	2.81[0.29]	2.67 [0.22]	2.67 [0.23]	2.65 [0.20]	2.96 [0.36]	2.82 [0.27]
Force (*N*)	4.5 [0.10]	4.6 [0.20]	4.6 [0.20]	4.5 [0.10]	4.6 [0.10]	4.5 [0.20]	4.6 [0.20]	4.6 [0.20]	4.6 [0.20]
	Ipsilateral M1								
Movement Onset (ms)	325 [13]	367 [10] *	401 [12] *	414 [12] *	430 [12] *	423 [9] *	437 [13] *	469 [18] *	466 [16] *
Movement Offset (ms)	1195 [20]	1224 [20]	1244 [20] *	1270 [24] *	1294 [21] *	1267 [19] *	1273 [22] *	1321 [21] *	1310 [17] *
Maximum Velocity ($m.s^{-1}$)	0.27 [0.01]	0.27[0.01]	0.27 [0.01]	0.27 [0.01]	0.27 [0.01]	0.28 [0.01]	0.28 [0.01]	0.27 [0.01]	0.28 [0.01]
Duration (ms)	870 [17]	854 [13]	844 [26]	855 [27]	864 [21]	844 [76]	835 [25]	854 [21]	844 [15]
Summed Error (distance: cm)	2.64 [0.24]	2.55 [0.18]	2.34 [0.15]	2.46 [0.19]	2.51 [0.17]	2.60 [0.22]	2.40 [0.19]	2.46 [0.16]	2.39 [0.12]
Force (*N*)	4.4 [0.21]	4.5 [0.20]	4.5 [0.20]	4.5 [0.23]	4.5 [0.25]	4.5 [0.21]	4.5 [0.20]	4.5 [0.19]	4.5 [0.20]

Significant findings (Student's t-tests) with Bonferroni correction for multiple comparisons are marked with an asterisk (*)

Symbols represent significance following post hoc testing:
* = significant difference vs 10ms for TIME factor

Figure 4.1[A-C]: Graphical presentation of the post-hoc testing results (based on table 4.3) for the significant kinematic variables:



4.6 Discussion

4.6.1 MEP responses:

ANOVA results revealed a significant main effect for the TIME factor for MEP amplitude ($p < 0.05$) demonstrating that as TMS pulses became closer to the onset of movement, MEP amplitudes of all muscles increased, although this was a small effect size as no further significance was illustrated in post-hoc testing (all $p > 0.006$). Additionally, no significant effect of MUSCLE factor or MUSCLE*TIME interaction was found. These results are similar to findings illustrated by Hunter, Sacco and Turner (2011) as they reported that TMS delivered to the contralateral M1 when reaching towards the body (270° target) induced MEP changes between the BB and the TB, with the BB exhibiting larger MEP responses, however this was not case when reaching away from the body (135° target as in this study). Direction MEP changes were also noted by Kantak *et al*., (2013) in upper-limb arm robotic reaching demonstrating an increase in TB MEP amplitude when reaching away from the body. It could be argued that the reason as to why MEP responses were not significantly altered in this experiment was due to the nature of the reaching protocol (i.e. 135° unperturbed reaching). Implementing different motor reaching protocols with different directions can demonstrate the complex mechanisms that underlie the time- and direction-tuning of an MEP. This thesis does not address directional tuning however. Furthermore, the impact of TMS on corticospinal projections during unperturbed reaching relies on the extent of training that has been undertaken (Kantak *et al*., 2013). For example, TB MEP responses during elbow extension reaching significantly increased following repeated reaching trials (160 reaching trials x 3 blocks of reaching) (Kantak *et al*., 2013). With regards to MEP findings in experiment 1, it could be suggested that MEP amplitudes between muscles may have significantly differed if subjects were exposed to a greater number of reaching trials. This is because practice-related activity can induce neuroplasticity, which can in turn effect muscle representations in the M1 (even in unperturbed reaching) (Kantak *et al*., 2013).

4.6.2 Kinematics:

Overall, experiment 1 illustrated the behavioural effects of TMS on reaching kinematics. For example, it was found that both contralateral and ipsilateral M1 TMS (right arm reaching) prolonged the movement onset time (also commonly known as

reaction time; this addresses experiment 1, hypothesis 2) and movement offset. More specifically for both hemispheres, the later the TMS pulse was delivered during movement onset, the greater the delay in movement onset, which was found in robust multiple comparisons testing ($p < 0.006$ - table 4.3).

The shift in movement onset reported in this experiment is in line with results from previous studies (Day, Rothwell and Marsden, 1983). Meyer and Voss (2000) noted that TMS can cause delays of up to 40ms in responses. However, it should be taken into account that previous experiments (e.g. Day, Rothwell and Marsden, 1983) reporting similar delays in movement onset have not explored upper limb reaching, but rather hand/finger pointing. Therefore experiment 1 demonstrated that similar delays can also be found during upper limb reaching (table 4.3).

A mechanistic effect of TMS on the M1 is that it excites pyramidal neurons trans-synaptically (via depolarised interneurons) (Rothwell *et al*., 1987; Terao and Ugawa, 2002; Hallett, 2007; Farzan *et al*., 2016; Goss, Hoffman and Clark, 2012). The delay in movement onset found in this experiment can be explained mechanistically by the inhibitory effects of TMS. More specifically, TMS inhibits the 'release channel' of neurons that are responsible for movement preparation, making them unresponsive for a brief period, thus causing delays in signals that facilitate movement onset. The movement command can still be released for motor output because 'pre-movement facilitation' in the M1 was initiated (i.e. motor planning) (Day, Rothwell and Marsden, 1983; Ziemann *et al*., 1997). Therefore, TMS can cause $GABA_b$-like activity effects (a neurotransmitter that influences inhibition processes) (Werhahn et al., 1999; Auriat *et al*., 2015).

An interesting finding from the RMANOVA was that maximum velocity during reaching was significantly increased during the latter time points of contralateral M1 stimulation, which was not the case for ipsilateral M1 stimulation. The state dependency theory, specifically dispersed excitation to other connected brain regions can explain this finding. This theory suggests that TMS may not only directly impact synaptic activity in the targeted region, but it could also indirectly influence cortical activity by affecting its connected networks (Siebner *et al*., 2009). Numerous regions make up the motor network including, the dorsolateral prefrontal cortex (DLPFC), the premotor cortices (PMC), the supplementary motor area (SMA), and the posterior parietal cortex (PPC) (Kantak *et al*., 2012). Studies exploring the functional role of the left M1 have

shown that during reaching tasks it encodes kinematic parameters, including velocity, and the speed of movement via neural communication with connecting regions, such as the SMA (Hore and Flament, 1988; Aizawa and Tanji, 1994; Tanji and Mushiake, 1996; Moran and Schwartz, 1999; Tankus et al., 2009; Teka et al., 2017). Based on this theory, and findings from functional motor connectivity imaging studies (i.e. contralateral vs. ipsilateral M1 – see Kim *et al*., 1993; Guye *et al*., 2003) it can be argued that TMS caused a significant change in velocity measures only in the contralateral M1, because it had a greater 'knock-on' effect on its connecting nodes, which have been found to be more extensively connected in the left hemisphere as opposed to the right hemisphere (Kim *et al*., 1993; Guye *et al*., 2003; Siebner *et al*., 2009).

Hemispheric asymmetries can also explain why TMS had a greater effect on kinematic variables in one hemisphere compared to another hemisphere (e.g. maximum velocity and movement offset in the contralateral M1 compared to the ipsilateral M1), which has been noted in fMRI and structural voxel based morphometry (VBM) studies. For example, in a resting fMRI study where connectivity patterns were correlated with motor performance, Barber *et al*., (2011) found a link between enhanced motor performance and increased left-hemispheric M1 connectivity, compared to right-hemispheric M1 activity in right handed participants. VBM imaging methods use volumetric measures to explore anatomical differences between structures in the left and right hemisphere (Ashburner and Friston, 2000; Watkins *et al*., 2001; Büchel *et al*., 2004). Diffusion tensor imaging (DTI) VBM studies in right-handed subjects revealed that the contralateral M1 had a greater volume, and greater degrees of dendrites and axons than the ipsilateral M1 (Amunts *et al*., 1996). Such hemispheric asymmetries help explain the concept of lateralisation which was found in this study when considering that movement preparation was effected differently between the ipsilateral and contralateral M1. Although the left M1 has been found to be more prominently active than the right M1 in right handed subjects during arm-reaching and pointing tasks (Kim *et al*., 1993; Muellbacher et al., 2000; Barber *et al*., 2011) it should be taken into account that in this study using TMS to disrupt ipsilateral M1 functioning also resulted in delays in reaction time, which is in line with previous research that has found the ipsilateral M1 to undergo task related changes to the moving body side (Van den Berg, Swinnen and Wenderoth, 2011). This indicates that the ipsilateral cortex is also

involved and interacts with movement preparation processes, even during unilateral reaching. Summed error values were not significantly affected with TMS to either the contralateral or ipsilateral M1. This result can be due to unperturbed reaching that was performed, as similar studies have also not demonstrated any changes in this variable during unperturbed reaching (Hunter, Sacco and Turner, 2011).

4.7 Chapter conclusions:

In this study, TMS stimulation was found to delay movement onset and movement offset responses during both contralateral and ipsilateral M1 stimulation which can be due to the inhibitory effects of SP-TMS. Significant changes were not observed in MEP responses between muscles which could have been be due to the nature of the task (e.g. direction of reaching), and the number of reaching trials that participants were exposed to, when considering that continuous repeated practice can influence MEP responses through inducing plasticity. The differences between the two hemispheres with regards to the degree of delay as well as other kinematic parameters (e.g. movement velocity) can be attributed to 1) hemispheric asymmetries noted in VBM studies, 2) lateralisation of motor function between the left and right M1, and 3) differences in functional connectivity which have been studied with resting state fMRI studies. Overall this chapter highlighted reaching processes that the contralateral and ipsilateral M1 contribute to (planning and preparation of reaching) and the kinematic behaviours that may be more distinct for one hemisphere only (e.g. velocity; left M1). In the upcoming chapters, motor adaptation will be studied in order to investigate whether such hemispheric differences are also evident with TMS during a force-field reaching paradigm.

Chapter 5

5 Experiment 2

The neural and behavioural mechanisms mediating right arm reaching in a force-field studied with single-pulse TMS to the left primary motor cortex (M1)

In the previous chapter, neural mechanisms and kinematic behaviour of unperturbed reaching were explored with contralateral and ipsilateral M1 TMS delivery. The purpose of this experiment was to introduce motor adaptation within the protocol. Therefore, this experiment aimed to investigate whether motor adaptation (i.e. force-field [FF] reaching) was accompanied by changes in corticospinal excitability (CSE) and in subsequent kinematic responses studied with TMS delivered to the left M1.

5.1 Introduction

Motor adaptation places emphasis on the brain's flexibility in meeting the demands of a changing environment compared to motor skill learning (Bastian, 2008). Motor adaptation is vital in the field of rehabilitation because repeated adaptation can lead to individuals learning a new motor skill (Bastian, 2008; Hunter *et al*., 2009). For example, in the study of Reisman (2005) stroke patients who had an impaired leg, were asked to adapt the affected leg to walk faster than the unaffected leg on a split-belt treadmill. Following motor adaptation trials, the patients gradually learned to walk with both legs at the same speed. It can thus be argued that motor adaptation can facilitate the re-learning of motor skills and aid neurological recovery. The motor adaptation process can be explored in robotic training with the robot in 'resistive mode' (see Section 3.4) (Patton *et al*., 2006). In this mode, the robot administers a force that opposes movements made by the patient. Forces can be applied in different directions and magnitude and aim to strengthen weakened muscles (Poli *et al*., 2013; Eiammanussakul and Sangveraphunsiri, 2018). Studies have shown that resistive robotic cycling training in stroke patients resulted in improved walking distance performance and an increase in comfortable speed – as quantified by walking assessments (both practical sessions and mobility scales) (Kamps and Schüle 2005; Eiammanussakul and Sangveraphunsiri, 2018). Therefore, the 'resistive mode' in robotic motor adaptation protocols can be used as an effective tool in assisting the recovery process in clinical populations (i.e. stroke patients).

Changes in corticospinal excitability have previously been investigated with TMS in motor adaptation paradigms. For example, an increase in BB compared to TB peak-to-peak MEP amplitude was demonstrated in the preparatory phase of reaching during motor adaptation (Orban de Xivry *et al*., 2013). More specifically, BB MEP increased when measured more closely to movement onset (Hunter, Sacco and Turner, 2011; Orban de Xivry *et al*., 2013). However, it should be considered that TMS to the left M1 has not been delivered during the whole preparation phase prior to FF reaching onset. This could be interesting to explore, as it is currently not known whether different kinematic parameters have specific time-related effects with TMS.

Errors during reaching are greater during the initial stages of motor adaptation, however they gradually reduce trial by trial following additional blocks of force-field reaching (Hunter *et al*., 2009; Hunter, Sacco and Turner 2011; Pizzamiglio *et al*., 2017a; Pizzamiglio *et al*., 2017b). Interestingly, studies with non-human primates have found that major changes within the M1 do not occur at the earlier stages of adaptation when errors are amplified, but rather at the latter stages when errors are reduced (Paz *et al*., 2003). However, this has not been established with TMS protocols in man.

The motor adaptation protocol implemented in this experiment, contains 8 blocks of force-field reaching (i.e. approximately 200 reaches in a force-field) which should allow a fuller degree adaptation and consolidate a robust change in left M1 function. Thus, we tested the hypothesis that the left M1 is functionally altered by motor adaptation. Secondarily, as TMS appears to alter subsequent movement kinematics in normal reaching (see chapter 4), this experiment also addresses whether the impact of TMS disrupts subsequent reaching in a different fashion in motor adaptation. This would further suggest an alteration in left M1 function occurs during adaptation.

5.2 Methodology

Table 3.2 outlines participant demographics for this experiment, as well as the number of participants excluded and the reasons why. The TMS protocol for this experiment including how RMT was identified as well as TMS coil position for left M1 location is described in section 3.3.2. This protocol differs from experiment 1, as motor adaptation was explored. The experimental set up and the full details of the instructions given to the participants is outlined in Section 3.4.1 and 3.4.2. Furthermore, figure 3.5

graphically demonstrates the protocol with regards to the different blocks of reaching (FAM, FF and WO).

5.3 Data acquisition: MEPs and Kinematics

When TMS was delivered to the left M1, MEPs were recorded from four muscles (BB, TB, ECR and FCR) with two disposable surface electrodes. The specific guidelines (SENIAM) that were used for electrode positioning are outlined in Section 3.3.1. The ways in which MEP responses were recorded and quantified for this experiment is described section 3.6.2 and illustrated in figure 3.8. The kinematic variables recorded and their quantification and analysis process (Matlab 2017b - The MathWorks Inc, Natick MA, USA) is explained in section 3.6.1.

5.4 Statistical analysis: MEPs and Kinematics

Section 3.7.2 describes the ways in which statistical testing was performed for this experiment using a three-factorial RMANOVA (RMANOVA) with TIME (T10 to T310), CONDITION (FAM, FF, WO) and MUSCLE (BB, TB, ECR and FCR) as main factors in SPSS 23 (IBM). The statistical analysis that was undertaken for kinematic parameters is described in section 3.7.1. Section 3.7.2 also outlines the procedure for sphericity testing and how post hoc testing was performed (i.e. Student's t-tests and correcting for multiple comparisons using Bonferroni methods).

5.5 Results

5.5.1 MEPs:

The results of the RMANOVA (table 5.1) revealed a significant main effect for TIME ($F: 9.86$, $p < 0.05$) and CONDITION ($F: 10.67$, $p < 0.05$). However, MEP responses did not significantly differ between MUSCLES ($F: 1.00$, $p > 0.05$). A significant interaction was found for TIME*CONDITION ($F: 6.00$, $p < 0.05$), but not for TIME*MUSCLE, MUSCLE*CONDITION and TIME*MUSCLE*CONDITION ($F < 2.22$, $p > 0.05$).

Post hoc testing for TIME (table 5.1) showed no significant differences in MEP amplitude for FAM reaching between T10 and all other TMS pulse times in the BB, TB, ECR and FCR (all $p > 0.006$). However, there was a significant increase in MEP amplitude in the BB at 220ms and 250ms compared to T10 in FF reaching ($p < 0.006$). There were no significant differences in MEP amplitude during FF reaching between T10 and all other TMS pulse times in the TB, ECR and FCR ($p > 0.006$). No significant differences in MEP amplitude were found during WO reaching between T10 and all

other TMS pulse times in the BB, TB and ECR (all $p > 0.006$), but there was a significant increase in MEP amplitude in the FCR at 130ms compared to T10 ($p < 0.006$).

Post hoc testing for CONDITION (table 5.1) for the BB showed a significant increase in MEP amplitude in FF reaching compared to FAM reaching (at 220ms, 250ms and 310ms $p < 0.016$). MEP amplitude in FF reaching compared to WO reaching was also significantly increased (at 160ms, 220ms, 250ms and 310ms $p < 0.016$). No significant differences in MEP amplitude were found for WO vs. FAM reaching. TB MEP amplitude was significantly increased in FF reaching compared to FAM reaching at 220ms ($p < 0.016$). No significant differences were found for FF vs. WO reaching in the TB. However, there was a significant increase in MEP amplitude in the TB during WO reaching compared to FAM reaching (only at 310ms $p < 0.016$). With regards to the ECR and FCR, there were no significant differences in MEP amplitude during FF vs. FAM reaching, FF vs. WO reaching, and FAM vs. WO reaching (all $p > 0.016$).

5.5.2 Kinematics:

Patterns of reaching were as follows: during TMS FAM reaching, participant's successfully familiarised themselves with the task. Motor adaptation introduced with FF reaching (no TMS) initially caused deviations in reaching trajectories. However, following blocks of repeated trials, participant's learned to adapt to the FF and optimise their reaching – which is indicative of successful motor adaptation. TMS FF reaching however disrupted reaching trajectories (see ANOVA, table – 5.2). When unperturbed reaching was re-introduced into the protocol (WO blocks), 'overshoot errors' were visible whereby participants reached in the direction of the expected force (clockwise) which resulted in a deviation in the opposite direction (counter-clockwise). The errors however faded quickly and reaching became ideal (indicative of a successful de-adaptation).

The results of the two-way repeated measures ANOVA (table 5.2) revealed a significant main effect of TIME for movement onset and offset (all $F > 30.71$, all $p < 0.05$), but not for summed error, maximum velocity, duration and maximum force (all $F < 0.778$ $p > 0.05$; table 4.2). A significant effect of CONDITION (FAM, FF and WO) was found for movement onset, maximum velocity, movement duration, summed error and maximum force (all $F > 9.066$, all $p < 0.05$) but not movement offset (F: 1.862, $p > 0.05$). With

regards to all kinematic variables explored, no significant interaction effects were found (all $F < 1.084$, < all $p > 0.05$).

Post hoc testing for TIME (table 5.3, figure 5.3[A-F]) revealed that during both FAM reaching and FF reaching, movement onset responses were significantly increased at all time points compared to T10 ($p < 0.006$). During WO reaching, movement onset was significantly increased at 190ms, 220ms, 250ms, 280ms and 310ms compared to T10 ($p < 0.006$). Movement offset was significantly increased at all time points compared to T10 during FAM reaching and FF reaching ($p < 0.006$), but not WO reaching (at all time points $p > 0.006$).

Post hoc testing for CONDITION (table 5.3, figure 5.3[A-F]) for movement onset showed no significant differences between FF and FAM reaching. However, movement onset in FF reaching was significantly increased compared to WO reaching (at 10ms, 190ms, 220ms, 250ms, 280ms and 310ms $p < 0.016$). No significant differences were revealed for movement onset during WO vs. FAM reaching ($p > 0.016$). Maximum velocity was significantly increased in FF reaching compared to FAM reaching (at 100ms, 130ms, 190ms, 220ms, 250ms, 280ms and 310ms $p < 0.016$). Maximum velocity was also significantly increased in FF reaching compared to WO reaching (at 250ms, $p < 0.016$). No significant difference in maximum velocity was found between WO vs. FAM reaching. Movement duration did not significantly differ between FF vs. FAM reaching. However, duration was significantly increased in FF reaching compared to WO reaching (at 100ms, 130ms, 160ms, 190ms, 220ms and 280ms, $p < 0.016$). Movement duration in FAM reaching was significantly increased compared to WO reaching (at 160ms and 280ms $p < 0.016$). Summed error was significantly increased in FF reaching compared to FAM reaching (at all time points, $p < 0.016$). Summed error was also significantly increased in FF reaching in contrast to WO reaching at all time points except for 100ms and 130ms ($p > 0.016$). There were no significant differences in summed error for FAM vs. WO reaching (all $p > 0.016$). Maximum force was significantly increased in FF reaching ($p < 0.016$) compared to both FAM and WO reaching which were not significantly different ($p > 0.016$).

All post-hoc testing results are shown in table 5.3 and figure 5.3[A-F].

Table 5.1. Results of three-factorial RMANOVA for peak-to-peak MEP responses, followed by post hoc testing:

Three-factorial RMANOVA		
TIME		
df(Error)	F	Sig.
3.0(38.2)	9.86	**0.001**
CONDITION		
df(Error)	F	Sig.
1.4(17.4)	10.67	**0.002**
MUSCLE		
df(Error)	F	Sig.
3(39)	1.00	0.400
TIME*CONDITION		
df(Error)	F	Sig.
5.5 (70.9)	6.00	**0.001**
TIME*MUSCLE		
df(Error)	F	Sig.
9.0(116.9)	1.20	0.305
MUSCLE*CONDITION		
df(Error)	F	Sig.
2.9(36.7)	2.22	0.106
TIME*MUSCLE*CONDITION		
df(Error)	F	Sig.
7.7(99.4)	1.52	0.165

	Post hoc testing								
	TIME								
	10ms Mean [SEM]	100ms Mean [SEM]	130ms Mean [SEM]	160ms Mean [SEM]	190ms Mean [SEM]	220ms Mean [SEM]	250ms Mean [SEM]	280ms Mean [SEM]	310ms Mean [SEM]
CONDITION				**BB**					
FAM	1.0 [0.0]	1.03 [.05]	1.09 [.07]	1.07 [.07]	1.02 [.05]	1.03 [.07] ■	1.09 [.08] ■	1.15 [.11]	1.09 [.12] ■
FF	1.0 [0.0]	1.19 [.11]	1.37 [.14]	1.39 [.13]✦	1.55 [.19]	1.98 [.26] * ✦	1.65 [.22] ✦	1.89 [.36]	2.49 [.42] * ✦
WO	1.0 [0.0]	1.05 [.06]	1.07 [.04]	1.07 [.05]	1.13 [.06]	1.13 [.11]	1.07 [.05]	1.12 [.09]	1.18 [.12]
				TB					
FAM	1.0 [0.0]	1.02 [.05]	1.00 [.06]	1.01 [.03]	1.05 [.04]	1.06 [.06] ■	1.07 [.08]	1.07 [.08]	1.09 [.08]▲
FF	1.0 [0.0]	1.24 [.08]	1.04 [.06]	1.22 [.08]	1.17 [.09]	1.30 [.10]	1.27 [.11]	1.29 [.18]	1.29 [.13]
WO	1.0 [0.0]	1.25 [.26]	1.21 [.13]	1.16 [.13]	1.24 [.25]	1.20 [.18]	1.28 [.19]	1.21 [.17]	1.28 [.11]
				ECR					
FAM	1.0 [0.0]	1.11 [.06]	1.04 [.07]	1.14 [.05]	1.09 [.05]	1.13 [.07]	1.18 [.11]	1.06 [.08]	1.14 [.05]
FF	1.0 [0.0]	1.04 [.05]	1.08 [.04]	1.13 [.07]	1.28[.17]	1.20 [.08]	1.23 [.09]	1.16 [.07]	1.50 [.22]
WO	1.0 [0.0]	1.11 [.06]	1.06 [.07]	1.09 [.06]	1.08 [.05]	1.06 [.05]	1.13 [.05]	1.18 [.08]	1.14 [.11]
				FCR					
FAM	1.0 [0.0]	0.99 [.06]	0.99 [.07]	1.03 [.05]	0.97 [.05]	1.00 [.07]	1.13 [.11]	1.06 [.08]	1.97 [.05]
FF	1.0 [0.0]	1.09 [.05]	1.24 [.10]	1.24 [.09]	1.41 [.24]	1.27 [.14]	1.57 [.38]	1.70 [.37]	1.98 [.52]
WO	1.0 [0.0]	1.14 [.08]	1.15 [.04] *	1.13 [.06]	1.08 [.05]	1.06 [.04]	1.08 [.04]	1.06 [.04]	1.07 [.05]

Table 5.2. Results of the two-way RMANOVA for kinematics:

	TIME:			CONDITION			TIME * CONDITION		
	df(Error)	F	Sig.	*df*(Error)	F	Sig.	*df*(Error)	F	Sig.
Movement Onset (ms)	3.0 [38.4]	30.71	**< 0.001**	2 [26]	10.25	**0.002**	16[208]	0.496	0.948
Movement Offset (ms)	8[2]	22.50	**< 0.001**	2[26]	1.862	0.175	16[208]	1.084	0.372
Maximum Velocity ($m.s^{-1}$)	3.4[44.1]	0.932	0.442	1.4 [18.2]	9.066	**0.004**	16[208]	0.837	0.643
Duration (ms)	8 [104]	0.778	0.569	2[26]	13.14	**0.001**	16[208]	0.973	0.487
Summed Error (distance: cm)	3.9 [49.5]	2.295	0.075	1.4 [18.1]	31.37	**< 0.001**	16[208]	1.358	0.165
Maximum Force (*N*)	8 [104]	1.443	0.187	1.3 [15.7]	313.06	**< 0.001**	16[208]	0.871	0.603

Table 5.3. Results of the two-way RMANOVA for kinematics:

The table shows kinematic responses during FAM, FF and WO blocks of reaching when TMS was applied to the left M1 at different time points during movement preparation. Values represent means and standard errors.

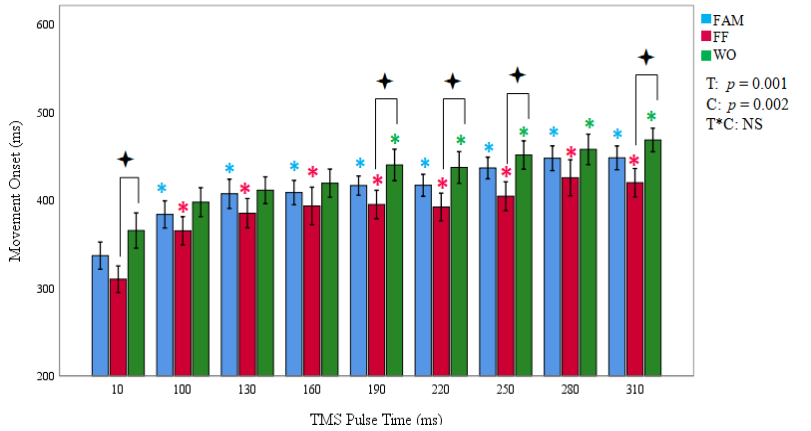
TIME	TMS: 10ms Mean [SEM]	TMS: 100ms Mean [SEM]	TMS: 130ms Mean [SEM]	TMS: 160ms Mean [SEM]	TMS: 190ms Mean [SEM]	TMS: 220ms Mean [SEM]	TMS: 250ms Mean [SEM]	TMS: 280ms Mean [SEM]	TMS: 310ms Mean [SEM]
CONDITION	Movement Onset (ms):								
FAM	337 [15]	384 [15]*	407 [17]*	408[14]*	416 [11]*	417 [13]*	436 [12]*	447 [14]*	448 [13]*
FF	310 [15]✦	365 [16]*	385 [17]*	393 [21]*	395 [17]*✦	392 [16]*✦	404 [16]*✦	425 [21]*	420 [16]*✦
WO	365 [20]	397 [17]	411 [15]	419 [16]	440 [18]*	437 [18]*	451 [16]*	457 [17]*	468 [13]*
	Movement Offset (ms):								
FAM	1185 [16]	1241 [15]*	1278 [17]*	1271 [14]*	1277 [13]*	1263 [22]*	1300 [21]*	1301 [19]*	1303 [18]*
FF	1166 [20]	1247 [14]*	1254 [16]*	1278[16]*	1291 [15]*	1283 [12]*	1268 [20]*	1295 [21]*	1284 [16]*
WO	1185 [17]	1220 [17]	1239 [14]	1233 [12]	1257 [17]	1236 [15]	1276 [9]	1266 [20]	1293 [17]
	Maximum Velocity ($m.s^{-1}$):								
FAM	0.28 [0.01]	0.28 [0.01]	0.28 [0.01]	0.28 [0.01]	0.28 [0.01]	0.28 [0.01]	0.28 [0.01]	0.28 [0.01]	0.28 [0.01]
FF	0.32 [0.02]	0.31 [0.01]■	0.31 [0.01]■	0.31 [0.01]	0.31 [0.02]■	0.31 [0.01]■	0.32 [0.01]■✦	0.31 [0.01]■	0.32 [0.01]■
WO	0.29 [0.01]	0.29 [0.01]	0.29 [0.01]	0.29 [0.01]	0.29 [0.01]	0.30 [0.01]	0.29 [0.01]	0.30 [0.01]	0.30 [0.01]
	Movement Duration (ms):								
FAM	848 [23]	858 [22]	871 [27]	863 [20]▲	861 [16]	847 [26]	862 [22]	854 [18]▲	855 [22]
FF	862 [20]	882 [15]✦	869 [22]✦	885 [23]✦	895 [18]✦	894 [17]✦	864 [21]	870 [23]✦	865 [14]
WO	816 [17]	818 [16]	823 [17]	814 [18]	819 [22]	796 [17]	824 [17]	803 [15]	821 [15]
	Summed Error (distance: cm)								
FAM	2.48[0.17]	2.46[0.21]	2.51[0.21]	2.78[0.19]	2.61[0.15]	2.50[0.18]	2.72[0.21]	2.63[0.21]	2.75[0.26]
FF	4.17 [0.29]■✦	4.94 [0.71]■	3.98 [0.29]■	4.25 [0.21]■✦	4.69 [0.34]■✦	5.20 [0.47]■✦	5.23 [0.43]■✦	4.59 [0.25]■✦	5.35 [0.41]■✦
WO	3.12 [0.32]	3.07 [0.41]	3.07 [0.37]	3.28 [0.26]	3.05 [0.35]	3.10 [0.49]	3.05 [0.33]	3.02 [0.35]	3.81 [0.56]
	Force (*N*):								
FAM	4.6[0.3]	4.7[0.3]	4.7[0.3]	4.7[0.3]	4.8[0.3]	4.6[0.3]	4.7[0.3]	4.7[0.3]	4.7[0.3]
FF	10.6[0.3]■✦	10.5[0.3]■✦	10.5[0.3]■✦	10.4[0.3]■✦	10.6[0.3]■✦	10.3[0.3]■✦	10.5[0.3]■✦	10.5[0.3]■✦	10.8 [0.3]■✦
WO	4.8[0.2]	4.9[0.2]	4.9[0.2]	4.9[0.2]	4.9[0.2]	4.9[0.2]	4.9[0.2]	4.9[0.2]	5.0[0.2]

Symbols represent significance following post hoc testing:

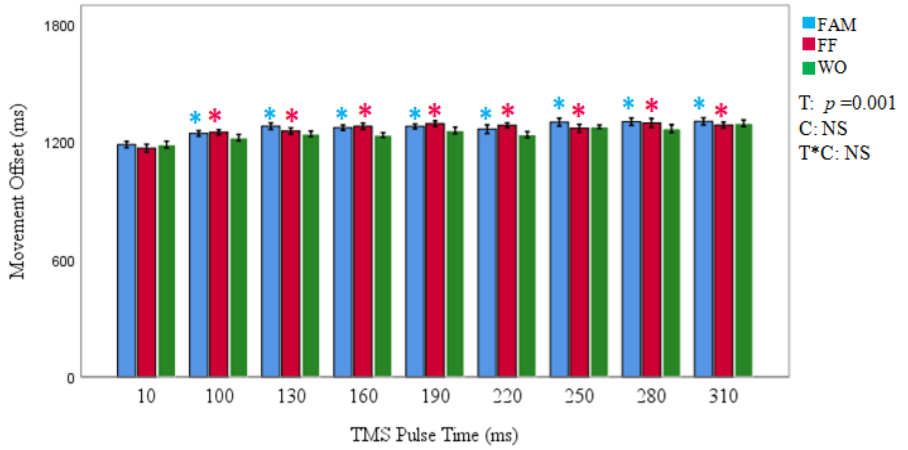
* = significant difference vs T10 for time in FAM blocks, * = significant difference vs T10 for time for FF blocks, * = significant difference vs T10 for time for WO blocks, ■ = significant difference between FAM and FF, ▲ = significant difference between FAM and WO, ✦= significant difference between FF and WO

Figure 5.1[A-F]: Graphical presentation of the post-hoc testing results (based on table 5.3) for the significant kinematic variables:

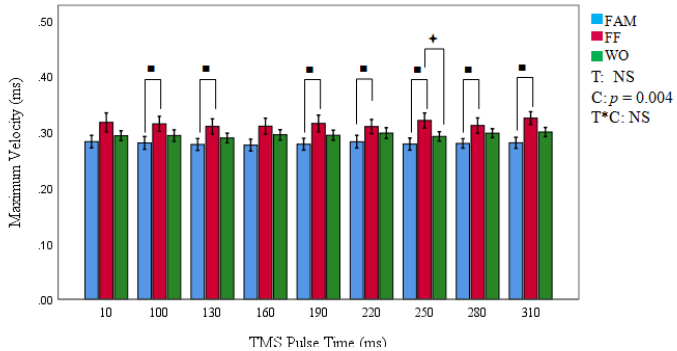
A) Movement onset (ms)



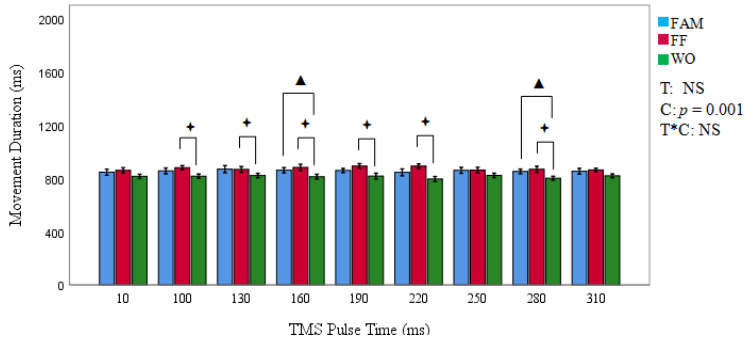
B) Movement offset (ms)

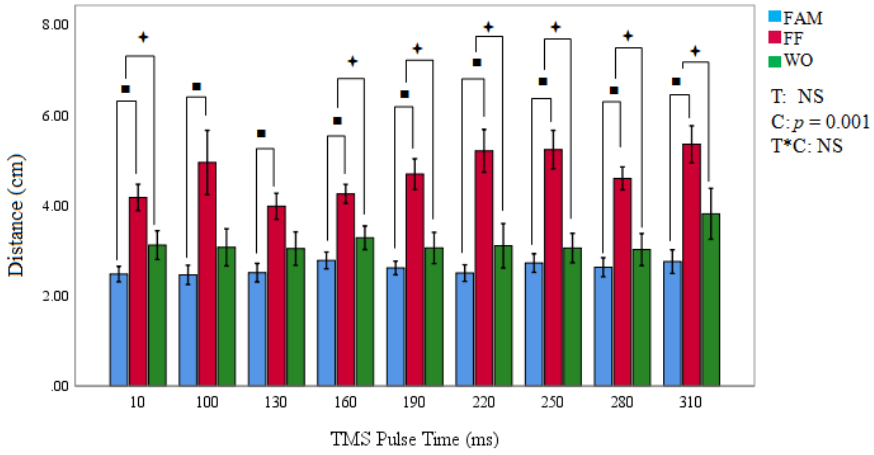
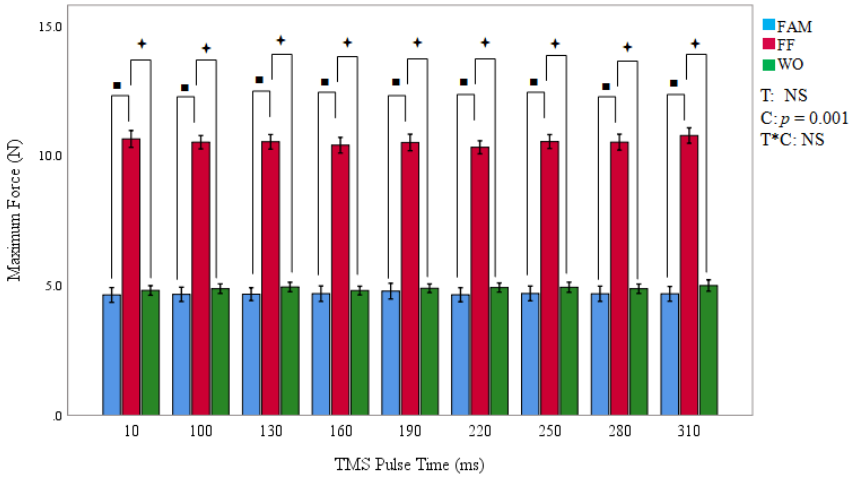


C) Maximum Velocity (m.s⁻¹):



D) Movement Duration (ms):



A) Summed error	B) Maximum force (N)
	

Symbols represent significance following post hoc testing:

* = significant difference vs T10 for time in FAM blocks, * = significant difference vs T10 for time for FF blocks, * = significant difference vs T10 for time for WO blocks,
■ = significant difference between FAM and FF, ▲ = significant difference between FAM and WO, ✦= significant difference between FF and WO

5.6 Discussion

The purpose of this chapter was to explore the effects of TMS delivered to the left M1 during reaching preparation in motor adaptation. Previous experiments investigating the role of the left M1 regarding motor function have implemented different TMS protocols and delivered TMS at different time points to target the M1 (Hunter, Sacco and Turner, 2011; Orban de Xivry *et al*., 2013). Studies have also been conducted in non-human primates to explore neuronal changes in the left M1 during the early stages of motor adaptation (Paz *et al*., 2003). This experiment aimed to provide novel findings regarding left M1 function in human subjects with single pulse TMS in a robotic-mediated upper-limb reaching FF paradigm.

5.6.1 MEP responses:

This study demonstrated significantly larger MEP responses in the BB muscle during FF reaching compared to both FAM and WO reaching, whereas MEP amplitude in the TB was significantly larger when comparing FF reaching to FAM reaching only. No other muscles (ECR and FCR) were significantly affected by CONDITION. The results from this study showed a significant increase in BB MEP amplitude as TMS pulses became closer to movement onset, and this trend for the increase in CSE during the latter stages of movement preparation is in line with previous studies (Leocani *et al*., 2000; Orban de Xivry *et al*., 2013).

Furthermore, the changes in peak-to-peak MEP responses that were greater in the BB muscle (compared to the TB muscle – whereby only FF reaching responses at 220ms differed from FAM reaching; see table 5.1) can be explained by the distribution of corticospinal projections (Richardson *et al*., 2006). For instance, studies in both human subjects and non-human primates have shown that significantly greater numbers of corticomotor neuronal cells project to the BB motor neurons compared to the TB motor neurons (Palmer and Ashby 1992; Richardson *et al*., 2006). Further evidence for this notion comes from patients with M1 lesions resulting in arm paresis, whereby weakness in the limbs have been found to be more prominent in elbow flexors as opposed to elbow extensors (Andrews and Bohannon, 2000; Richardson *et al*., 2006). Therefore MEP findings in this study provided evidence for the notion that adaptive changes are

affected differently in muscles, resulting in their varying CSE, possibly driven by different neural pathways (Hunter, Sacco and Turner, 2011).

5.6.2 Kinematics:

The results of this experiment demonstrated that TMS to the left M1 had a behavioural effect by prolonging the movement onset time. This addresses hypothesis two for this experiment. The findings showed that the later the TMS pulse was delivered during movement preparation, the greater the delay in movement onset. TMS to the left M1 during movement preparation had both time and condition effects, which was not the case for the other kinematic variables explored (movement offset, duration, maximum velocity, summed error and maximum force). These results with regards to the delay in movement onset have been similarly highlighted by Day, Rothwell and Marsden (1983) and Meyer and Voss (2000). Day, Rothwell and Marsden (1983) proposed that TMS stimulation leads to neuronal inhibition, which results in neurons becoming unresponsive for a brief moment, therefore delaying the signals that facilitate movement onset. Kimura, Haggard and Gomi (2006) similarly reported that the effect of TMS during perturbed reaching significantly postponed movement onset. The cause of the delay following stimulation that were found can thus be attributed to the inhibitory effects of SP-TMS (see Section 4.6.2).

The delay that occurred in movement onset and offset can also be explained by the 'waiting period' phenomena as described by Hasegawa *et al*., (2017). Prior to motor output there is a waiting period (i.e. the wait when preparing for action). Movement preparation has been argued to be a result of cortical changes that occur during the waiting period (Wise, 1985; Hasegawa *et al*., 2017). Using calcium imaging methods to explore motor cortical neuronal activity in mice during preparation for reaching, Hasegawa *et al*., (2017) found that motor preparation was accompanied by a selective inhibition of neural networks mediated by interneurons (Pfeffer *et al*., 2013) which resulted in delays in movement responses due to the waiting period. This finding was therefore important because it highlighted the link between motor behaviours and the M1 circuitry, specifically how the neural networks can influence reaching preparation.

An additional behavioural finding from this study was the significant increase in maximum velocity during FF TMS reaching compared to TMS FAM reaching. Motor adaptation paradigms without TMS have also demonstrated that FF reaching increases

the speed of movements during a reach (Pizzamiglio *et al*., 2017a). Researchers have argued that when there is a sudden change in the environment (e.g. a perturbation), velocity shifts occur (i.e. larger peaks in movement) to allow more time for participants to reach a target (Izawa *et al.,* 2008).

Furthermore, in this study TMS interfered with novel reaching, as summed error was significantly larger during FF reaching compared to both FAM and WO reaching. This result could be due to TMS disrupting neural communication processes between the M1 and other motor regions. For example, the cerebellum plays a key role in transmitting signals to the M1 to enable accurate motor reaching (i.e. straight and smooth trajectories) (Bastian, 2011). However it has been argued that following neuroplasticity, cells in the M1 become altered and motor responses in reaching occur as a result of input from other cortical structures, such as the pre-motor cortex and parietal cortex (rather than the cerebellum), which can cause errors in reaching (Tseng *et al*., 2007; Orban de Xivry *et al*., 2013). Errors in FF reaching could have also been a result of the recruitment of other brain regions (e.g. pre-motor cortex, posterior parietal regions, and the cerebellum) (Lee, *et al*., 2003). For example, stimulation could have effected related motor cortical structures via trans-synaptic transmission (Chouinard *et al*., 2003; Richardson *et al*., 2006).

Overall, although various behaviours (neural and kinematics) were investigated in this experiment there are a number of factors to consider. For example, only individuals aged between 18 - 37 were tested, therefore these findings may not be generalisable to other age groups (e.g. older adults). Furthermore, motor adaptation learning without TMS was confined to four blocks only. It could be argued that these four blocks of reaching may not have been enough to fully explore the learning process and adding additional blocks may have warranted different results with TMS to the left M1. However, this would have been too demanding and fatiguing for the participant, particularly with TMS stimulation delivered after FF blocks of reaching. Therefore, there was a trade-off between participants completing the full motor adaptation and avoiding fatigue.

5.7 Chapter conclusions:

The purpose of this chapter was to illustrate the neural and behavioural effects of TMS to the left M1 during right arm novel reaching. Behavioural changes that were observed

such as delays in movement onset and offset can be attributed to the inhibitory effects of SP-TMS to the motor cortex. Additionally the effects of TMS on trajectory errors (summed error) were significantly larger during FF reaching as opposed to FAM and WO reaching, showing the specific disruptive effect of stimulation during novel TMS reaching only. This can be a result of various factors, including 1) neuroplasticity affecting communication between different cortical motor structures, and 2) the possible trans-synaptic effect of TMS to related cortical regions. Furthermore, MEP findings were also in line with previous studies, showing an increase in BB amplitude as opposed to TB amplitude when reaching away from the body (135° target) during FF reaching. MEPs were also found to be time- and condition-tuned, with significantly larger responses when TMS pulses became closer to movement onset, and mainly in FF blocks of reaching (see table 5.1). The differences in CSE muscles responses (i.e. flexors vs. extensors) in adaptive reaching in this study can be attributed to a possible difference in neural pathways between muscles, a notion that has been further supported by patients with M1 lesions. The next experimental chapter in this thesis explores whether TMS to the left PPC results in similar behavioural findings, especially when considering that the left PPC plays a vital role along with the M1 in novel reaching.

Chapter 6

6 Experiment 3

The impact of SP-TMS to the left posterior parietal cortex (PPC) during right arm reaching in a motor adaptation protocol - A virtual disruption study

6.1 Introduction

TMS has been used as a virtual disruption tool to gain an insight into the functional role of different brain regions (Della-Maggiore *et al*., 2004; Sliwinska, Vitello and Devlin, 2014). The current that is induced in the brain when TMS is delivered to a specific site can have an impact on local brain activity and functional connectivity with other more remote regions such that disruptions in behavioural responses can result (Bolognini and Ro, 2010). Therefore, TMS can explore whether a cortical region is necessary for a particular function and this makes it different from other imaging modalities, such as functional magnetic resonance imaging (fMRI), which is more correlation-oriented, rather than casual-oriented in studying brain-behaviour functions (Bolognini and Ro 2010; Sliwinska, Vitello and Devlin, 2014).

Virtual disruption effects can be explored when TMS is delivered before and during a behavioural task. The changes that can occur in behavioural responses range from changes in the behavioural reaction time in response selection (this can be either increased or decreased) to enhanced errors rates in performance (Della-Maggiore *et al*., 2004; Paus 2005; Sack, 2006; Sliwinska, Vitello and Devlin, 2014). For example, repetitive TMS (rTMS) to the left inferior frontal cortex has been found to induce errors in speech production (Pascual-Leone, Gates and Dhuna, 1991; Sliwinska, Vitello and Devlin, 2014), whereas single-pulse to the visual cortex has been reported to disturb processes of visual perception (Corthout *et al*., 1999; Bolognini and Ro 2010).

Throughout this thesis, a robot-mediated force-field learning paradigm was used to explore novel motor learning. Although various regions in the neural motor circuit are involved in motor skill learning and aid the motor adaptation process, the left posterior parietal cortex (PPC) has been reported to be a key region that facilitates novel motor learning. The left PPC contributes to movement preparation and motor planning, as well as navigation and spatial awareness (Kaas and Stepniewska, 2016; Whitlock, 2017). For example, in a functional magnetic resonance imaging study (fMRI) study in which taxi

drivers carried out a virtual driving task by imagining driving passengers through a route, findings showed an increase in cortical activity within the parietal regions, particularly during the planning stage of the virtual journey (Maguire, Woollett and Spiers, 2006). The left PPC also has specific functions related to motor reaching, with evidence pointing to a posterior parietal reach region (PPR) in both macaques and human subjects (Connolly, Andersen and Goodale, 2003; Kaas and Stepniewska, 2016). In non-human primates, reaching and pointing tasks showed maximum neuronal firing in the PPR region, and in human imaging studies an area, homologous to where it was found in monkeys was activated (Batista *et al*., 1999; Connolly, Andersen and Goodale, 2003; Whitlock, 2017).

The PPC is also involved in motor sequence learning (Jenkins *et al*., 1994; Catalan *et al*., 1998). Positron emission tomography (PET) studies exploring regional cerebral blood flow (rCBF) during sequential finger and thumb tapping have demonstrated that rCBF in parietal regions is specific to the length and complexity of the motor sequence; the longer and more complex the sequence, the greater the rCBF (Jenkins *et al*., 1994; Catalan *et al*., 1998). This activation has been explained by the link between the prefrontal cortex and the PPC which enables sustained attention during complex sequencing task (Friston *et al*., 1991; Catalan *et al*., 1998). As well as sequential motor learning, the function of the left PPC in novel motor learning was demonstrated by Della-Maggiore *et al*., (2004). In a robotic reaching task, they delivered single-pulse TMS to both the left PPC and an area of the occipital lobe (as a control) following movement onset and explored differences in reaching trajectories between the two regions during FAM and FF reaching. They found that FAM reaching with TMS did not affect kinematics of reaching and similar reaching performance was noted between the two regions when stimulated. During FF TMS reaching however, although performance was similar between the two regions in the initial stages of reaching, this was not the case in the final stages of FF reaching. Reaching deviated from the ideal path only with left PPC stimulation and not with occipital stimulation, demonstrating the importance of the left PPC in signalling the correct motor responses for regulating reaching trajectories during novel motor learning (Della-Maggiore *et al*., 2004).

The left PPC was targeted in this experiment (with TMS) due to its functions in motor reaching and purported importance in novel motor learning. This experiment provides a novel insight into kinematic parameters related to reaching that have not previously

been explored with left PPC stimulation such as movement onset, movement offset and maximum velocity. However, in line with other experiments (i.e. Della-Maggiore *et al*., 2004) errors in reaching will also be explored (summed error).

TMS has been noted to disrupt behaviours when delivered at specific times. For example, single-pulse TMS to the visual cortex between 80ms to 140ms impaired visual perception processes (Amassian *et al*., 1989; Bolognini and Ro, 2010). In this experiment TMS was administered at a range of different time points during reaching preparation. This is because it is currently unknown whether TMS during motor preparation impacts behavioural responses, as time-related disruptions of the left PPC have only been studied following movement onset (Della-Maggiore *et al*., 2004). This experiment therefore set out to provide a novel insight into left PPC function with regards to its role in motor planning during a novel form of motor adaptation.

6.2 Methodology

Table 3.2 illustrates participant demographics for this experiment. Section 3.3.2.2 highlights how regions with no visible experimental output (i.e. an MEP) were identified (with an EEG cap) and how TMS intensity was set using functional measures. Section 3.3.2.2.1 specifically describes the location that was used for left PPC stimulation (P3 electrode) and the coil position employed. This is also graphically illustrated in figure 3.3. Furthermore, the reaching task used for motor adaptation is described in section 3.4.1 and 3.4.2, and is shown in figure 3.5.

6.3 Data acquisition: MEPs and Kinematics

MEP responses were only obtained and recorded when locating the motor hotspot for the BB. This was carried out in order to identify the participant's resting motor threshold (RMT) (left M1) to deliver TMS to the left PPC at 110% of their RMT. MEPs were not elicited during left PPC stimulation. The main data from this experiment were kinematics; section 3.6.1 describes how kinematic parameters were all analysed and quantified offline in MatLab 2017b (The MathWorks Inc, Natick MA, USA).

6.4 Statistical analysis: Kinematics

The analysis performed for the kinematic variables, including the statisitical tests carried out (RMANOVA), how sphericity assumptions were met and the steps taken for post-hoc testing (Student's t-test) for the main factors of TIME and CONDITION, and for TIME*CONDITION interactions is described in section 3.7.1.

6.5 Results

6.5.1 Kinematics - parameters and trajectories of reaching:

When TMS was introduced in FF reaching, trajectory deviations were visible (even during the final block of reaching), which was not the case for FAM and WO reaching (see figure 6.1). This demonstrated that TMS had a specific disruptive effect only during novel motor learning.

The RMANOVA (table 6.1) revealed a significant main effect for TIME on movement onset and movement offset ($p < 0.05$), but not for maximum velocity, movement duration, summed error and maximum force ($p > 0.05$). There was also a significant main effect of CONDITION for movement onset, maximum velocity, movement duration, summed error and maximum force ($p < 0.05$) but not for movement offset ($p > 0.05$). There were no significant interaction effects found for any of the kinematic variables ($p > 0.05$) (see table 6.1).

Post hoc testing for TIME (table 6.2, figure 6.2[A-F]) demonstrated that during FAM reaching with TMS, movement onset was significantly increased compared to T10 at all time points apart from T100. Movement offset was significantly increased from T10 during 190ms, 220ms, 250ms, 280ms and 310ms. During FF reaching with TMS, movement onset was increased at all time points compared to T10 (all $p < 0.006$). Movement offset was significantly increased at all time points apart from 100ms and 250ms compared to the T10. During WO reaching, movement onset was significantly increased compared to the T10 response at 190ms, 220ms, 280ms and 310ms ($p < 0.006$), whilst movement offset was only significantly increased at 280ms compared to T10.

Post hoc testing for CONDITION (table 6.2, figure [6.2A-F]) comparing FF vs. FAM found no significant differences between responses for movement onset ($p > 0.016$). Maximum velocity was greater in FF reaching compared to FAM reaching (all time points; $p < 0.016$). Movement duration was greater in FF reaching although only at 130ms ($p < 0.016$). Summed error and maximum force were both increased in FF reaching compared to FAM reaching (at all time points all $p < 0.016$). Generally, kinematics values returned to or towards FAM values in WO reaching.

Post hoc testing results are shown in table 6.2 and figure 6.2[A-F].

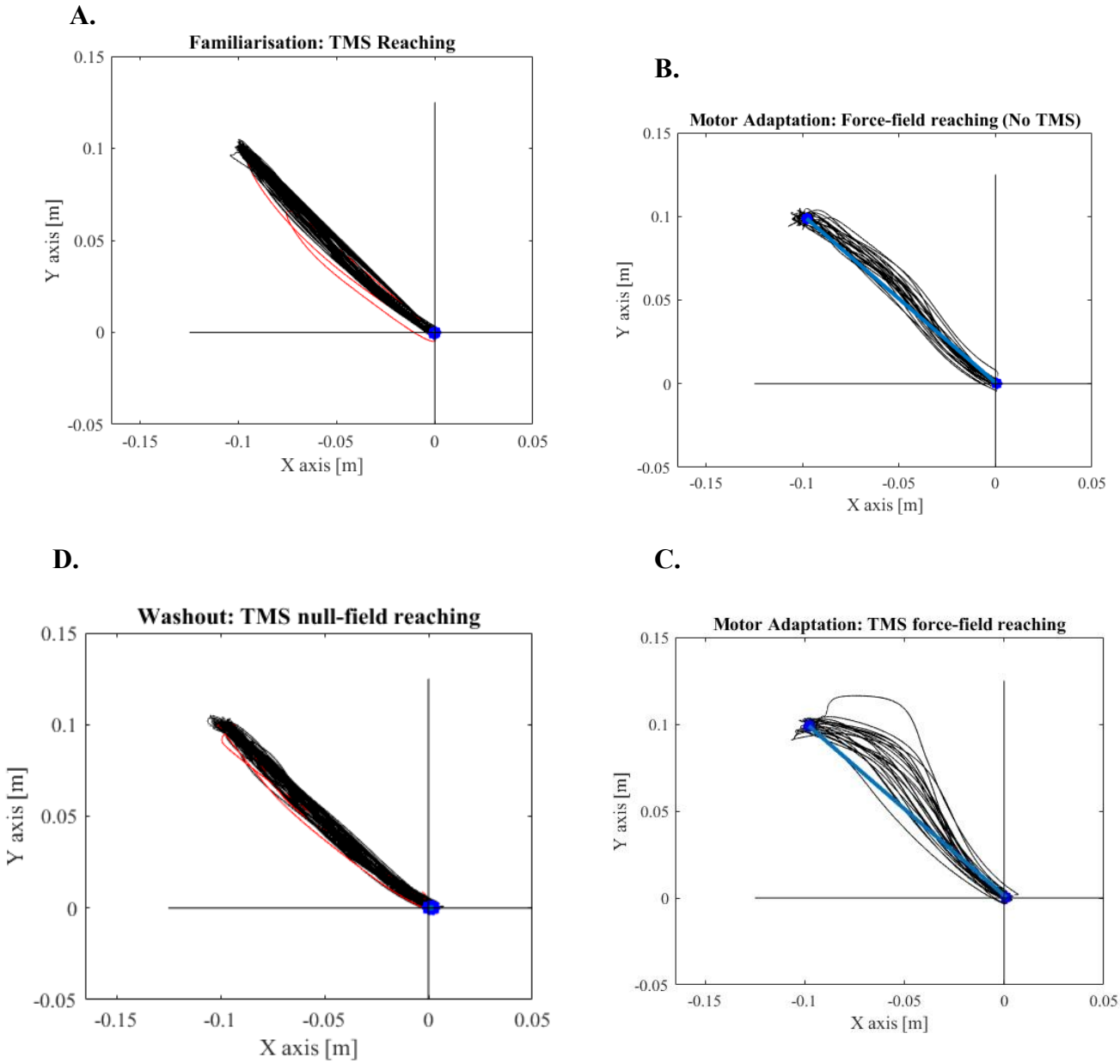


Figure 6.1: Reaching block trajectories with TMS delivered to the left PPC in a single-participant

TMS to the left PPC during FAM reaching only resulted in a slight deviation from the ideal reaching trajectory in the first few trials (red coloured traces - A). FF reaching trajectories are shown in figures 6.2B and 6.2C. Figure 6.2B illustrates reaching trajectories in the final block of FF reaching without TMS, and figure 6.2C shows reaching trajectories in the final block of FF reaching with TMS. It can be seen that in the final block of FF reaching with no TMS delivered, the participant was able to adapt to the force-field because reaching became closer to the ideal, however, when TMS was introduced into the FF reaching, this resulted in major deviations from the ideal reaching trajectory (C). During WO, reaching trajectories returned to FAM values with or without TMS (D).

Table 6.1. Results of the two-way RMANOVA:

	TIME:			CONDITION			TIME * CONDITION INTERACTION		
	df(Error)	F	Sig.	*df*(Error)	F	Sig.	*df*(Error)	F	Sig.
Movement Onset (ms)	3.0 [38.1]	17.15	**< 0.001**	2 [26]	9.11	**< 0.001**	16[208]	0.568	0.906
Movement Offset (ms)	8[104]	8.511	**< 0.001**	2[26]	0.176	0.840	16[208]	1.285	0.209
Maximum Velocity ($m.s^{-1}$)	8[104]	0.257	0.916	2 [26]	10.15	**0.001**	16[208]	0.935	0.530
Duration (ms)	4.6 [58.7]	0.538	0.729	2[26]	5.159	**0.019**	16[208]	1.233	0.245
Summed Error (distance: cm)	3.3 [42.5]	1.374	0.263	1.2 [14.8]	13.34	**< 0.001**	16[208]	1.363	0.162
Maximum Force (*N*)	3.1 [40.2]	1.362	0.268	1.2 [14.4]	243.01	**< 0.001**	16[208]	1.119	0.339

Table 6.2. Post-hoc testing results

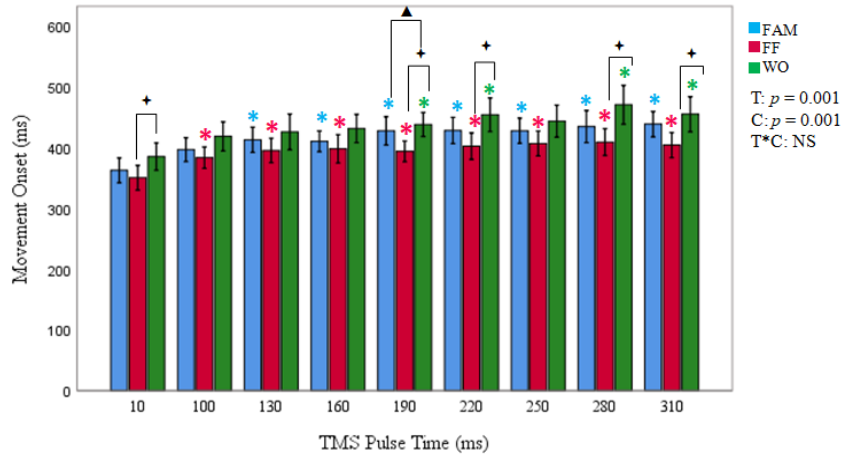
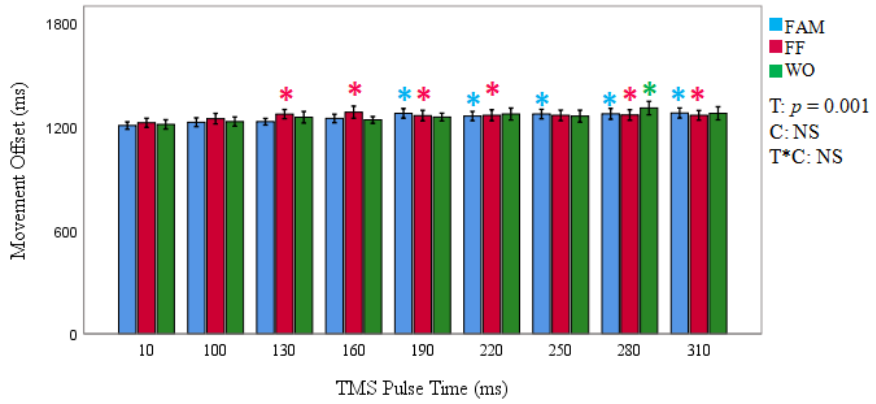
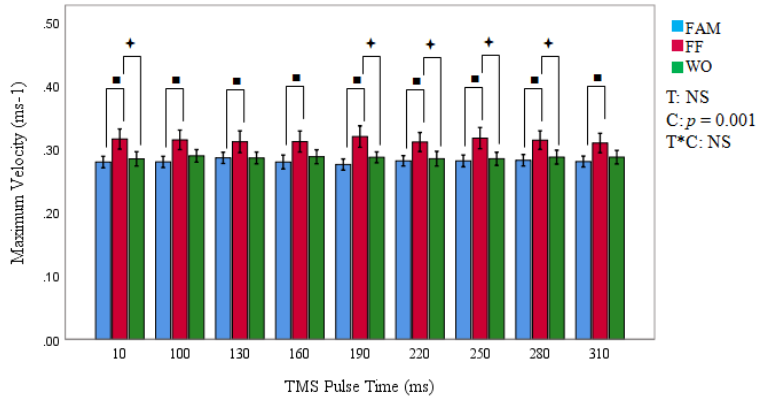
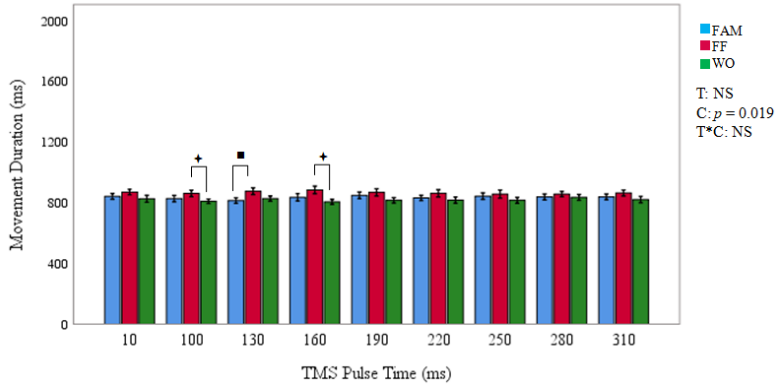
The table shows kinematic responses during FAM, FF and WO blocks of reaching when TMS was applied to the left PPC at different time points. Values represent means and standard error means (SEM).

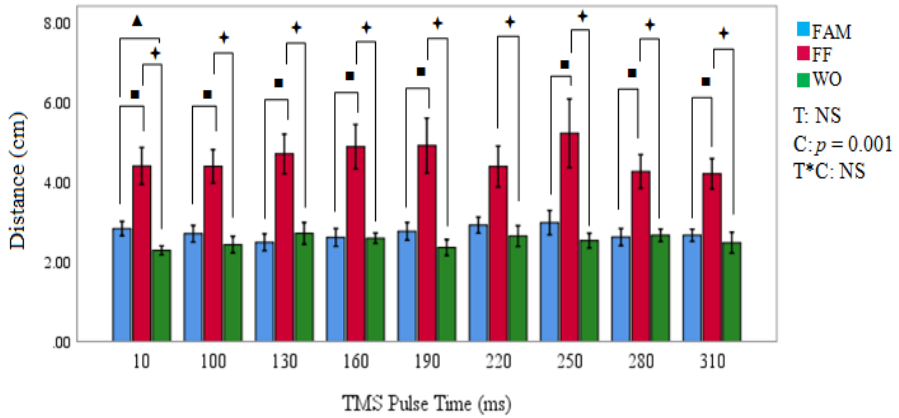
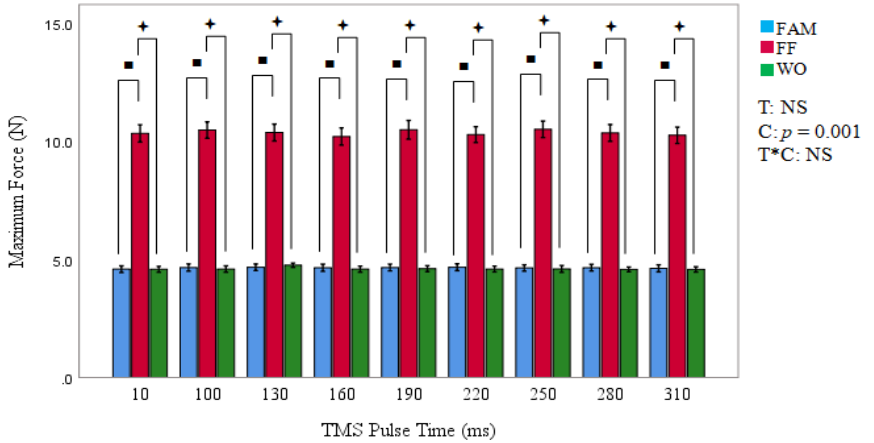
TIME	TMS: 10ms Mean [SEM]	TMS: 100ms Mean [SEM]	TMS: 130ms Mean [SEM]	TMS: 160ms Mean [SEM]	TMS: 190ms Mean [SEM]	TMS: 220ms Mean [SEM]	TMS: 250ms Mean [SEM]	TMS: 280ms Mean [SEM]	TMS: 310ms Mean [SEM]
CONDITION	Movement Onset (ms):								
FAM	362 [20]	396 [20]	412 [21]*	362 [17]*	427 [23]*▲	428 [22]*	428 [21]*	434 [26]*	438 [21]*
FF	350 [20]✦	383 [18]*	395 [20]*	350 [23]*	393 [17]*✦	402 [23]*✦	406 [20]*	408 [22]*✦	403 [21]*✦
WO	384 [22]	418 [24]	425 [29]	384 [23]	437 [20]*	453 [28]*	443 [26]	470 [32]*	454 [39]*
	Movement Offset (ms):								
FAM	1204 [21]	1223 [26]	1226 [16]	1245 [24]	1274 [21]*	1259 [26]*	1270 [28]*	1272 [31]*	1276 [29]*
FF	1220 [26]	1244 [30]	1270 [27]	1281 [35]*	1261 [30]*	1264 [32]*	1263 [31]	1265 [30]*	1263 [28]*
WO	1210 [27]	1227 [27]	1252 [33]	1237 [20]	1253 [22]	1271 [34]	1258 [34]	1305 [39]*	1275 [38]
	Maximum Velocity ($m.s^{-1}$):								
FAM	0.28 [0.01]	0.28 [0.01]	0.29 [0.01]	0.28 [0.01]	0.28 [0.01]	0.28 [0.01]	0.28 [0.01]	0.28 [0.01]	0.28 [0.01]
FF	0.32 [0.02] ✦■	0.31 [0.02] ■	0.31 [0.02] ■	0.31 [0.02] ■	0.32 [0.02]✦■	0.31 [0.02] ✦■	0.32 [0.02] ✦■	0.31 [0.01] ✦■	0.33 [0.02] ■
WO	0.28 [0.01]	0.29 [0.01]	0.29 [0.01]	0.29 [0.01]	0.29 [0.01]	0.28 [0.01]	0.28 [0.01]	0.29 [0.01]	0.29 [0.01]
	Movement Duration (ms):								
FAM	842 [19]	827 [21]	814 [18]	836 [24]	849 [22]	832 [17]	843 [21]	838 [19]	839 [19]
FF	870 [18] ✦	861 [21]✦	876 [22] ■	884 [25] ✦	868 [24]	862 [24]	857 [27]	857 [18]	864 [20]
WO	826 [23]	809 [15]	827 [17]	806 [16]	816 [18]	817 [20]	815 [19]	835 [19]	821 [21]
	Summed Error (distance: cm):								
FAM	2.83[0.18] ▲	2.71 [0.21]	2.49[0.21]	2.61[0.22]	2.77[0.22]	2.92[0.20]	2.98[0.31]	2.62[0.22]	2.67[0.15]
FF	4.41[0.46] ✦■	4.40[0.42] ✦■	4.71[0.50] ✦■	4.89[0.56] ✦■	4.92[0.69] ✦■	4.39[0.51] ✦■	5.23[0.86] ✦■	4.27[0.42] ✦■	4.21[0.38] ✦■
WO	2.29[0.11]	2.43[0.21]	2.72[0.27]	2.59[0.13]	2.36[0.20]	2.65[0.26]	2.53[0.19]	2.67[0.16]	2.48[0.26]
	Force (*N*):								
FAM	4.6[0.1]	4.7[0.2]	4.7[0.1]	4.7[0.2]	4.7[0.1]	4.7 [0.2]	4.7[0.1]	4.7[0.1]	4.6[0.2]
FF	10.0[0.4] ✦■	10.5[0.4] ✦■	10.4[0.4]✦■	10.2[0.4]✦■	10.5[0.4] ✦■	10.3[0.3] ✦■	10.5[0.4] ✦■	10.4[0.4] ✦■	10.3[0.4] ✦■
WO	4.6[0.1]	4.6[0.1]	4.8[0.1]	4.6[0.1]	4.6[0.13]	4.6[0.1]	4.6[0.2]	4.6[0.1]	4.6[0.1]

Symbols represent significance following post hoc testing:

* = significant difference vs T10 for time in familiarisation blocks, * = significant difference vs T10 for time for FF blocks, * = significant difference vs T10 for time for WO blocks, ■ = significant difference between FAM and FF, ✦= significant difference between FF and WO, ▲ = significant difference between FAM and WO

Figure 6.2[A-F]: Graphical presentation of the post-hoc testing results (based on table 6.2) for the significant kinematic variables:

A) Movement onset (ms)	B) Movement offset (ms)
	
C) Maximum Velocity ($m.s^{-1}$):	**D) Movement Duration (ms):**
	

E) Summed error	F) Maximum force (N)
	

Symbols represent significance following post hoc testing:

* = significant difference vs T10 for time in familiarisation blocks, * = significant difference vs T10 for time for FF blocks, * = significant difference vs T10 for time for WO blocks, ■ = significant difference between FAM and FF, ✦= significant difference between FF and WO, ▲ = significant difference between FAM and WO

6.6 Discussion

The results of this experiment demonstrated the effects of single-pulse TMS to the left PPC during a novel motor task. Previous research of left PPC stimulation have not examined whether TMS at various of different time points during the preparation of a reach affects specific kinematic variables, such as movement onset and movement offset, but have rather placed emphasis on trajectory errors of reaching that occur after movement onset (Della-Maggiore *et al*., 2004). This experiment therefore provided a novel insight into how TMS delivered to the left PPC during motor preparation can have an impact on different kinematic variables.

6.6.1 Kinematics - The shift in movement onset:

Stimulation the left PPC with TMS during motor preparation for reaching delayed the movement onset time, in FAM and FF reaching (this addresses hypothesis 2 - experiment 3). Similar delays also occurred in movement offset.

This delay in movement onset and offset can be explained in terms of the state-dependency TMS theory (Silvanto and Muggleton, 2008). This theory proposes that the impact of TMS depends on the degree of excitability that the stimulated region exhibits. In this study, the subjects were already involved in the task, i.e. preparing themselves for action (in this case reaching), the region was therefore pre-activated. It has been suggested that the effects of stimulation on an area that has been pre-activated can result in neuronal noise, which can interrupt the region's functioning, therefore resulting in delayed responses (Miniussi, Ruzzoli and Walsh, 2010; Busan *et al*., 2012). Although previous studies have used other quantification techniques to determine when motor preparation occurred (e.g. participant's mean reaction time) for TMS to be delivered, the results regarding movement onset are similar. For example, it has been found that stimulating mid-point through the preparation phase leads to a delay in movement onset, which is not the case when stimulating prior to movement preparation (Busan *et al*., 2009; Busan *et al*., 2012). In this experiment, TMS was administered during reaching preparation, and not prior preparation (i.e. before visual cue), therefore the delayed responses that occurred regarding reaction times are in line with previous studies.

6.6.2 Kinematics - Impact of TMS on trajectories of reaching (summed error) and reaching velocity:

Another key finding in this experiment was that disrupting the left PPC with TMS during preparation for novel reaching impaired reaching performance as revealed by greater trajectory errors (this addresses hypothesis 1 - experiment 3). Left PPC stimulation significantly impaired reaching only during motor adaptation (FF reaching). The fact that TMS did not cause disruption during FAM and WO reaching suggests that the left PPC has specific functions related to novel motor learning per se. These findings are in line with what has previously been reported by Della-Maggiore *et al*., (2004) who suggested that during FF reaching, different brain regions, including the PPC feed into other cortical structures, signalling commands for successful motor output. Disrupting PPC function with TMS may lead to error signal processing in visuo-motor transformations, thus causing trajectory errors in FF reaching (Chouinard *et al*., 2003; Della-Maggiore, Malfait and Ostry, 2004). Experiment 3 therefore provided further evidence for the importance of the PPC in adjusting arm position to meet the requirements of a novel task.

The role of the left PPC in error signal processing has been further identified by researchers (Oliveira *et al*., 2010), who have argued that the specific network connecting the left PPC with other cortical structures enables the formation of an internal model of error-driven responses for motor output (Oliveira *et al*., 2010; Smith and Shadmehr, 2005). These regions therefore store movement dynamic information (Kawato 1999; ; Della-Maggiore *et al*., 2004; Malfait and Ostry, 2004; Oliveira *et al*., 2010;). In this experiment, TMS to the left PPC over repeated trials led to errors in responses, which based on the error-signal processing theory, could have been due to a disruption of movement dynamics (i.e. deviated reaching responses) being stored as an internal model for novel reaching.

It can be argued TMS to the left PPC creates a virtual disruption model of optic ataxia. Optic ataxia is a neurological condition that causes impairments in visually guided behaviour, and in many patient cases, lesions to the PPC contributes to the condition (Cavina-Pratesi, Connolly and Milner, 2013; Andersen *et al*., 2014). Using similar reaching paradigms, increased trajectory errors have also been found among patients with optic ataxia (Pisella *et al*., 2000) who were not able produce an ideal reach to a target of interest during novel reaching.

Furthermore, TMS stimulation to the left PPC increased maximum velocity responses during FF reaching compared to FAM and WO reaching. It could be argued that participant's increase their speed because they require more time to reach towards the target (due to the robotic perturbation). Specific structures in the motor network system connected to the left PPC have also been found to facilitate this action. For example, the cerebellum and the premotor cortices have been suggested to provide the appropriate strategies to respond to movements, through eliciting fast responses or slow responses depending on the task (Desmurget and Grafton, 2000). Based on this notion, various networks in the M1 enable individuals to adjust their speed of movements which can help explain why velocity responses differ between reaching blocks.

6.7 Chapter conclusions:

The purpose of this chapter was to explore the effects of left PPC stimulation during novel motor learning. TMS only had a significant disruptive impact on summed error during novel reaching, which is in line with conclusions drawn from previous research and can be explained by disrupted error-signal processing. Considering that TMS did not disrupt reaching processes in null-field reaching (FAM and WO) implies that the left PPC has a specific function related to novel motor learning. Overall, this experiment demonstrated that TMS to the left PPC caused a virtual disruption in learning. The mechanism may be via disruption of local processing or disrupted pathways involving the PPC and more remote nodes of the motor network circuit. Investigating whether novel motor learning is also disrupted during stimulation of other motor regions could help in developing a model of cortical regions that are specific only for novel motor reaching.

Chapter 7

7 Experiment 4

Exploring the impact of SP-TMS to the supplementary motor area (SMA) during right arm reaching in a novel motor learning protocol

7.1 Introduction

The supplementary motor area (SMA) is located in the frontal lobe of the brain and is situated near motor regions, such as the pre-motor cortex (PMC) and M1 (Nachev *et al*., 2007). It consists of two regions; the pre-SMA and the SMA proper, and their functions differ regarding neural input and output underpinning motor behaviours. For example, the pre-SMA receives input from the prefrontal cortex, whereas the SMA-proper projects the input to the M1 for motor output (Tanji, 1994).

The SMA is known to have multiple functions which facilitate motor learning. For example, it assists skilled motor performance, plans movements for execution, helps retrieve motor memories and is also involved in sequential motor learning (i.e. learning patterns of movements; Tanji, 1994; Borich *et al*., 2015). Early imaging studies, including positron emission tomography (PET) scans have illustrated the role of the SMA in motor behaviours. For example, Roland *et al*., (1980) reported an increase in SMA neural activity when subjects imagined producing finger sequencing movements. Functional MRI neuro-feedback studies have also demonstrated the active role of the SMA in motor imagery. For instance, Mehler *et al*., (2019) found increased blood oxygenation level dependent (BOLD) responses in the SMA compared to the M1 (which was de-activated) during a hand motor imagery task.

Other PET imaging studies have explored SMA patterns of cortical activity during motor skill learning and have found increased levels of practise induced activity in the SMA, but not in other cortical regions, such as the cerebellum and right PMC (van Mier, Perlmutter and Petersen, 2004). Functional magnetic resonance imaging (fMRI) studies have compared differences in neural activity between the SMA and the pre-SMA with results illustrating that fast motor learning is accompanied with greater SMA activity but decreased pre-SMA activity (Grafton, Hazeltine and Ivry, 1995; Sakai *et al*., 1999; Floyer-Lea and Matthews, 2005).

Although neuroimaging studies have enabled researchers to explore the role of the SMA in motor skill learning, the specific functions of the SMA in relation to novel motor learning (i.e. motor adaptation) have primarily been investigated in non-human primates. Animal studies have provided an insight into how neuronal activity is changed in the SMA during motor adaptation compared to null-field reaching. For example, in a motor adaptation paradigm, Padoa-Schioppa, Li and Bizzi (2004) found that SMA neurons exhibited plasticity following a novel motor task and cells became differently tuned. Therefore it can be argued that induced plasticity in the SMA facilitates novel motor learning (Padoa-Schioppa, Li and Bizzi 2004).

Studies applying TMS to disrupt the functioning of the SMA have mainly been investigated during motor sequencing tasks and motor tasks performed with both hands (bimanual). For example, Gerloff *et al*., (1997) used repetitive TMS (rTMS) to target the SMA during complex and simple finger motor sequencing tasks. They found that rTMS only reduced motor accuracy in the complex sequencing task. With regards to bimanual motor paradigms, rTMS delivered to the SMA had a detrimental impact in performance during anti-phase (asymmetrical movements) bimanual hand movements compared to in-phase (synchronised movements) hand movements (Serrien *et al*., 2002; Steyvers *et al*., 2003). Therefore, the disruption of the SMA with TMS depends on the complexity of the task (Gerloff *et al*., 1997; Hallett, 2007; Kim and Shin, 2014). Paired pulse TMS (PP-TMS) protocols targeting the SMA, specifically the pre-SMA have shown its involvement in higher cognitive functions (Nachev, Kennard and Husain, 2008). For instance, in a motor response selection paradigm, the pre-SMA was reported to influence selection responses and only effected the excitability of the M1 when motor selection responses were switched in trials (Mars *et al*., 2009; Chouinard and Paus, 2010).

Although studies have been conducted with TMS to demonstrate the functional role of the SMA for motor behaviours, these experiments have mostly been conducted with:

1. rTMS and paired-pulse TMS protocols as opposed to single-pulse TMS protocols.
2. Motor sequencing and bimanual tasks compared to motor adaptation tasks.
3. Non-human primates (in studies concerning motor adaptation) in contrast to human subjects.

Therefore, it is currently unknown whether single-pulse TMS to the SMA during motor preparation disrupts novel motor reaching (i.e. motor adaptation protocol) in human subjects and it is for this reason that this experiment was conducted. The experiment specifically investigated whether trajectory errors or other kinematic measures of reaching (such as movement onset, movement offset, maximum velocity, and movement duration) were affected by applying TMS to the SMA.

7.2 Methodology

Table 3.2 demonstrates the participant demographics for SMA stimulation. TMS intensity was set using functional measures for each participant (section 3.2.2.2). The location of the SMA and coil orientation that was used for stimulation is described in section 3.3.2.2 and graphically demonstrated in figure 3.3 (the orientation and position used was based on Cona, Marino and Semenza, 2017 protocol). Furthermore, the reaching task for this experiment is outlined in section 3.4.1 and figure 3.5.

7.3 Data acquisition: MEPs and Kinematics

MEPs were only acquired during assessment of RMT for each participant at the start of the experiment (see section 3.3.1). Therefore, MEPs were not elicited or collected during SMA stimulation. Kinematic data were collected in this experiment and were analysed and quantified offline in MatLab 2017b (The MathWorks Inc, Natick MA, USA) (section 3.6.1).

7.4 Statistical analysis: Kinematics

A two-way RMANOVA was performed to explore whether different kinematic variables in different reaching blocks (FAM, FF and WO) were affected by TMS to the SMA during reaching preparation. Main effects for TIME, CONDITION and interactions (TIME*CONDITION) were obtained. Section 3.7.1 outlines how sphericity assumptions were tested and the steps taken for post-hoc testing with regards statistically significant findings.

7.5 Results

7.5.1 Kinematics - Repeated measures ANOVA and post-hoc testing:

The RMANOVA (table 7.1) revealed a significant effect of TIME for movement onset and movement offset ($F > 8.102$, $p < 0.05$), but not for maximum velocity, movement duration, summed error and maximum force (all $F < 0.351$, all $p > 0.05$). The RMANOVA showed that TMS to the SMA had a significant effect on CONDITION,

for kinematic variables including movement onset, maximum velocity, summed error and maximum force (all $F > 3.989$, all $p < 0.019$), but not movement offset and duration (all $F < 0.16$, all $p > 0.05$). No interaction effects were found with SMA stimulation (all $F > 0.378$, all $p > 0.05$).

Post hoc testing for TIME (table 7.2, figure 7.1[A-E]) demonstrated a significant increase in all time points except 280ms in FAM reaching for movement onset ($p < 0.006$). For FF reaching, movement onset was significantly increased at all time points compared to T10 ($p < 0.006$). In WO reaching, movement onset only at 220ms and 280ms were significantly increased compared to T10 ($p < 0.006$). Movement offset significantly increased only at 130ms compared to T10 during FAM reaching ($p < 0.006$). During FF reaching, all time points for movement offset were significantly increased compared to T10 ($p < 0.006$). In WO reaching, no significant differences were found at any time points compared to T10 ($p < 0.006$).

Post hoc testing for movement onset for CONDITION (table 7.2, figure 7.1[A-E]) for movement onset demonstrated a significant reduction in the FF condition compared to FAM reaching (only at 190ms; $p < 0.016$). A significant increase in movement onset was found in WO reaching compared to FF reaching (only 220ms; $p < 0.016$). There were no significant differences in WO vs. FAM reaching (all $p > 0.016$). Maximum velocity was significantly increased in FF reaching compared to FAM reaching (only 280ms; $p < 0.016$). There was a significant decrease in maximum velocity in WO compared to FF reaching (only 280ms and 10ms; $p < 0.016$). There were no significant differences in WO vs. FAM reaching (all $p > 0.016$). Summed error (SE) was significantly increased in FF compared to FAM reaching (100ms and 130ms; $p < 0.016$). SE was significantly increased in FF reaching compared to WO reaching (100ms, 130ms, 160ms, $p < 0.016$). There were no significant differences in WO vs. FAM SE responses ($p > 0.016$). Maximum force was significantly increased in FF compared to FAM and WO reaching as expected (all time points; $p < 0.016$). There were no significant differences in WO vs. FAM reaching.

Table 7.1. Results of the two-way RMANOVA:

	TIME			CONDITION			TIME*CONDITION INTERACTION		
	df(Error)	F	Sig.	*df*(Error)	F	Sig.	*df*(Error)	F	Sig.
Movement Onset (ms)	8[104]	13.26	**< 0.001**	2 [26]	3.989	**0.031**	16[208]	0.722	0.770
Movement Offset (ms)	8[104]	8.102	**< 0.001**	2[26]	0.157	0.856	16[208]	0.378	0.903
Maximum Velocity ($m.s^{-1}$)	8[104]	0.351	0.857	2 [26]	4.079	**0.033**	16[208]	0.636	0.852
Duration (ms)	8 [104]	1.127	0.352	2[26]	1.953	0.162	16[208]	0.494	0.948
Summed Error (distance: cm)	8 [104]	0.837	0.572	1.3[16.0]	6.597	**0.016**	16[208]	1.387	0.150
Maximum Force (*N*)	8 [104]	0.80	0.608	1.1 [13.4]	223.72	**< 0.001**	16[208]	1.163	0.301

Table 7.2. Results following post-hoc testing

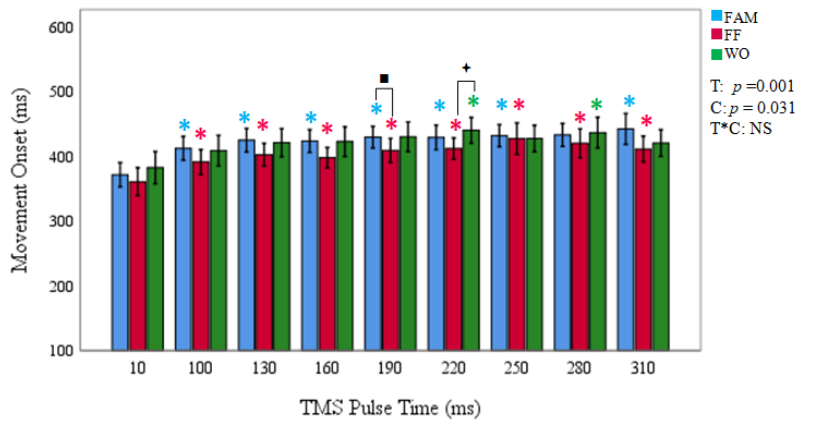
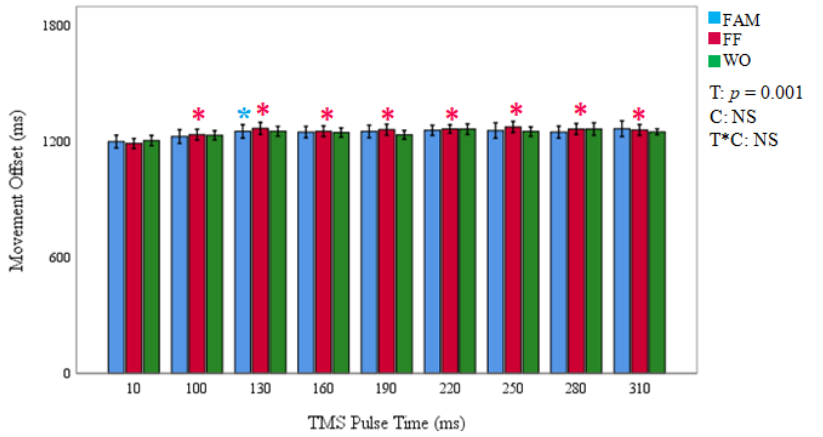
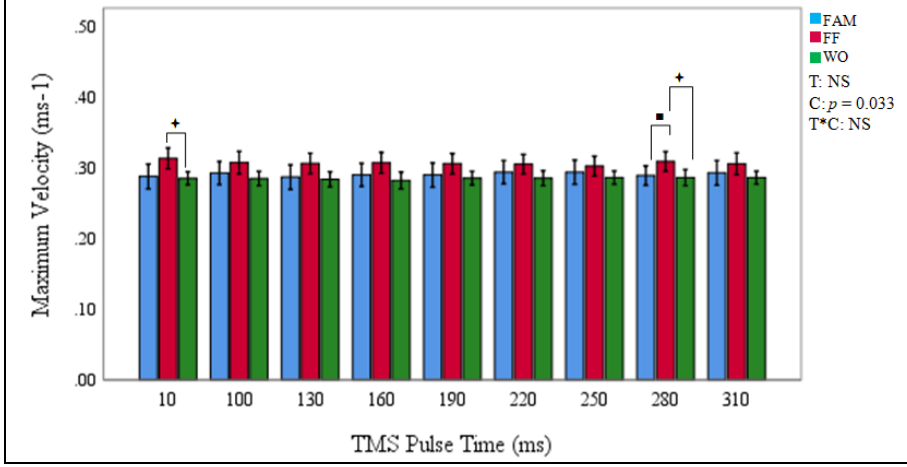
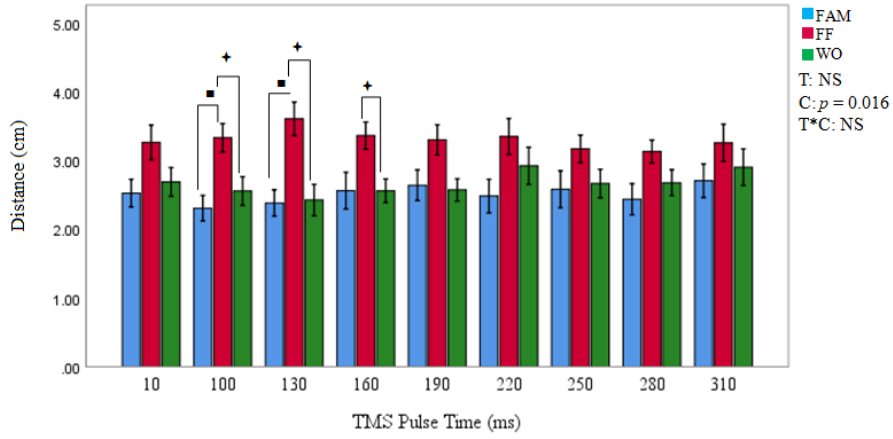
The kinematic data shown in this table is based on FAM, FF and WO blocks of reaching when TMS was delivered to the SMA. Means, ± the standard error mean (SEM) are shown.

TIME	TMS: 10ms Mean [SEM]	TMS: 100ms Mean [SEM]	TMS: 130ms Mean [SEM]	TMS: 160ms Mean [SEM]	TMS: 190ms Mean [SEM]	TMS: 220ms Mean [SEM]	TMS: 250ms Mean [SEM]	TMS: 280ms Mean [SEM]	TMS: 310ms Mean [SEM]
CONDITION	Movement Onset (ms):								
FAM	371 [19]	412 [18] *	425 [18] *	423 [18] *	429 [17] *	429 [19] *	432 [17] *	433 [18]	442 [24] *
FF	361 [22]	391 [19] *	403 [18] *	398 [16] *	409 [19] *■	412 [16] *✦	427 [24] *	420 [22] *	411 [20] *
WO	382 [25]	409 [24]	421 [22]	423 [23]	430 [23]	440 [20] *	427 [21]	436 [24] *	420 [21]
	Movement Offset (ms):								
FAM	1197 [33]	1223 [35]	1250 [35] *	1246 [30]	1249 [33]	1255 [26]	1254 [40]	1246 [31]	1264 [41]
FF	1187 [26]	1233 [28] *	1265 [31] *	1251 [27] *	1259 [28] *	1262 [22] *	1273 [29] *	1262 [29] *	1257 [28] *
WO	1203 [27]	1230 [24]	1251 [26]	1244 [24]	1232 [23]	1261 [27]	1249 [24]	1262 [32]	1247 [16]
	Maximum Velocity ($m.s^{-1}$):								
FAM	0.29[0.02]	0.29[0.02]	0.29[0.02]	0.29[0.02]	0.29[0.02]	0.29[0.02]	0.29[0.02]	0.29[0.01]	0.29[0.02]
FF	0.31[0.01]	0.31[0.02] ✦	0.31[0.01]	0.31[0.01]	0.31[0.01]	0.31[0.01]	0.30[0.01]	0.31[0.01] ■✦	0.31[0.02]
WO	0.29[0.01]	0.29[0.01]	0.28[0.01]	0.28[0.01]	0.29[0.01]	0.29[0.01]	0.29[0.01]	0.29[0.01]	0.29[0.01]
	Movement Duration (ms):								
FAM	826 [31]	813 [31]	825 [30]	823 [28]	820 [29]	823 [28]	822 [34]	813 [25]	822 [32]
FF	826 [24]	842 [22]	862 [21]	853 [21]	850 [20]	851 [17]	847 [25]	843 [19]	848 [21]
WO	821 [22]	820 [20]	830 [25]	824 [25]	803 [21]	820 [24]	822 [20]	825 [28]	827 [21]
	Summed Error (distance: cm):								
FAM	2.53[0.20]	2.31 [0.19]	2.38[0.19]	2.56[0.27]	2.64[0.22]	2.48[0.24]	2.58[0.27]	2.44[0.23]	2.71[0.24]
FF	3.26[0.25]	3.33[0.21] ■✦	3.61[0.24] ■✦	3.36[0.20] ✦	3.30[0.22]	3.35[0.26]	3.17[0.20]	3.13[0.17]	3.26[0.27]
WO	2.69[0.21]	2.56[0.21]	2.43[0.23]	2.56[0.17]	2.57[0.16]	2.92[0.27]	2.67[0.21]	2.68[0.19]	2.90[0.27]
	Force (*N*):								
FAM	4.6 [0.2]	4.5[0.2]	4.5 [0.2]	4.5[0.2]	4.6 [0.2]	4.6[0.2]	4.5[0.1]	4.6 [0.2]	4.6 [0.2]
FF	10.0[0.4] ■✦	9.9[0.4] ■✦	9.8 [0.3] ■✦	9.8[0.4] ■✦	9.9 [0.4] ■✦	9.9[0.3] ■✦	9.8[0.4] ■✦	10.0[0.4] ■✦	9.9 [0.4] ■✦
WO	4.5[0.1]	4.5[0.1]	4.5 [0.1]	4.4[0.1]	4.5 [0.2]	4.4[0.1]	4.5[0.1]	4.5 [0.1]	4.5 [0.1]

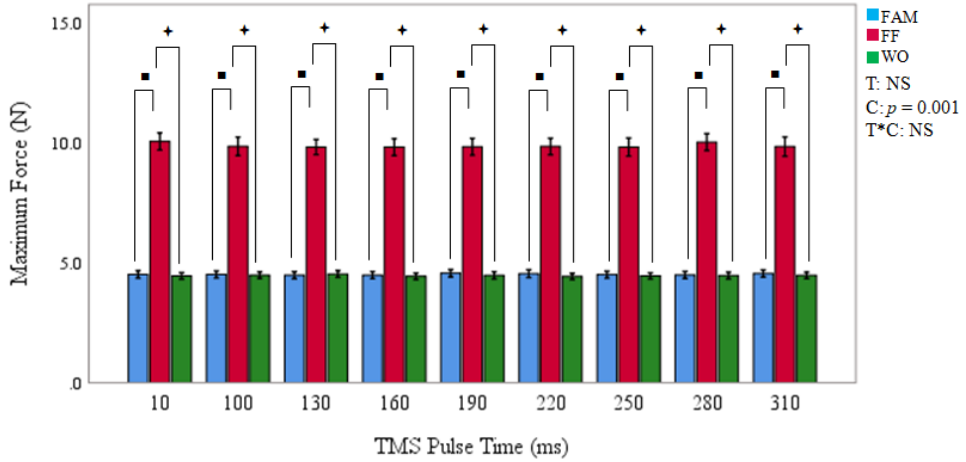
Symbols represent significance following post hoc testing:

* = significant difference vs T10 for time in familiarisation blocks, * = significant difference vs T10 for time for FF blocks, * = significant difference vs T10 for time for WO blocks, ■ = significant difference between FAM and FF, ✦= significant difference between FF and WO, ▲ = significant difference between FAM and WO

Figure 7.1 [A-E]. Graphical presentation of the post-hoc testing results (based on table 7.2) for the significant kinematic variables:

A) Movement onset (ms)	B) Movement offset (ms)
	
C) Maximum Velocity (m.s^{-1}):	D) Summed error:
	

E) Maximum force (N)



Symbols represent significance following post hoc testing:

* = significant difference vs T10 for time in familiarisation blocks, * = significant difference vs T10 for time for FF blocks, * = significant difference vs T10 for time for WO blocks, ■ = significant difference between FAM and FF, ✦= significant difference between FF and WO, ▲ = significant difference between FAM and WO

7.6 Discussion

This main purpose of this chapter was to investigate whether TMS delivered to the SMA during preparation for novel motor reaching impairs performance and whether TMS delivered at different time points had an impact on different kinematic variables. This experiment provided a novel approach in exploring behavioural mechanisms operating in the SMA during preparation for novel reaching. It employed a single-pulse TMS approach and used human subjects in a robot-mediated FF paradigm, as opposed to previous studies that have used rTMS protocols, motor sequencing tasks and focused mainly on non-human primate responses (Padoa-Schioppa, Li and Bizzi 2004; Serrien *et al*., 2002; Steyvers *et al*., 2003).

7.6.1 Kinematics

7.6.1.2 Shift in movement onset and offset:

TMS delivered to the SMA had time specific effects for movement onset and movement offset. As with previous experiments conducted (left M1 and left PPC stimulation), in this study a significant delay in movement onset was noted (this addresses hypothesis 2, experiment 4), when TMS was applied during FAM and FF reaching, whereas in WO reaching significant delays were minimal. Similar shifts in responses were found for movement offset in FAM and FF reaching, but not during WO reaching. This study therefore provided a novel insight into time-specific differences that can occur during SMA stimulation. The shift that occurred in movement onset can be explained by the 'functional overlap' in motor regions (Alexander and Crutcher, 1990; Scott and Kalaska, 1997). Interactions exist between motor networks during planning and reaching execution (He, Dum and Strick, 1995; Padoa-Schioppa, Li and Bizzi, 2004). For example, corticospinal projections from the SMA feed to the premotor cortices and the M1, which project onto the spinal cord for movement execution (Padoa-Schioppa, Li and Bizzi, 2004). This neural communication enables the movement dynamic processing which can influence kinematic behaviours (He, Dum and Strick, 1995).

7.6.1.3 Impact of SMA stimulation on reaching trajectories (SE):

RMANOVA testing revealed a significant effect of condition on SE induced by TMS with significantly greater trajectory errors in FF reaching compared to FAM and WO reaching. Therefore it can be argued that TMS to the SMA disrupted novel reaching performance. However, robust multiple comparisons testing (table 7.2) showed that SE

errors induced by TMS in FF reaching as opposed to other conditions (FAM and WO) were not as prominent as the deviations noted in TMS FF reaching in other experiments (e.g. left M1 and left PPC).

The SMA consists of two sub-regions; the pre-SMA and the SMA-proper and imaging studies (namely fMRI) have aimed to provide functional distinctions between these two sub-structures. For example increased neural activations have been revealed in the pre-SMA in complex motor tasks, whereas the SMA-proper has been found to be activated more so during motor planning and execution (Bates and Goldman-Rakic, 1993; Picard and Strick 2003; Shen and Alexander, 1997; Moran and Schwartz, 1999; Padoa-Schioppa, Li and Bizzi, 2004). In this study it could be argued that the pre-SMA was more likely stimulated because SMA-proper stimulation may have resulted in greater disruptions in reaching considering that it is more involved in motor preparation than the pre-SMA. Furthermore, stimulation of the SMA-proper can cause an indirect activation of the motor cortex and elicit MEPs which is not the case for pre-SMA stimulation (Narayana *et al*., 2012; Cona, Marino and Semenza, 2017). In this study no MEPs were elicited (as inspected with EMG signals recorded throughout the experiment) and this provides further evidence supporting the notion that the pre-SMA was stimulated here.

However, there are challenges when trying to distinctively define activation patterns between sub-regions of the SMA because both the pre-SMA and SMA-proper are similarly activated in various types of motor states (Wang *et al*., 2010; Courson, Macoir and Tremblay, 2017). This is supported by fMRI studies that have illustrated similar neural activation patterns in SMA sub-regions during motor learning (Hardwick *et al*., 2013). Different co-ordinate systems including Montreal Neurological Institute (MNI) templates have been used to locate SMA sub-regions (Chau and McIntosh, 2005; Bracht *et al*., 2012; Chung et al., 2005). In this experiment, using individual subject structural-MRI scans to locate different SMA sub-regions (with an MNI co-ordinate system) could have been a solution in determining the region of the SMA that was stimulated. Nonetheless, based on previous SMA TMS protocols (Cona, Marino and Semenza, 2017), it could be speculated that the pre-SMA was stimulated in this experiment because no visible physiological responses were noted in EMG signals which has been found with SMA-proper stimulation. Pre-SMA stimulation can also explain why trajectory errors did not occur at all time points of SMA stimulation in FAM and FF

reaching blocks (only significant for 100ms, 130ms and 160ms), in other words motor planning has not been *as* associated with the pre-SMA, whereas it has been with the SMA-proper.

7.7 Chapter conclusions:

The purpose of this chapter was to provide a novel insight into how delivering SP-TMS at different times to the SMA during the preparation of a reaching affected kinematic measures of reaching. TMS was found to delay movement onset and offset, particularly during preparation for FF reaching, which can be explained in terms of the functional overlap that has been found between different motor regions. Time specific differences of SMA TMS were also found in this study which can be due to the transient nature of TMS. TMS to the SMA during novel reaching did not have as much of a disruptive impact on reaching trajectories when compared to other regions explored in this thesis (such as the left M1 and left PPC) which could have been be due to the pre-SMA being stimulated as opposed to the SMA-proper. This finding could be further determined by employing structural MRI scans for subjects and locating sub-regions of the SMA for stimulation which have previously been conducted using different MRI co-ordinate systems. Exploring whether TMS delivered to other regions in the motor circuitry result in similar outcomes can be important in developing a cortical network model of brain structures that are specific for novel reaching.

Chapter 8

8 Experiment 5

The impact of SP-TMS to the right primary motor cortex (M1) during right arm reaching in a novel motor learning protocol

8.1 Introduction

To move voluntarily, a region of the brain called the primary motor cortex (M1) sends complex descending signals via the corticospinal tract to motor neurons that innervate skeletal muscles (Drew, Prentice and Schepens, 2004). The crossing of the corticospinal pathway has resulted the right side of our brain being responsible for moving the left side of our body and vice versa (Sun and Walsh, 2006). This has been demonstrated experimentally with TMS to the M1 of one hemisphere and by recording MEPs (Hallett, 2007).

Although contralateral motor activation patterns occur during unilateral movements, (shown both experimentally with TMS and in imaging studies) (Barber *et al*., 2011; Hardwick *et al*., 2013), researchers have shown lateralisation between the two hemispheres (Barber *et al*., 2011). For example, findings from Kim *et al*., (1993) concluded that although right handed and left handed finger movements resulted in similar left M1 cortical activation patterns, cortical activity in the right M1 was only noted during left-handed finger movement. Further hemispheric asymmetries were noted by Verstynen *et al*., (2005) who reported greater cortical activity in the left hemisphere during left hand movements compared to the right hemisphere during right hand movements.

Motor network connectivity enables the transfer of information between different cortical areas and this facilitates synaptic plasticity during motor adaptation (Shannon *et al*., 2016). Resting-MRI studies have found an association between enhanced motor performance and increased left-hemispheric motor network connectivity, as opposed to right-hemispheric motor connectivity in right handed subjects (Barber *et al*., 2012). Voxel based connectivity techniques have been used to further illustrate hemispheric connectivity differences. For example Buckner *et al*., (2011) reported a greater number of voxels in the right-cerebellar hemisphere which were connected to the left M1, in contrast to the quantity of voxels that were found in the left cerebellar-hemisphere which were connected to the right M1 (Schlerf *et al*., 2014). Generally, the right M1 has

been found to exhibit less motor network connectivity than the left M1 (Guye *et al*., 2003). Considering that hemispheric connectivity differences have been established between the right and left M1, this experiment employed SP-TMS as a virtual disruption tool to test the hypothesis that that TMS to the right M1 may not have a detrimental impact on reaching trajectories, because less network communication processes may be interrupted.

Furthermore, this experiment employed a motor adaptation paradigm and a single-pulse TMS protocol to explore the functional role of right M1 in novel reaching. This differs from previous studies that have implemented visuo-motor adaptation tasks and paired-pulse TMS protocols (Schlerf *et al*., 2014). In this theses, in experiment 2, TMS to the left M1 was found to have a disruptive impact on right arm reaching, however, whether this is the case for TMS delivered to the right M1 is yet to be established. Considering that asymmetries between the two hemispheres have been found, and the connectivity of right motor regions are not as prominent as the left M1, particularly during right hand movements (Cramer *et al*., 1999; Verstynen *et al*., 2005; Schlerf *et al*., 2014), it can be argued that TMS to the right M1 may not have as much of a disruptive impact that was noted in the left M1 during motor adaptation. This study therefore set out to explore whether the asymmetries that have been noted in the literature, effect the process of motor adaptation, and whether TMS has a disruptive effect on the right M1 during ipsilateral reaching.

8.2 Methodology

Participant demographics for this experiment are shown in table 3.2. The ways in which RMT was identified for right M1 stimulation is described in section 3.3.1 of the general methodology chapter. The location for right M1 TMS and the coil orientation is highlighted in figure 3.3. Additionally, the reaching paradigm for this experiment is outlined in section 3.4.1 and figure 3.5.

8.3 Data acquisition: MEPs and Kinematics

No MEPs were measured from the right arm in this experiment and data acquisition was based on kinematics only. Kinematic data were analysed and quantified offline in MatLab 2017b (The MathWorks Inc, Natick MA, USA) (section 3.6.1).

8.4 Statistical analysis: Kinematics

A two-way RMANOVA for each kinematic variable was performed in SPSS 23 (IBM). The main factors (TIME and CONDITION) and interactions explored (TIME*CONDITION), as well as the ways in which sphericity assumptions were tested, and how post-hoc testing was were carried out are explained in section 3.7.1.

8.5 Results

8.5.1 Kinematics: Repeated measures ANOVA and post-hoc testing:

The RMANOVA revealed a significant effect for TIME on movement onset and offset (all $F > 4.342$, all $p < 0.05$) but not for maximum velocity, movement duration, summed error and maximum force (all $F < 0.849$, all $p > 0.05$) (table 8.1). There was also a significant main effect of CONDITION for movement duration, summed error and maximum force (all $F > 5.635$, all $p < 0.05$), but not for movement onset, movement offset and maximum velocity (all $F < 0.802$, $p > 0.05$) (table 8.1). No significant interaction effects were found for any of the kinematic variables (all $F < 0.517$, all $p < 0.05$, table 8.1).

Post-hoc testing for TIME (see table 8.2, figure 8.2[A-E]) for movement onset showed that during FAM reaching all time points, apart from 100ms were significantly increased compared to T10. During FF reaching all time points were significantly increased compared to T10 (all $p < 0.006$), but in WO reaching only responses during 280ms and 310ms were significantly increased from T10 ($p < 0.006$). For movement offset, all time points apart from 190ms and 220ms were significantly increased compared to T10 during FF reaching ($p < 0.006$). However, there were no significant differences from T10 in movement offset during FAM and WO reaching (all $p > 0.006$).

Post-hoc testing for CONDITION (see table 8.2, figure 8.1[A-E]) showed that movement duration was significantly increased in FF reaching compared to FAM reaching (only at 130ms $p < 0.016$). Movement duration during FF reaching was significantly longer compared to WO reaching (at 130ms, 160ms, 250ms, 280ms and 310ms, $p < 0.016$). There were no significant differences regarding FAM vs. WO reaching (all $p > 0.016$). Summed error was significantly increased in FF vs. FAM reaching at all time points ($p < 0.016$). Trajectory errors were significantly increased (160ms, 190ms, 20ms, 280ms and 310ms) during FF vs. WO reaching. There were no significant differences in FAM vs. WO reaching. Maximum force was significantly

increased in FF reaching at all time points compared to both FAM and WO reaching as expected.

All post-hoc testing results are illustrated in table 8.2 and figure 8.1[A-E].

Table 8.1. Results of the two-way RMANOVA:

	TIME			CONDITION			TIME *CONDITION INTERACTION		
	df(Error)	F	Sig.	*df*(Error)	F	Sig.	*df*(Error)	F	Sig.
Movement Onset (ms)	8[96]	12.27	**< 0.001**	2 [24]	1.696	0.213	16[192]	1.010	0.447
Movement Offset (ms)	8[96]	4.342	**< 0.001**	2 [24]	2.200	0.133	16[192]	0.834	0.645
Maximum Velocity ($m.s^{-1}$)	8[96]	1.526	0.158	2 [24]	0.802	0.460	16[192]	1.179	0.288
Duration (ms)	8[96]	0.873	0.542	2 [24]	5.635	**0.010**	16[192]	1.093	0.364
Summed Error (distance: cm)	3.2 [38.1]	0.849	0.481	1.2 [13.4]	12.92	**0.003**	16[192]	0.944	0.520
Maximum Force (*N*)	8[96]	0.972	0.463	1.1 [12.6]	176.78	**< 0.001**	16[192]	0.517	0.936

Table 8.2. Post-hoc testing results: The table below shows kinematic responses during FAM, FF and WO reaching when TMS was delivered to the right M1 at different time points during reaching preparation. Values represent means, ± the standard error mean (SEM).

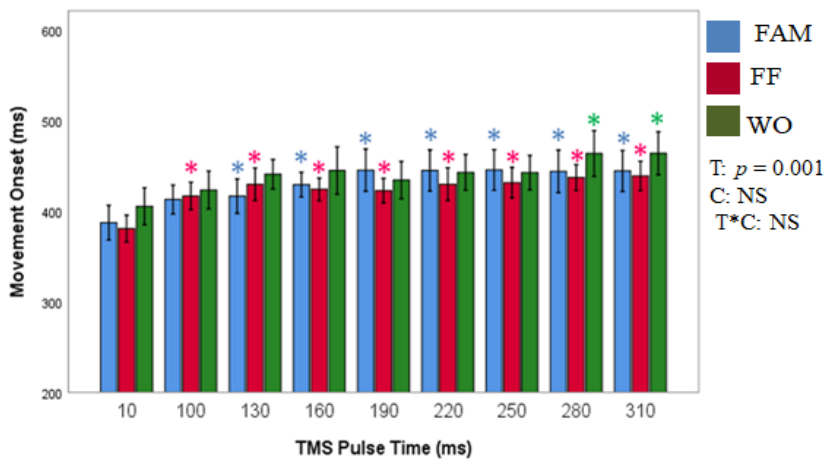
TIME	TMS: 10ms Mean [SEM]	TMS: 100ms Mean [SEM]	TMS: 130ms Mean [SEM]	TMS: 160ms Mean [SEM]	TMS: 190ms Mean [SEM]	TMS: 220ms Mean [SEM]	TMS: 250ms Mean [SEM]	TMS: 280ms Mean [SEM]	TMS: 310ms Mean [SEM]
CONDITION	Movement Onset (ms):								
FAM	387 [19]	413 [16]	416 [19] *	429 [14] *	445 [23] *	445 [22] *	445 [22] *	444 [23] *	444 [23] *
FF	381 [15]	417[15] *	430 [18] *	424 [13] *	423 [14] *	430 [18] *	431 [17] *	437 [14] *	439 [16] *
WO	405 [20]	423 [21]	441 [16]	445 [26]	434 [21]	443 [20]	443 [19]	464 [25] *	464[24] *
	Movement Offset (ms):								
FAM	1215 [26]	1223 [30]	1228 [33]	1249 [37]	1239 [33]	1254 [33]	1251 [36]	1243 [36]	1250 [37]
FF	1216 [17]	1272 [22] *	1278 [25] *	1272 [22] *	1263 [21]	1269 [19]	1274 [24] *	1291 [24] *	1296 [23] *
WO	1225 [25]	1223 [25]	1228 [24]	1245 [31]	1238 [24]	1246 [29]	1233 [24]	1249 [28]	1263 [28]
	Maximum Velocity ($m.s^{-1}$):								
FAM	0.29 [0.01]	0.29 [0.02]	0.29 [0.02]	0.28 [0.02]	0.30 [0.02]	0.29 [0.02]	0.29 [0.02]	0.29 [0.02]	0.29 [0.02]
FF	0.30 [0.01]	0.30 [0.01]	0.30 [0.02]	0.30 [0.01]	0.30 [0.02]	0.30 [0.01]	0.30 [0.02]	0.29 [0.01]	0.30 [0.01]
WO	0.28 [0.01]	0.29 [0.01]	0.29 [0.01]	0.29 [0.01]	0.29 [0.01]	0.29 [0.01]	0.30 [0.01]	0.29 [0.01]	0.29 [0.01]
	Movement Duration (ms):								
FAM	827 [27]	810 [27]	812 [33]	820 [36]	804 [31]	809 [30]	805 [31]	799 [26]	806 [26]
FF	835 [21]	855 [24]	849 [24] ■✦	848 [21] ✦	841 [20]	840 [16]	843 [22] ✦	855 [23] ✦	858 [16] ✦
WO	820 [20]	800 [19]	787 [19]	800 [21]	803 [16]	803 [22]	791 [17]	785 [19]	800 [21]
	Summed Error (distance: cm):								
FAM	2.17 [0.19]	2.35 [0.27]	2.15 [0.21]	1.91 [0.18]	1.93[0.14]	2.13[0.15]	2.02 [0.16]	1.90 [0.18]	2.00 [0.16]
FF	3.44 [0.44] ■	3.86 [0.59] ■	3.44 [0.44] ■	3.99 [0.69] ■✦	3.06 [0.34] ■✦	3.79 [0.47] ■✦	3.81 [0.60] ■	3.83 [0.63] ■✦	3.59 [0.41] ■✦
WO	2.24 [0.18]	2.22 [0.17]	2.21[0.12]	1.99 [0.09]	2.20 [0.14]	2.08 [0.10]	2.26[0.13]	2.14[0.14]	2.21[0.12]
	Force (*N*):								
FAM	4.7 [0.1]	4.7 [0.2]	4.8 [0.2]	4.7 [0.2]	4.8 [0.2]	4.8 [0.2]	4.8 [0.2]	4.8 [0.2]	4.8 [0.2]
FF	9.9 [0.4] ■✦	9.8 [0.4] ■✦	9.9 [0.4] ■✦	9.8 [0.3] ■✦	10.0 [0.4] ■✦	9.9 [0.3] ■✦	10.0 [0.4] ■✦	9.9 [0.4] ■✦	9.9 [0.3] ■✦
WO	4.7 [0.1]	4.8 [0.2]	4.8 [0.2]	4.8 [0.2]	4.8 [0.2]	4.8 [0.2]	4.8 [0.2]	4.7 [0.1]	4.8 [0.2]

Symbols represent significance following post hoc testing:

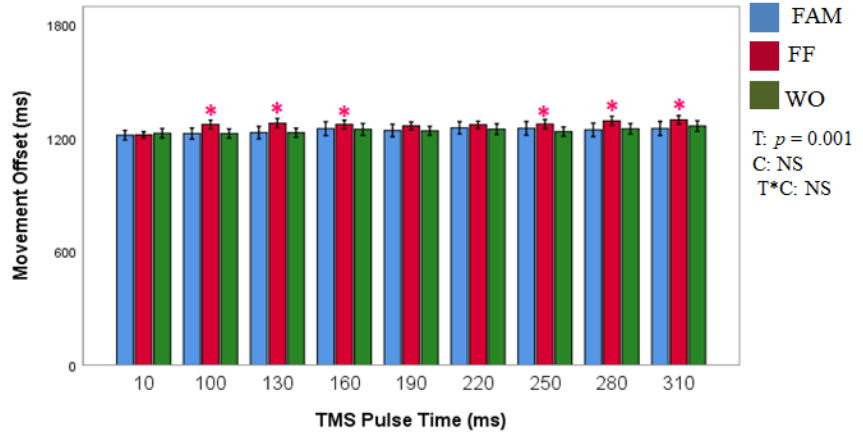
* = significant difference vs T10 for time in familiarisation blocks, * = significant difference vs T10 for time for FF blocks, * = significant difference vs T10 for time for WO blocks, ■ = significant difference between FAM and FF, ✦= significant difference between FF and WO, ▲ = significant difference between FAM and WO

Figure 8.1 [A-E]: Graphical presentation of the post-hoc testing results (based on table 8.2) for the significant kinematic variables:

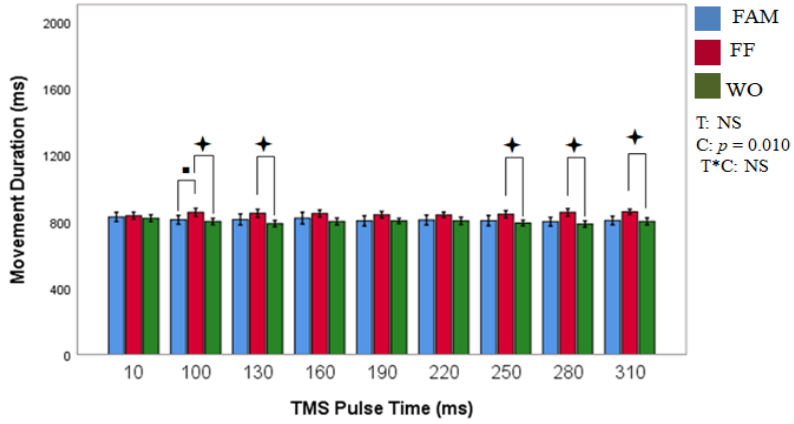
A) Movement onset (ms)



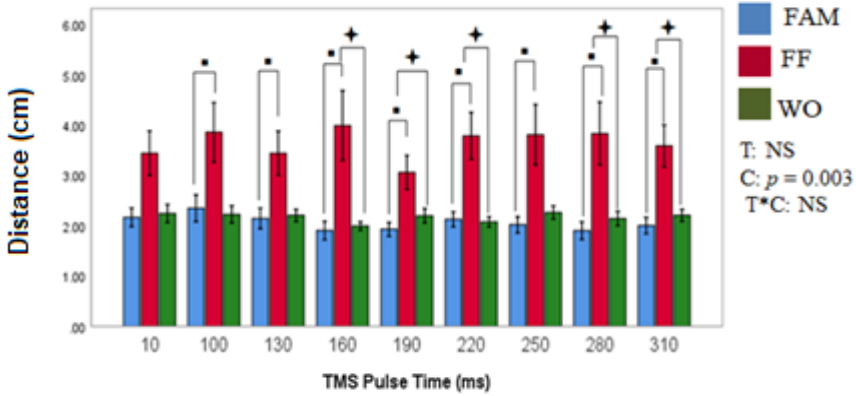
B) movement offset (ms)



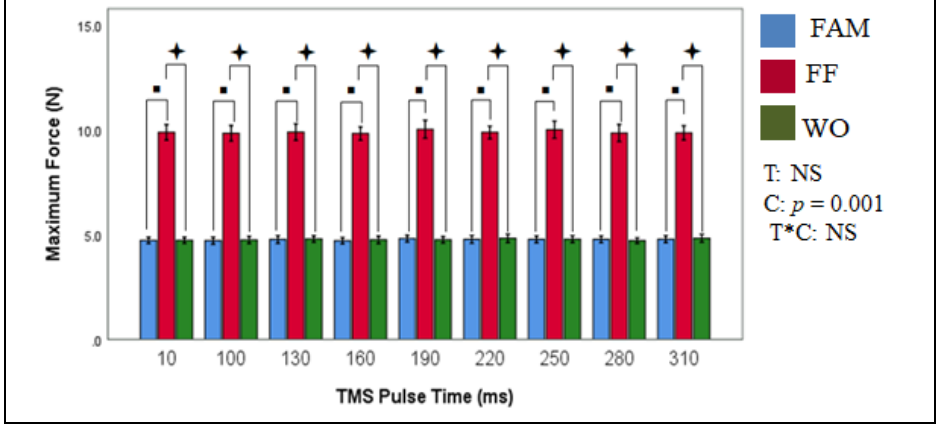
D) Movement duration (ms)



E) Summed error



A) Maximum force (N)



Symbols represent significance following post hoc testing:

* = significant difference vs T10 for time in familiarisation blocks, * = significant difference vs T10 for time for FF blocks, * = significant difference vs T10 for time for WO blocks, ■ = significant difference between FAM and FF, ✦= significant difference between FF and WO, ▲ = significant difference between FAM and WO

8.6 Discussion

As the left M1 was stimulated in chapter 5 of this thesis, the main aim of this chapter was to explore the effects of TMS delivered to the right M1 during right arm reaching preparation. Previous experiments investigating left and right hemispheric differences have implemented visuo-adaptation reaching protocols as opposed to robotic adaptation protocols and have explored other kinematic variables such as reach amplitude and the travel distance time to reach a target (Schlerf *et al*., 2014). This study therefore aimed to provide novel findings regarding right M1 function using a robot-mediated FF paradigm and a single-pulse TMS protocol.

8.6.1 Kinematics

8.6.1.2 The shift in movement onset and offset:

Results from this experiment revealed a significant delay in movement onset (FAM, FF and WO) and offset (FF only) responses (see table 8.2). This finding therefore suggests a functional role of the ipsilateral M1 during motor preparation for unilateral reaching. This result is in line with findings from non-human primates, where for example neuronal unit activity recordings via implanted electrodes in the motor cortex of Rhesus monkeys have illustrated correlations between neuronal activity in the ipsilateral M1, and movement preparation and motor output (Ganguly *et al*., 2009).

The delay that occurred in movement onset and offset can be explained by the 'waiting period' phenomena which results in cortical changes (see section 5.6.2) as described by Hasegawa *et al*., (2017). More specifically, motor preparation resulted in inhibition of neural networks which was accompanied by a selective inhibition of neural networks mediated by interneurons (Pfeffer *et al*., 2013). This result demonstrated that there may be similar mechanisms occurring in the right and left M1 because the shifts that occurred with regards to movement onset in relation to the 'waiting period' theory was also noted during left M1 stimulation. This finding was important because it highlighted the link between motor behaviours and the M1 circuitry, in particular how the neural networks can have an influence reaching preparation.

8.6.1.3 Right M1 connectivity in facilitating novel reaching:

TMS delivered to the right M1 had a significantly disruptive effect on reaching trajectories during FF reaching, compared to FAM and WO reaching.

TMS virtual lesion studies have mainly reported that in right handed subjects, there are greater disruptions in motor output when TMS is delivered to the left M1 compared to when it is delivered to the right M1 (Van den Berg, Swinnen and Wenderoth, 2011). However, in this study we demonstrated that disruptions are also caused when TMS is administered to the right M1, thus illustrating that the ipsilateral M1 also undergoes modulations of activity during right arm reaching. This view has been supported with studies in stroke patients. For example, it has been reported that following lesions to one hemisphere, the contra-lesional hemisphere becomes important in aiding ipsilateral movements (Dancause *et al*., 2006; Hummel and Cohen, 2006; Ganguly *et al*., 2009). Findings from an fMRI study conducted by Grefkes *et al*., (2008) showed that when stroke patients made hand movements (the affected hand), the contra-lesional hemisphere (unaffected) influenced neural activity of the ipsi-lesional motor cortex. The left M1 is not the only region that facilitates neuronal activity of the right M1, and other areas such as the posterior parietal cortices also play a role. For example, using a twin-coil TMS protocol, Koch *et al*., (2008b) reported that the right PPC influences the right M1 when participants performed a leftward reach. Similarly in this study, participants were instructed to reach towards a target that was presented on the left side of the screen (north-west - 135°). Based on these findings, it could be argued that TMS to the right M1 caused a disruption in neural network communication (i.e. between the PPC and right M1, or left M1 and right M1) which affected the final output of reaching (i.e. increase in summed error).

Brain machine/computer interfaces (BMI/BCI) are based on measuring activity (i.e. neural) and converting it to an artificial output to replace or restore behaviours, this can be done either invasively (i.e. via implants) or non-invasively (i.e. via neural signals) (Wolpaw *et al*., 2002; Daly and Huggins, 2015). Therefore, signals can be used to control functions in patients (McFarland and Vaughan, 2016) and can provide the brain with channels that depend on cortical activity to perform actions (Ranjangam *et al*., 2016). The use of BMIs has been successful in assisting cortical recovery in stroke patients (Carmena *et al*., 2003; Daly *et al*., 2009; Ang *et al*., 2010; Daly and Huggins 2015). For example in motor learning following stroke, physical therapy training combined with EEG-BMI training vs. physical therapy training alone resulted in enhanced motor performance (quantified with Fugl-Meyer scores) (Ramos-Murguialday *et al*., 2013). In this experiment, summed error results demonstrated the importance of

ipsilateral arm-reaching neural responses in novel motor learning. The data in this study could be important in brain machine interfaces and restoring "functional cortical reorganisation" in patients who have had a severe stoke (Carmena *et al*., 2003). In other words, the right M1 can be used as a site for extracting signals to use for BMIs (as previously emphasised with the motor cortex – Schroeder and Chestek, 2016; Hatsopoulos and Suminksi, 2011) because signals from this region may be better suited for assisting novel reaching compared to signals from other regions that are damaged (Friehs *et al*., 2004).

In this study, maximum force was greater in FF reaching as expected (table 8.2). However, maximum velocity was not modulated, which was not the case in experiment 2 with TMS to the left M1 (maximum velocity was significantly increased in FF reaching). This can be because of the lateralisation of function between the left and right M1, which has been illustrated in both human subjects, and non-human primates. For example, Ganguly *et al*., (2009) carried out invasive motor unit recordings (electrode implantation) in macaque monkeys and found that the contralateral M1 is more directly associated with movement velocity and has a greater influence in coding velocity parameters during reaching compared to the ipsilateral M1.

No right or left upper limb MEPs were collected were collected in this experiment. It would be interesting in future studies to collect MEPs to provide a more detailed insight into the role of ipsilateral corticospinal projections to the right arm during motor adaptation. This might also have impact for future design of contralesional BMI design (see above). Furthermore, testing left handed participants during right M1 stimulation may be warranted because studies have reported the importance of hand dominance in effecting M1 hemispheric asymmetries during ipsilateral movement (Van den Berg, Swinnen and Wenderoth, 2011). Given the possible role of right M1 in right arm reaching, it would be interesting to study IHI between left-right and right-left M1s during preparation for reaching in motor adaptation as this "balance" of inhibition is thought to be important in recovery from stroke.

8.7 Chapter conclusions:

This chapter demonstrated that TMS delivered to the right M1 at different time points during reaching preparation had a significant impact on movement onset and movement offset, particularly during novel reaching. This finding can be attributed to the 'waiting

period' phenomena, which was similarly noted during left M1 stimulation. Based on this finding, it could be argued that the right and left M1 undergo similar mechanistic processes when TMS is delivered during the preparation of a novel reach, and this could have been a result of the contralateral M1 exerting an influence on the ipsilateral M1 (which has been shown in stroke patient studies). The data in this study demonstrated the possible role of the ipsilateral M1 in novel right-arm reaching, whether it be direct or indirect via the left M1 connections, which can be important finding in the field of BMIs in terms of assisting functional recovery in stroke patients. Overall this experiment highlighted the functional role of right M1 in motor preparation and the importance of motor connectivity in facilitating preparation for novel reaching. Due to the interesting findings that were illustrated between the right and left M1 (chapter 5), additional right and left hemispheric regions were targeted with TMS in the final chapters of this thesis (e.g. the right and left dPMC, and the right and left PPC) to explore hemispheric asymmetries and similarities between regions during novel reaching.

Chapter 9

9 Experiment 6

Exploring impact of SP-TMS to the left dorsal pre-motor cortex (dPMC) during right arm reaching in a novel motor learning protocol

9.1 Introduction

The premotor cortex (PMC) is situated between the dorsal prefrontal cortex and the primary motor cortex (Kantak *et al*., 2012) and has a vast range of functions that contribute to motor performance including movement control, skilled performance and reaching (Halsband *et al*., 1993; Cao *et al*., 2013; Kantak et al., 2012). The PMC is key for sequential motor learning, as lesions to this region has led to poor performance in motor sequencing tasks (Tranel *et al*., 2003; Gross and Grossman 2008; Ohbayashi, Picard and Strick, 2016; Solopchuk, Alamia and Zenon 2016).

The PMC has two sub-structures; the ventral PMC (vPMC) and the dorsal PMC (dPMC). As well as its role in language production and comprehension, the vPMC is also involved in spatial perception and motor imagery (Rizzolatti, Fogassi and Gallese, 2002; Binkofski and Buccino, 2006). For example, Binkofski *et al*., (2000) conducted an fMRI study which illustrated neural activations of ventral regions of the PMC when participants were asked to imagine making finger movements. The dPMC on the other hand, plays a role in cued response selection and goal directed behaviour which may be important for motor adaptation (Beck et al., 2009; Yamagata *et al*., 2012). For example, dPMC neuronal activity was tuned with target location and arm use during the preparation phase of a reaching action (Tanji and Hoshi, 2001).

Generally, movements are prepared via the use of cues and waiting for information before preparing an action (Dekleva, Kording and Miller, 2018). Visual cues are vital in aiding dPMC motor functions and this has been noted in studies of non-human primates whereby dPMC resection resulted in the inability to use cues to initiate or suppress movements (Petrides 1982; Halsband and Passingham, 1985; Chouinard, Leonard and Paus, 2005). With regards to motor output behaviour, the dPMC has also been noted to be involved in encoding kinematic parameters that help in the formation of motor memories (Overduin, Richardson, and Bizzi, 2009; Meehan *et al*., 2011; Meehan *et al*., 2013).

Considering that this thesis will focus on the dPMC, and target both the left and right dPMC, it is important to take into account whether differences have been demonstrated between the two during reaching and adaptation. In motor paradigms where there is a change in the motor task, action-reprogramming is necessary and the left dPMC in particular has been noted to be involved in this (Hartwigsen *et al*., 2012). For example, experiments have shown that the left dPMC plays a role in immediately abandoning previously prepared motor action behaviours and replacing them with new ones, in order to accurately meet the demands of a task (Hartwigsen *et al.,* 2012). The left dPMC contributes to reaching behaviours because cells within its region transmit signals that are associated with the visual control of reaching (Cisek and Kalaska, 2002; Lee and Van Donkelaar, 2006), therefore using TMS to target the dPMC could be important in further demonstrating its functional role during motor reaching adaptation (Clower *et al*., 1996; Lee and Van Donkelaar, 2006).

Thus far, different TMS protocols have been used to explore dPMC function. For example, paired pulse TMS to the left dPMC led to an increase in the decision making time of movement onsets (Mochizuki *et al*., 2005). However, this was not the case when the right dPMC was stimulated (Mochizuki *et al*., 2005). In a visual perturbation prism adaptation task, Lee and Van Donkelaar (2006) targeted the left dPMC and found that it did not significantly contribute in trial-to-trail learning. On the other hand, TMS to the left dPMC could disrupt adaptation performance depending on the time point at which it is delivered. For example, slower adaptation rates were found when TMS was administered at movement onset, compared to when it was delivered at movement offset (Lee and Van Donkelaar, 2006). An additional important factor to consider is that dPMC function could depend upon handedness. For example, neuron activation recordings from non-human primates in bimanual and unimanual tasks demonstrated greater left dPMC activation when actions were performed with one hand, whereas greater right dPMC activation was found when actions and tasks were performed with two hands (Kermadi, Liu and Roullier, 2000).

Currently the impact of single pulse TMS to the left dPMC during right arm reaching in a motor adaptation task is unknown as most research has focused on:

1) Studies in non-human primates rather than human subjects (Overduin, Richardson, and Bizzi, 2009).

2) Visuo-motor adaptation paradigms compared to robot induced perturbations (Lee and Van Donkelaar, 2006).

Based on findings that have illustrated the role of the left dPMC in motor memory and response selection it can be argued that in this study TMS could disrupt the left dPMC functions in a motor adaptation task.

9.2 Methodology

The details for participant demographics regarding left dPMC stimulation are shown in table 3.2. Prior to stimulation during reaching, functional measures were implemented to identify RMT for each participant (section 3.2.2.2 details this). Section 3.3.2.2.3 and figure 3.3 outlines the location and coil orientation chosen for left dPMC stimulation (based on protocols from Fink et al., 1997, Münchau *et al*., 2002, Lee and Van Donkelaar, 2006; Zanon et al., 2013 and Lega et al., 2016). The reaching task for this experiment is explained in section 3.4.1 and graphically shown in figure 3.5.

9.3 Data acquisition: MEPs and Kinematics

MEPs were only elicited when identifying the participants RMT (section 3.6.2). No MEPs were collected during left dPMC stimulation. Kinematics were of main interest in this study, and section 3.6.1 provides details with regards to how kinematic data were analysed and quantified offline in MatLab 2017b (The MathWorks Inc, Natick MA, USA).

9.4 Statistical analysis: Kinematics

A two-way RMANOVA was performed in SPSS 23 (IBM) for each kinematic variable. Factors such as TIME, CONDITION and TIME*CONDITION were investigated. Section 3.7.1 describes the ways in which sphericity assumptions were tested and how post-hoc testing was performed (paired Student's t-test with Bonferroni correction for multiple comparisons).

9.5 Results

9.5.1 Kinematics:

The RMANOVA revealed a significant main effect for TIME on movement onset and movement offset ($p < 0.05$), but not for maximum velocity, movement duration, summed error and maximum force ($p > 0.05$) (see table 9.1). There was also a significant main effect of CONDITION on summed error and maximum force ($p < 0.05$), but not for movement onset, movement offset, maximum velocity and movement

duration ($p > 0.05$) (table 9.1). A significant interaction was found for movement onset ($p < 0.05$), but this was not the case for movement offset, maximum velocity, summed error, movement duration and maximum force ($p > 0.05$) (table 9.1).

Post hoc testing for TIME (table 9.2, figure 9.1[A-D]) for movement onset showed that during FAM reaching responses were significantly increased at all time points ($p < 0.006$) apart from 160ms ($p > 0.006$) compared to T10. In FF reaching, responses at 100ms, 190ms, 220ms, 250ms, 280ms and 310ms were significantly increased compared to T10 ($p < 0.006$). Movement onset during WO reaching was significantly increased at 100ms, 160ms, 190ms, 220ms, 250ms, 280 and 310ms compared to T10 ($p < 0.006$). Movement offset was significantly increased at all time points compared to T10 during FAM reaching ($p < 0.006$). During FF reaching, only TMS delivered at 100ms, 190ms, 220ms and 310ms was significantly increased compared to T10. WO reaching responses were significantly increased at 160ms and 280ms in contrast to T10 ($p < 0.006$).

Post-hoc testing for CONDITION (table 9.2, figure 9.1[A-D]) regarding summed error revealed that errors in reaching were significantly increased in FF reaching vs. FAM reaching (at all time points $p < 0.016$). Summed error in FF reaching was significantly increased compared to WO reaching (at 100ms, 160ms, 190ms, 220ms, 280ms and 310ms $p < 0.016$). Summed error was significantly increased in WO vs. FAM reaching (only at 160ms $p < 0.016$). Maximum force was significantly increased in FF reaching as expected ($p < 0.016$), compared to FAM and WO reaching, which in turn were similar.

Table 9.2 and figure 9.1[A-D] illustrates the results from post-hoc testing.

Table 9.1. Results of the two-way RMANOVA:

	TIME			CONDITION			TIME*CONDITION INTERACTION		
	df(Error)	F	Sig.	*df*(Error)	F	Sig.	*df*(Error)	F	Sig.
Movement Onset (ms)	8 [96]	17.20	**< 0.001**	1.4 [16.2]	0.606	0.554	16 [192]	2.032	**0.013**
Movement Offset (ms)	8 [96]	10.64	**< 0.001**	2 [24]	1.543	0.234	16 [192]	1.675	0.054
Maximum Velocity ($m.s^{-1}$)	2.9 [34.7]	0.247	0.856	2 [24]	1.129	0.340	16 [192]	0.358	0.990
Duration (ms)	4.4 [52.2]	1.27	0.293	2 [24]	3.070	0.065	16 [192]	0.887	0.585
Summed Error (distance: cm)	8 [96]	0.478	0.869	2 [24]	24.80	**< 0.001**	16 [192]	0.936	0.529
Maximum Force (*N*)	1.4 [15.8]	0.124	0.769	1.2 [13.3]	280.50	**< 0.001**	16 [192]	0.179	0.100

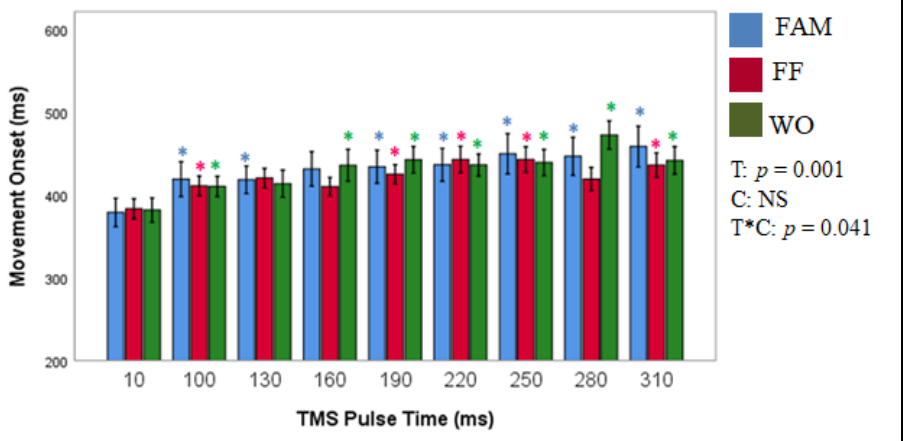
Table 9.2. Post-hoc testing results:

The table shows kinematic responses during FAM, FF and WO blocks of reaching when TMS was applied to the left dPMC at different time points. Values represent means and standard error means.

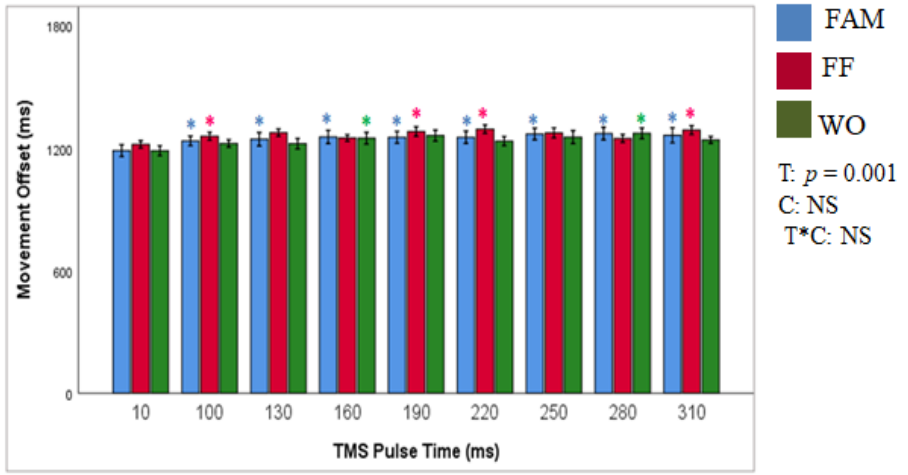
TIME	TMS: 10ms Mean [SEM]	TMS: 100ms Mean [SEM]	TMS: 130ms Mean [SEM]	TMS: 160ms Mean [SEM]	TMS: 190ms Mean [SEM]	TMS: 220ms Mean [SEM]	TMS: 250ms Mean [SEM]	TMS: 280ms Mean [SEM]	TMS: 310ms Mean [SEM]
CONDITION	Movement Onset (ms):								
FAM	379 [17]	419 [21] *	418 [17] *	431 [21]	434 [20] *	436 [20] *	449 [24] *	446 [23] *	458 [25] *
FF	383 [12]	411 [12] *	420 [12]	410 [11]	425 [12] *	443 [16] *	443 [15] *	419 [14]	436 [15] *
WO	382 [15]	410 [12] *	413 [16]	436 [19] *	442 [16] *	436 [13] *	439 [16] *	472 [17] *	442 [17] *
	Movement Offset (ms):								
FAM	1188 [29]	1236 [23] *	1244 [33] *	1255 [33] *	1254 [29] *	1254 [30] *	1270 [29] *	1272 [31] *	1263 [37] *
FF	1219 [18]	1259 [19] *	1276 [18]	1250 [16]	1282 [23] *	1294 [21] *	1275 [24]	1248 [19]	1289 [21] *
WO	1188 [24]	1223 [19]	1222 [25]	1249 [29] *	1262 [27]	1235 [22]	1254 [32]	1273 [26] *	1241 [17]
	Maximum Velocity ($m.s^{-1}$):								
FAM	0.29 [0.02]	0.29 [0.02]	0.29 [0.02]	0.29 [0.02]	0.29 [0.02]	0.29 [0.02]	0.29 [0.02]	0.29 [0.01]	0.29 [0.02]
FF	0.30 [0.01]	0.30 [0.01]	0.30 [0.01]	0.30 [0.01]	0.30 [0.02]	0.30 [0.01]	0.30 [0.01]	0.30 [0.01]	0.30 [0.01]
WO	0.29 [0.01]	0.29 [0.01]	0.30 [0.02]	0.29 [0.01]	0.29 [0.01]	0.29 [0.01]	0.29 [0.02]	0.30 [0.01]	0.29 [0.01]
	Movement Duration (ms):								
FAM	809 [28]	818 [26]	826 [32]	824 [28]	816 [29]	818 [29]	820 [27]	825 [26]	804 [29]
FF	835 [21]	848 [22]	856 [18]	840 [15]	858 [25]	851 [15]	833 [20]	829 [21]	853 [20]
WO	805 [25]	813 [21]	809 [28]	813 [27]	819 [31]	799 [27]	815 [29]	800 [24]	803 [23]
	Summed Error (distance: cm):								
FAM	1.99 [0.09]	1.86 [0.12]	1.91 [0.16]	1.92 [0.10] ▲	2.13 [0.12]	2.06 [0.16]	1.82 [0.09]	2.01 [0.12]	2.05 [0.16]
FF	3.04 [0.26] ■	3.55 [0.39] ■✦	3.41 [0.33] ■	3.41 [0.35] ■✦	3.40 [0.26] ■✦	3.38 [0.30] ■✦	3.13 [0.25] ■	3.24 [0.36] ■✦	3.23 [0.31] ■✦
WO	2.25 [0.29]	2.25 [0.24]	2.29 [0.16]	2.50 [0.22]	2.22 [0.29]	2.13 [0.17]	2.59 [0.32]	2.15 [0.21]	2.19 [0.23]
	Force (*N*):								
FAM	4.7 [0.2]	4.7 [0.2]	4.7 [0.2]	4.7 [0.2]	4.7 [0.2]	4.7 [0.2]	4.8 [0.2]	4.8 [0.2]	4.7 [0.2]
FF	9.9 [0.4] ■✦	10.0 [0.4] ■✦	9.9 [0.3] ■✦	10.0 [0.4] ■✦	10.0 [0.4] ■✦	9.9 [0.4] ■✦	9.9 [0.3] ■✦	9.9 [0.4] ■✦	9.8 [0.3] ■✦
WO	4.7 [0.1]	4.7 [0.1]	4.8 [0.1]	4.7 [0.1]	4.7 [0.1]	4.7 [0.1]	4.7 [0.1]	4.7 [0.1]	4.7 [0.1]

Figure 9.1 [A-D]. Graphical presentation of the post-hoc testing results (based on table 9.2) for the significant kinematic variables:

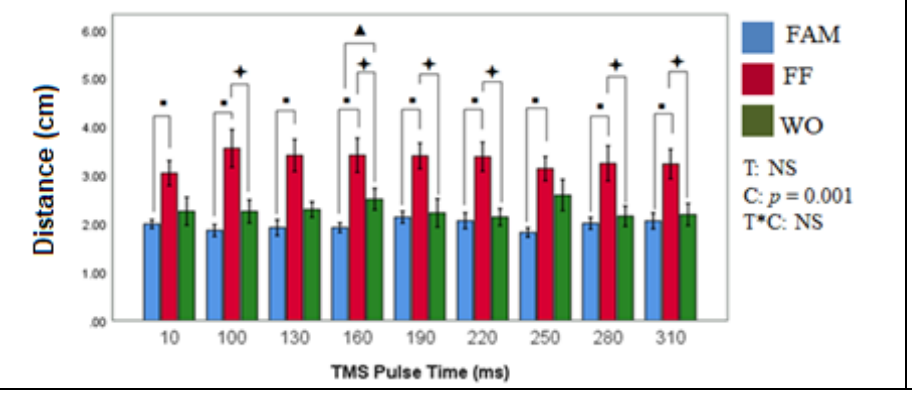
A) Movement onset (ms)



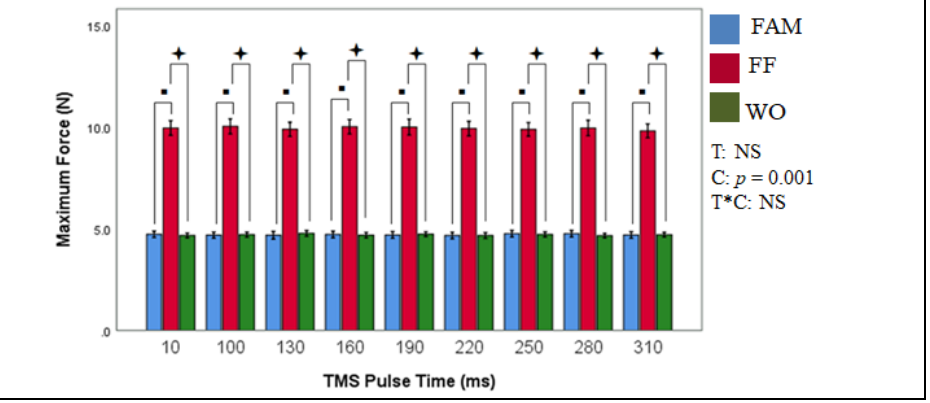
B) Movement offset (ms)



C) Summed error:



D) Maximum force (N)



Symbols represent significance following post hoc testing:

* = significant difference vs T10 for time in familiarisation blocks, * = significant difference vs T10 for time for FF blocks, * = significant difference vs T10 for time for WO blocks, ■ = significant difference between FAM and FF, ✦= significant difference between FF and WO, ▲ = significant difference between FAM and WO

9.6 Discussion:

The purpose of this chapter was to explore the effects of TMS delivered to the left dPMC during reaching preparation. Previous experiments investigating the role of the dPMC regarding motor function have implemented visuo-adaptation pointing paradigms (Lee and Van Donkelaar, 2006) and have also explored non-human primate neural responses of reaching compared to human subjects (Kermadi, Liu and Roullier 2000; Overduin, Richardson and Bizzi, 2009). This experiment therefore aimed to provide novel findings regarding left dPMC function in human subjects with single pulse TMS in a robotic-mediated upper-limb reaching FF paradigm.

9.6.1 Kinematics

9.6.1 The role of the dPMC in reaching preparation:

The findings from this experiment revealed that TMS caused a significant shift in movement onset and offset responses (FAM, FF and WO) at different time points (see table 9.2). Similarly, repetitive TMS studies have illustrated delayed responses during finger action-selection tasks when the left dPMC was targeted (Hartwigsen *et al*., 2012). This particular result is important because it illustrates the role of the left dPMC in reaching preparation. For example, studies have demonstrated heightened neural responses in the dPMC during motor preparation when selecting actions for execution (Boussaoud and Wise, 1993; Hoshi and Tanji, 2006; Hartwigsen *et al*., 2012).

The nature of the reaching task in this experiment can be a reason as to why preparatory action was affected during left dPMC stimulation. This is because activity in dPMC neurons have been noted when reaching tasks were based on target-location and arm-use (Hoshi and Tanji, 2000; Hoshi and Tanji, 2006) (which were two factors in this experiment; i.e. reaching towards a 135° target and using the upper-limb right arm to do so). Studies that have explored functional differences between the dPMC and vPMC have also noted greater dPMC neuronal activity during movement execution towards targets compared to greater vPMC neuronal activity during visual processing of information when reaching towards targets (Boussaoud and Wise, 1993; Hoshi and Tanji, 2002).

The neural functions of the dPMC facilitates its role in reaching preparation. For example, neurons in the dPMC exhibit sustained activity during what is known as a ‘motor-set period’ (Hoshi and Tanji, 2002). The motor-set period is a phase in which

subjects prepare themselves for a movement-trigger in order to begin arm-reaching in time (Hoshi and Tanji, 2002). This sustained neuronal activity enables the dPMC to respond to upcoming movements (Johnson et al., 1996; Hoshi and Tanji 2002; Messier and Kalaska, 2000). In this experiment it could be argued that TMS disrupted the motor-set period which resulted in delayed movement responses (onset and offset) during reaching preparation. The findings obtained from this experiment are important because they describe behavioural left dPMC functions related to reaching preparation which have not previously explored with these protocols.

9.6.2 Disrupted novel reaching with dPMC stimulation:

A key finding from this experiment was that disrupting the left dPMC with SP-TMS during preparation for novel reaching, impaired performance which was revealed by increased summed error trajectory responses. Left dPMC TMS during FF reaching compared to FAM and WO reaching significantly induced trajectory errors in reaching (see table 9.2). Considering that TMS did not cause major disruptions during FAM and WO reaching suggests that the left dPMC has a specific function in novel reaching.

Similar trajectory errors have been noted in prism-adaptation finger-movement paradigms whereby TMS delivered to the left dPMC slowed down adaptation rates and subjects were not able to correct movement trajectories to facilitate successful motor adaptation (Lee and Van Donkelaar, 2006). It has been suggested that corrections in reaching and adaptation depend upon 1) knowing that the error has occurred and 2) the extent of visual feedback is available in a task (Lee and Van Donkelaar, 2006). By remapping the visual representation of the arm, errors induced by perturbations can be minimised (Lee and Van Donkelaar, 2006). The dPMC is involved in reaching because its neurons have been found to transmit signals that are linked to the visual control of movements to the M1 (Cisek and Kalaska 2002; Lee and Van Donkelaar, 2006). The role of other regions that facilitate left dPMC motor functions are also important to take into account. For example, MRI studies have demonstrated a stronger functional link between the left dPMC and the submarginal gyrus following rTMS which was associated with decreases in error rates during a visuo-spatial task (Ward *et al*., 2010; Hartwigsen *et al*., 2012). Based on these findings it could be argued that errors in trajectories occurred because TMS disrupted and impaired neural communication between the left dPMC and other cortical regions (e.g. the visual cortex and

submarginal gyrus) that contribute to successful reaching and motor learning Hartwigsen *et al*., 2012).

For motor output to occur, planning and preparation takes place. However, when there is a change in the environment (e.g. a perturbation) re-programming is essential in order to replace old plans with new plans, and this is known as action re-programming (Chambers *et al*., 2007; Neubert et al., 2010; Hartwigsen *et al*., 2012). Although the parietal cortex plays a role in action re-programming (Chambers *et al*., 2007) other cortical regions are also involved, particularly the left dPMC. The left dPMC has been reported to carry out prompt response mapping in order to provide the appropriate motor output for a task (Christensen *et al*., 2007; Hartwigsen *et al*., 2012). Studies have also supported this notion, for example rTMS delivered to the left dPMC resulted in a significant delays in action re-programming (Hartwigsen *et al*., 2012). When considering this, it could be suggested that in this experiment TMS caused disruptions in novel reaching because it impaired left dPMC action re-programming functions (i.e. the left dPMC was not able to map out new planning actions during perturbed reaching). This study was therefore important in illustrating the ways in which the left dPMC contributes to different motor function processing, in this case – action re-programming.

9.7 Chapter conclusions:

This chapter demonstrated that TMS delivered to the left dPMC at different time points during reaching preparation had a significant impact on movement onset and movement offset during FAM, FF and WO reaching. This finding can be attributed to the functional role of the left dPMC in the planning and preparation of reaching, as well as the type of motor task that was undertaken in this experiment. TMS disrupted the motor-set period whereby the left dPMC could not sustain its motor activity in order to begin arm reaching promptly – thus causing a delay in responses. Interestingly, FF reaching resulted in larger trajectory errors as opposed to FAM and WO reaching, and this could be due to TMS impairing neural communication between the left dPMC and key cortical areas that it is highly connected with that facilitate successful motor adaptation, such as the visual cortex and the submarginal gyrus. As opposed to the other experiments in this thesis whereby movement duration and maximum velocity were affected with TMS, this was not the case for the left dPMC. Therefore, this experiment was able to highlight specific neural processes of the left dPMC using behavioural

output measures. Whether the right dPMC also exhibits similar behavioural outputs can be important to explore as it could help provide explanations into possible asymmetries between the two hemispheres (this region was therefore targeted in experiment 8). Whether similar responses are demonstrated with right PPC stimulation would also be interesting to explore, and this was therefore investigated in the next chapter.

Chapter 10

10 Experiment 7

Exploring the impact of SP-TMS to the right posterior parietal cortex (PPC) during right arm reaching in a novel motor learning protocol

10.1 Introduction

In chapter 6 of this thesis, the left PPC was targeted and findings from the experiment revealed that left PPC function was significantly disrupted with TMS during novel force-field reaching, compared to FAM and WO reaching (see Section 6.6.1). The purpose of this chapter was to explore the functional role of the right PPC and whether the same behavioural findings could be established, or whether the left and right PPC have distinct functions related to novel reaching.

As opposed to the left PPC which has been linked to functions including movement preparation and planning, as well as navigation (Kaas and Stepniewska, 2016; Whitlock, 2017), the right PPC has been associated with functions such as maintaining alertness and spatial attention during a task (Posner and Peterson, 1990; Malhotra, Coulthard and Husain, 2009). Support for the role of the right PPC in spatial-attention comes from patients with right PPC lesions who exhibit spatial neglect (Vallar and Perani, 1986; Husain and Nachev, 2007). Patients with impaired right PPC function are often unaware of contra-lesional stimuli (i.e. objects in the left hemi-field) (Husain and Nachev, 2007) and this differs from patients with left PPC damage who have impairments in action control (i.e. ideomotor apraxia) (Husain and Nachev, 2007). This provides evidence that the two hemispheres do have separate behavioural roles because damage to the left- and right-PPC results in distinct functional impairments. Based on this it could be argued that TMS may have a different impact when it is delivered to the right PPC compared to what was found in the left PPC.

Asymmetries in motor behaviours do exist and can be due to left and right hemispheric differences between cortical regions, including the PPC (Schluter *et al*., 2001). For example in a visuospatial motor paradigm which was based on cues specifying which finger patients should use to respond to trials in a task, Rushworth *et al*., (1997) demonstrated that patients with left hemispheric parietal impairments as opposed to those with right hemispheric parietal impairments had slower responses. In this study, TMS will be applied during the preparation phase of a reach and neuroimaging studies

including positron emission tomography (PET) scans have provided an insight into the role of the right PPC with regards to movement preparation. For example, Coull and Nobre (1998) found less neural activity in the right PPC compared to the left intraparietal cortex when participants were required to prepare and execute finger movements during specific times in a task. Coull and Nobre (1998) did however find that the right PPC exhibited increased activity in spatial orientation tasks. Similarly, PET scans during finger-movement reaction time tasks have revealed greater activity in the left PPC during the preparation phase of movement, and this was found in finger-movements of both the left and right hand (Deiber *et al*., 1996). This shows that the left PPC as opposed to the right PPC is involved in the motor preparation tasks involving both hands (Krams et al., 1998; Rushworth, Krams and Passingham, 2001; Schluter et al., 2001). Furthermore, with regards to reaching tasks, less reaching-activity has been noted in the right PPC compared to the left PPC (Diedrichsen *et al*., 2006; Oliveira *et al*., 2010). Such findings therefore illustrate that the left hemisphere has a greater role and is more dominant than the right hemisphere during reaching tasks, specifically during motor preparation for movement execution (Schluter *et al*., 2001), therefore it could be argued that right PPC stimulation may not cause significant impairments when delivered during reaching preparation.

TMS studies targeting the right PPC have mainly explored its functions in saccadic visual memory tasks as well as visuo-spatial attention task. For example, SP-TMS protocols targeting the right PPC as opposed to the left PPC resulted in impaired visual-memory performance, thus demonstrating its role in visual spatial processing (Prime, Vesia and Crawford, 2008). TMS to the right PPC resulted in a 'virtual disruption' during a visuo-spatial attention task, more specifically TMS impaired neural activity in the task and caused delays in performance (Chambers *et al*., 2004; Woo, Kim and Lee, 2009). With regards to reaching tasks, twin-coil TMS studies targeting the right PPC and the ipsilateral M1 have found TMS to the right PPC had a facilitatory effect on the ipsilateral M1 during movement planning, and these were also found to be time specific (Koch *et al*., 2008b) therefore the relationship between different cortical regions is important in facilitating reaching preparation.

Although studies have previously explored the role of the left PPC (Della-Maggiore et al., 2004) and have highlighted its importance in the motor network in terms of facilitating motor preparation for novel reaching (including experiment 6 in this thesis),

the functional role of the right PPC with regards to this is unknown. This is because studies have mainly explored its role in spatial attention using rTMS protocols (as emphasised by Woo, Kim and Lee, 2009). This experiment is therefore the first experimental attempt to provide behavioural findings regarding novel reaching functions of the right PPC with SP-TMS using a robot-mediated upper-limb (right arm) reaching paradigm.

10.2 Methodology

Participant demographic details for this experiment are highlighted in table 3.2. Once RMT was identified for each participant (section 3.2.2.2 and 3.6.2 and details this), right PPC location and coil orientation for was chosen for stimulation, and this is outlined in section 3.3.2.2.4, and illustrated in figure 3.3. Figure 3.5 demonstrates the reaching paradigm for this experiment.

10.3 Data acquisition: MEPs and Kinematics

MEPs were only collected to identify participants RMT (section 3.6.2). Throughout the duration of the reaching experiment, no MEPs were elicited during stimulation. Only kinematic data were acquired and analysed. Section 3.6.1 outlines the ways in which kinematic data were analysed and quantified offline in MatLab 2017b (The MathWorks Inc, Natick MA, USA).

10.4 Statistical analysis: Kinematics

A two-way RMANOVA was performed for each kinematic parameter. Factors including TIME, CONDITION and TIME*CONDITION interactions were investigated. Sphericity assumptions were tested and post-hoc testing with paired Student's t-tests was carried out for the significant findings (see section 3.7.1 for further detail).

10.5 Results

10.5.1 Kinematics

Findings from the RMANOVA revealed a significant main effect for TIME on movement onset and movement offset ($p < 0.05$), but not for maximum velocity, summed error, movement duration and maximum force ($p > 0.05$) (see table 10.1). A significant main effect of CONDITION was found for movement offset, summed error, movement duration and maximum force ($p < 0.05$), but not for movement onset and

maximum velocity ($p > 0.05$) (see table 10.1). No significant interaction effects were found for any of the kinematic parameters ($p > 0.05$).

Post hoc testing for TIME (table 10.2, figure 10.1[A-E]) for movement onset showed that during FAM reaching, all time points were significantly increased compared to T10 ($p < 0.006$). During FF reaching, only TMS delivered at 160ms, 250ms, 280ms and 310ms were significantly increased compared to T10 ($p < 0.006$). In WO reaching responses at 160ms, 250ms and 280ms were significantly increased compared to T10 ($p < 0.006$). Movement offset during FAM reaching was only significantly increased at 220ms and 280ms when compared to T10. During FF reaching, movement offset was only significantly increased at 190ms compared to T10. There were no significant changes in WO reaching for movement offset ($p > 0.006$).

Post hoc testing for CONDITION (table 10.2, figure 10.1[A-E]) showed that movement offset was significantly increased during FF reaching compared to FAM reaching (at 10ms, 100ms, 190ms and 310ms, all $p < 0.016$). Movement offset during FF reaching was significantly increased compared to WO reaching (at 160ms and 190ms $p < 0.016$). There were no significant differences regarding FAM vs. WO reaching ($p > 0.016$). Summed error was significantly increased in FF reaching compared to FAM reaching (but only at 130ms, 250ms and 280ms; $p < 0.016$). FF summed error was also significantly increased compared to WO summed error (at 100ms, 160ms and 280ms; $p < 0.016$). There were no significant differences in post hoc testing for FAM vs. WO reaching. Movement duration was significantly increased in FF reaching compared to FAM reaching (at 10ms, 100ms, 220ms and 280ms $p < 0.016$). Movement duration was also significantly increased in FF reaching compared to WO reaching (at 10ms, 100ms, 160ms, 220ms and 280ms $p < 0.016$). There were no significant differences in movement duration for FAM vs. WO reaching ($p > 0.016$). Maximum force was significantly increased in FF reaching ($p < 0.016$) compared to FAM and WO reaching, which did not significantly differ ($p > 0.016$).

Post hoc testing results are shown in table 10.2 and figure 10.1[A-E].

Table 10.1. Results of the two-way RMANOVA:

	TIME			CONDITION			TIME*CONDITION INTERACTION		
	df(Error)	F	Sig.	*df*(Error)	F	Sig.	*df*(Error)	F	Sig.
Movement Onset (ms)	4.0 [47.3]	7.876	**< 0.001**	2 [24]	1.397	0.267	16 [192]	0.467	0.960
Movement Offset (ms)	3.7 [43.5]	3.825	**0.012**	2 [24]	8.27	**0.003**	16 [192]	0.475	0.956
Maximum Velocity ($m.s^{-1}$)	2.1 [25.6]	0.152	0.864	2 [24]	0.471	0.630	16 [192]	0.260	0.998
Duration (ms)	3.0 [35.6]	0.359	0.780	2 [24]	11.11	**< 0.001**	16 [192]	0.404	0.980
Summed Error (distance: cm)	8 [96]	1.042	0.410	1.3 [14.5]	7.557	**0.012**	16 [192]	1.570	0.080
Maximum Force (*N*)	1.7 [19.8]	0.245	0.743	1.2 [13.6]	213.87	**< 0.001**	16 [192]	0.190	0.100

Table 10.2. Post-hoc testing results

The table shows kinematic responses during FAM, FF and WO blocks of reaching when TMS was applied to the right PPC at different time points. Values represent means and standard errors means.

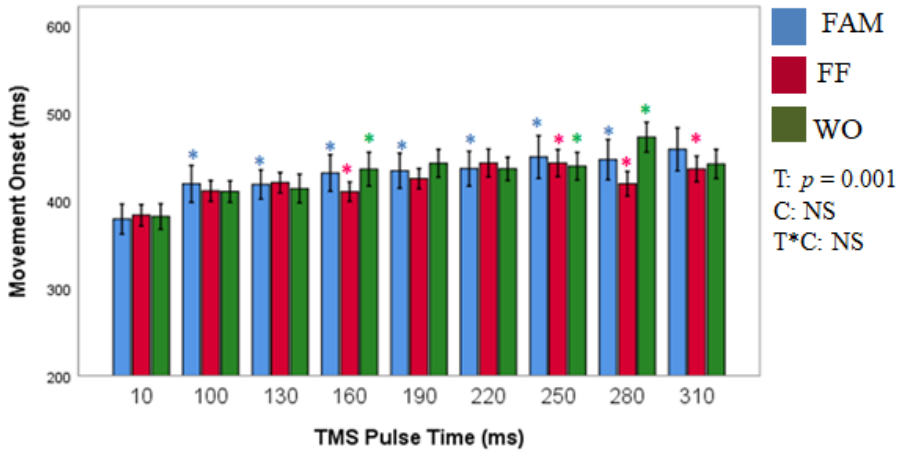
TIME	TMS: 10ms Mean [SEM]	TMS: 100ms Mean [SEM]	TMS: 130ms Mean [SEM]	TMS: 160ms Mean [SEM]	TMS: 190ms Mean [SEM]	TMS: 220ms Mean [SEM]	TMS: 250ms Mean [SEM]	TMS: 280ms Mean [SEM]	TMS: 310ms Mean [SEM]
CONDITION	Movement Onset (ms):								
FAM	385 [16]	409 [17] *	415 [14] *	429 [18] *	420 [19] *	432 [19] *	435 [19] *	440 [23] *	439 [18] *
FF	393 [21]	418 [17]	419 [16]	440 [20] *	439 [20]	438 [21]	426 [17] *	434 [22] *	438 [18] *
WO	401 [21]	427 [19]	428 [19]	434 [24] *	441 [22]	431 [23]	445 [26] *	454 [20] *	450 [25]
	Movement Offset (ms):								
FAM	1158 [30]	1173 [27]	1202 [29]	1193 [27]	1193 [28]	1197 [29] *	1197 [32]	1201 [32] *	1199 [34]
FF	1209 [29] ■	1250 [25] ■	1238 [22]	1267 [28] ✦	1270 [28] *■✦	1248 [29]	1239 [24]	1262 [29]	1245 [29] ■
WO	1160 [36]	1175 [40]	1185 [39]	1190 [38]	1196 [36]	1193 [35]	1204 [40]	1220 [38]	1211 [38]
	Maximum Velocity ($m.s^{-1}$):								
FAM	0.31 [0.02]	0.31 [0.02]	0.31 [0.02]	0.32 [0.02]	0.32 [0.02]	0.32 [0.02]	0.32 [0.02]	0.32 [0.02]	0.32 [0.02]
FF	0.32 [0.02]	0.31 [0.02]	0.32 [0.02]	0.30 [0.02]	0.31 [0.02]	0.31 [0.02]	0.32 [0.02]	0.31 [0.02]	0.31 [0.02]
WO	0.32 [0.02]	0.32 [0.02]	0.32 [0.02]	0.32 [0.02]	0.32 [0.02]	0.32 [0.02]	0.32 [0.02]	0.32 [0.02]	0.32 [0.02]
	Movement Duration (ms):								
FAM	773 [27]	764 [25]	787 [29]	764 [25]	774 [29]	765 [26]	762 [28]	762 [26]	760 [28]
FF	816 [23] ■✦	832 [24] ■✦	819 [24]	827 [27] ✦	831 [22]	810 [26] ■✦	812 [21]	829 [18] ■✦	807 [26]
WO	759 [29]	749 [34]	757 [34]	755 [29]	755 [32]	762 [27]	759 [35]	766 [31]	760 [27]
	Summed Error (distance: cm):								
FAM	2.36 [0.22]	2.38 [0.19]	2.17 [0.14]	2.47 [0.18]	2.30 [0.19]	2.49 [0.23]	2.13 [0.21]	2.32 [0.22]	2.19 [0.22]
FF	3.05 [0.35]	3.11 [0.32] ✦	3.23 [0.38] ■	3.00 [0.29] ✦	2.84 [0.30]	2.84 [0.34]	3.01 [0.28] ■	3.28 [0.34] ■✦	2.99 [0.30] ✦
WO	2.33 [0.22]	2.11 [0.13]	2.31 [0.15]	2.16 [0.14]	2.26 [0.13]	2.19 [0.18]	2.31 [0.15]	2.31 [0.15]	2.16 [0.17]
	Force (*N*):								
FAM	4.8 [0.1]	4.8 [0.1]	4.8 [0.1]	4.8 [0.1]	4.8 [0.1]	4.8 [0.1]	4.8 [0.1]	4.8 [0.1]	4.9 [0.1]
FF	10.6 [0.5] ■✦	10.5 [0.5] ■✦	10.7 [0.5] ■✦	10.4 [0.5] ■✦	10.6 [0.5] ■✦	10.6 [0.5] ■✦	10.7 [0.4] ■✦	10.6 [0.4] ■✦	10.6 [0.5] ■✦
WO	5.0 [0.2]	5.0 [0.2]	5.0 [0.2]	5.0 [0.2]	4.9 [0.2]	4.9 [0.2]	5.0 [0.2]	4.9 [0.2]	4.8 [0.2]

Symbols represent significance following post hoc testing:

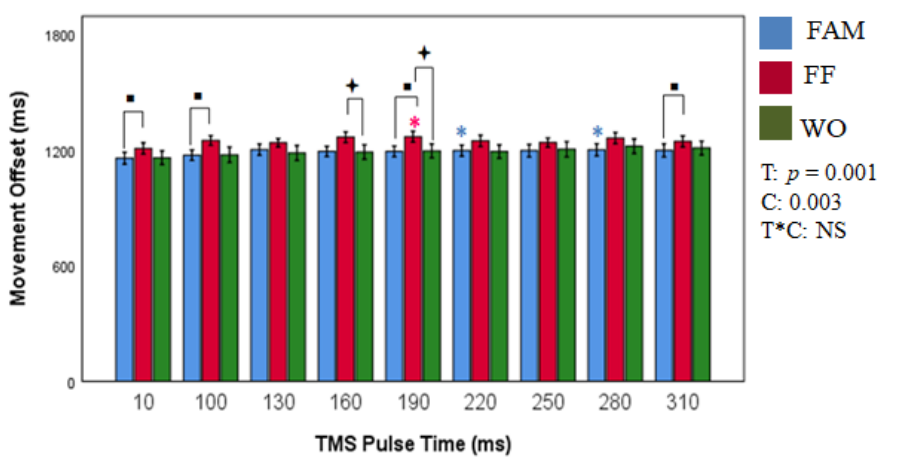
* = significant difference vs T10 for time in familiarisation blocks, * = significant difference vs T10 for time for FF blocks, * = significant difference vs T10 for time for WO blocks, ■ = significant difference between FAM and FF, ✦= significant difference between FF and WO, ▲ = significant difference between FAM and WO

Figure 10.1 [A-E]. Graphical presentation of the post-hoc testing results (based on table 10.2) for the significant kinematic variables:

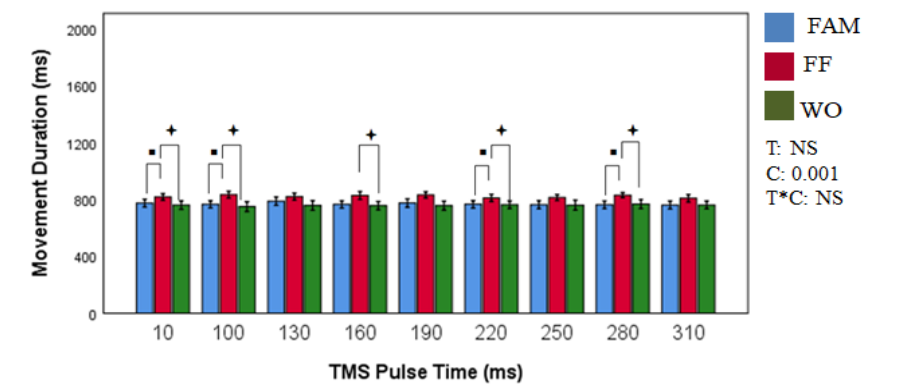
A) Movement onset (ms)



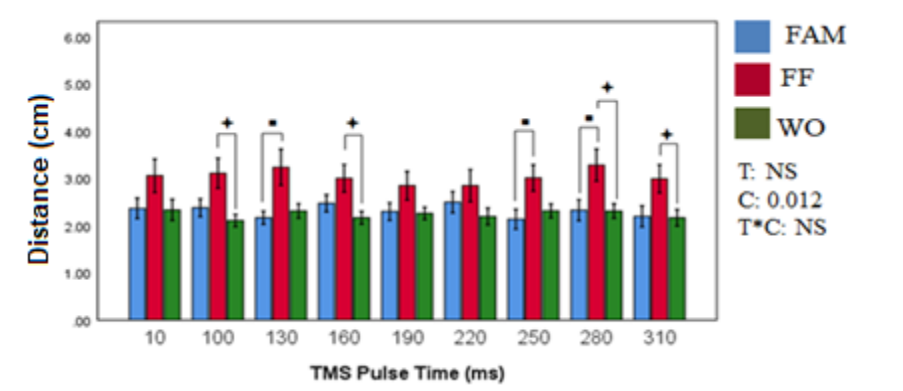
B) Movement offset (ms)



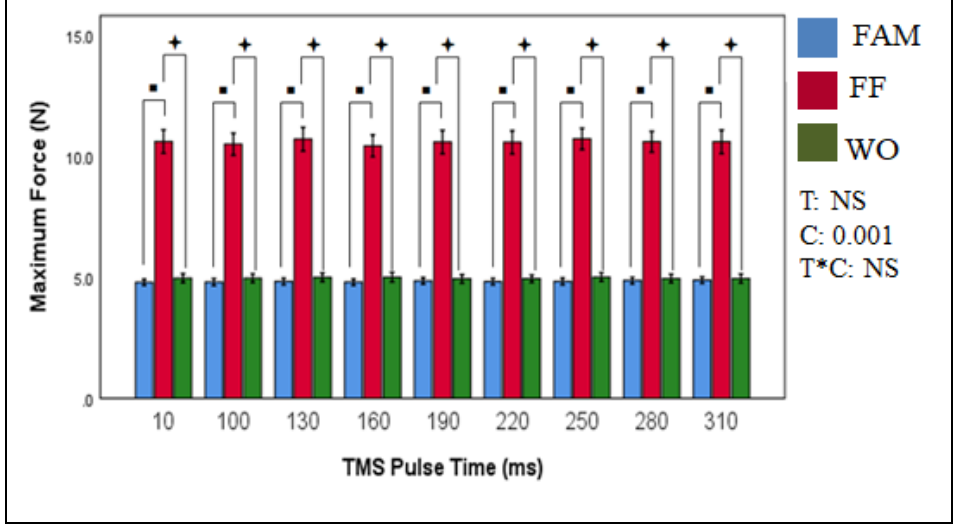
C) Movement duration (ms)



D) Summed error



E) Maximum force (N)



Symbols represent significance following post hoc testing:

* = significant difference vs T10 for time in familiarisation blocks, * = significant difference vs T10 for time for FF blocks, * = significant difference vs T10 for time for WO blocks, ■ = significant difference between FAM and FF, ✦= significant difference between FF and WO, ▲ = significant difference between FAM and WO

10.6 Discussion

This results of this experiment demonstrated the effects of single-pulse TMS to the right PPC during novel reaching preparation. Although studies have revealed that the left PPC is involved in novel reaching (Della-Maggiore *et al*., 2004) which was also illustrated in chapter 6 within this thesis, researchers have not targeted the right PPC with SP-TMS during reaching preparation. This study therefore provided a novel insight into the ways in which TMS can disrupt right PPC function in a motor adaptation paradigm via exploring different kinematic parameters as behavioural measures.

10.6.1 Kinematics

10.6.1.2 The shift in movement onset and movement offset:

The findings of this experiment illustrated that stimulation to the right PPC during motor preparation for reaching delayed the movement onset responses during FAM, FF and WO reaching and movement offset responses during FAM and FF reaching. The results regarding the shift were similar to what was found when the left PPC was stimulated with TMS (see chapter 6, table 6.2).

The delays that were noted in the preparation of reaching have similarly been demonstrated in rTMS protocols of visuo-spatial attention tasks (Xu *et al*., 2016) as well as SP-TMS FAM reaching tasks (Busan *et al*., 2009). For example, Busan *et al*., (2009) reported that a specific network in the motor circuit including areas in the posterior parietal cortex enables the preparation of reaching. They specifically found that TMS delivered to regions of the right PPC during reaching preparation resulted in delayed responses (similar to findings in this experiment), however when TMS was delivered prior to the reaching preparation phase there was an effect of facilitation (i.e. faster movement onset responses). The results regarding the shift that was found can be explained by the TMS state-dependent theory which was proposed by Silvanto and Muggleton (2008) (Busan *et al*., 2009). This theory poses the notion that because the PPC is already involved (i.e. pre-activated) in planning motor behaviours for execution (via corticospinal projections to areas of the premotor cortex and primary motor cortex), TMS delivered to its region can cause ‘neural noise’. This then interferes with the region’s functioning and as a result leads to slower responses in a task (Busan *et*

al., 2009; Miniussi, Ruzzoli and Walsh, 2010).

It can be argued that the behavioural responses of both hemispheres for movement onset are alike (as TMS similarly affected the right and left PPC; chapter 6, table 6.2), and this poses questions regarding possible asymmetries that have been noted between the two hemispheres which have been suggested to contribute to their distinct functions. This notion is supported by patient lesion studies. For example, although apraxia has been linked to being caused by lesions in the left PPC, as opposed to the right PPC (Vallar and Perani, 1986; Husain and Nachev, 2007), studies have demonstrated that some forms of apraxia are in fact associated with right posterior lesions (as reported by *Hamser, 1998*). Neural activation studies have also demonstrated that both hemispheres can be similarly activated during motor tasks (Calton, Dickinson and Snyder, 2002; Busan *et al*., 2012). On the other hand, it should be taken into account that in this experiment TMS did not have a significant main effect on the condition of reaching for movement onset, whereas TMS to the left PPC significantly affected movement onset responses between different reaching conditions (FAM, FF and WO; see chapter 6, table 6.2). This finding thus does in fact offer evidence for different functional roles between the two hemispheres which is in line with evidence proposed by researchers such as Husain and Nachev (2007) and Vallar and Perani (1986). In summary, TMS-induced shifts in timing is present in both PPCs, whereas simulating the left PPC appears to preferentially be involved in modulation of timing during novel reaching adaptation. These findings were important in showing the ways in which some behavioural functions between the two hemispheres are specialised and how some are not (e.g. TMS effects for time vs. condition). The differences and similarities regarding behavioural functions between the two hemispheres can be explained by the functional connections in the motor network (Gharbawie *et al*., 2010). For example, the two hemispheres may be connected to similar functional zones in the motor circuit which as a result facilitates similar behavioural responses, however some regions in one hemisphere may share greater connections with sub-structures in the motor network, and therefore cause differences in behavioural responses (Gharbawi *et al*., 2010).

10.6.1.3 Errors in reaching with right PPC TMS:

Another key finding from this experiment was that disrupting the right PPC with TMS during preparation for FF reaching compared to FAM and WO reaching impaired performance, therefore demonstrating that the right PPC also plays a functional role in novel reaching, which was similarly shown with left PPC stimulation (Della-Maggiore *et al.,* 2004). Although post-hoc testing revealed that FF reaching trajectories were significantly impaired during right PPC stimulation, this was not illustrated at all time points of stimulation. However, during left PPC stimulation, FF reaching was significantly disrupted at all time of TMS delivery (10ms-310ms) (see chapter 6, table 6.2). Studies have shown the left hemisphere to be the dominant hemisphere in right-handed subjects (Busan *et al*., 2012; Vingerhoets *et al*., 2013). The left hemisphere as opposed to the right hemisphere has also been reported to play a role in facilitating motor actions for movement execution, particularly in visually-guided reaching (Goodale 1988; Busan *et al*., 2012). Studies have also illustrated that the right PPC is involved only in planning left hand reaches compared to the left PPC which is activated during both left and right hand reaching motions (Schluter *et al*., 2001; Oliveira *et al*., 2010). Therefore, based on these studies, the less robust reaching disruptions in the right PPC (based on post-hoc testing results in this chapter) can be attributed to its less important functional role in reaching preparation of the right arm.

It could be argued that the nature of the motor task in this experiment could have also contributed to the lack of reaching deviations that were found during right PPC stimulation. For example, the experimental task was associated with reaching towards one target (135°), however if the motor task was based on random reaching targets, right PPC neural activity may have been heightened due to the region's involvement in attention selection-response behaviours (Posner and Peterson, 1990; Malhotra, Coulthard and Husain, 2009), and as a result trajectories in reaching may have been severely impaired. Nonetheless in this experiment TMS did have significant detrimental impact (albeit a smaller impact than what was found in the left PPC) on right PPC function. Considering that the right PPC plays a key role in enabling individuals to uphold an alert state during a task (Malhotra, Coulthard and Husain, 2009), it could be suggested that TMS interfered with this particular specialised right PPC function, thus impacting reaching.

10.7 Chapter conclusions:

The purpose of this chapter was to explore the effects of right PPC stimulation during novel reaching and to investigate whether TMS administered at different times of motor preparation had an effect on motor output. TMS only had a significant time-related impact on movement onset, and no significant effect of condition for movement onset was found – which was not the case for left PPC stimulation. This shows that the two hemispheres exhibit distinct functions, which is in line with most lesion studies that have illustrated different symptomologies associated with left and right hemispheric PPC lesions. Although findings illustrated that TMS significantly increased summed error during FF reaching compared to FAM and WO reaching, summed error responses were not as significantly impaired in this experiment compared to what was found during left PPC stimulation (chapter 6, table 6.2). This study was important in establishing distinct hemispheric PPC functions (left vs. right) related to the preparation for novel reaching. Whether other cortical regions in different hemispheres exhibit distinct differences were investigated, for example in the next experimental chapter in this thesis the right dPMC was targeted with TMS to investigate whether it plays a similar functional role when compared to the left dPMC (chapter 9) with regards to novel reaching.

Chapter 11

11 Experiment 8

Exploring the impact of SP-TMS to right dorsal pre-motor cortex (dPMC) during right arm reaching in a novel motor learning protocol

11.1 Introduction

In Chapter 9, the left dPMC was stimulated during preparation for reaching and findings revealed that trajectory errors were significantly impaired with TMS during FF reaching, but not during FAM or WO reaching at all time points in which TMS was delivered. Other kinematic measures however were not significantly affected with TMS. The aim of this study was to investigate whether the right dPMC also exhibited similar behavioural responses with TMS, or whether it has separate functions with regards to reaching preparation.

Premotor structures are important for upper limb movement particularly during complex tasks (Pollok *et al*., 2017). The left dPMC, but not the right dPMC has been reported to be involved in response selection and goal directed behaviour (Hoshi and Tanji, 2002; Beck *et al*., 2009; Yamagata *et al*., 2012). Studies have also demonstrated functional hemispheric differences between the right and left dPMC (Genon *et al*., 2017) particularly during motor sequence tasks. For example, when motor sequences performed with either the dominant or non-dominant hand, the left dPMC was reported to have a greater neural activation during the earlier learning phase of a motor sequence, whereas the right dPMC has been found to have greater activity in the advanced learning phase and when the sequences had greater degrees of complexity (Sadato *et al*., 1996; Grafton, Hazeltine and Ivry, 2002; Schubotz and von Cramon, 2003). The right dPMC has also been noted to have a greater involvement in spatial tasks compared to the left dPMC. For instance, functional MRI studies have highlighted increased neural activity in the right dPMC during spatial attention tasks (Gitelman et al., 1999; Schubotz and von Cramon, 2003). The role of the right dPMC in spatial tasks has also been demonstrated in the cognitive domain (Jonides *et al*., 1993; Schubotz and von Cramon, 2003; Genon et al., 2017). For example, positron emission tomography (PET) scans have revealed enhanced right hemispheric dPMC activity during spatial working memory tasks (Jonides *et al*., 1993). Further evidence for functional hemispheric

differences between the right and left dPMC comes from patients with PMC lesions who exhibit different symptoms. For example, left dPMC lesions have been associated with dystonia (Ceballos-Baumann and Brooks, 1998; Beck et al., 2009) which is a condition of abnormal muscle activity that results in impaired muscle function, and its symptoms range from tremors to jerked muscle movement (Fahn 1984; Elble 2013; Jinnah and Factor 2015). On the other hand, right dPMC lesions have been associated with symptoms of ideomotor apraxia; which demonstrates the role of the right hemisphere in skilled motor functions (Schnider *et al*., 1997; Gross and Grossman, 2008; Wheaton *et al.,* 2008). Previous studies that have implemented TMS protocols have mainly explored functional differences between the two regions with precision hand grasping and lifting tasks. For example, with an rTMS protocol, Davare *et al*., (2006) revealed a disruption in left dPMC function regarding a shift and delay in muscle response lifting times, whereas right dPMC rTMS did not cause such disruptions and did not significantly impair dominant hand movements during the task. It is important to explore whether reaching preparation during motor adaptation is affected when TMS is applied to the right dPMC, because most studies exploring reaching have mainly targeted the left dPMC rather than the right dPMC. For example, a visual perturbation prism adaptation task with SP-TMS to the left dPMC revealed slower rates of motor adaptation when TMS was delivered during movement onset in contrast to when it was delivered at movement offset (Lee and Van Donkelaar, 2006). However, the right dPMC has been found to be associated with motor planning, as demonstrated in visuo-motor learning tasks. For example, Praeg *et al*., (2005) targeted the right dPMC and a control region with TMS in a visuo-motor task and their findings revealed that TMS to the right dPMC caused a disruption in responses during preparation for learning, which was not the case when the control region was stimulated.

On the other hand, the functional role of the right dPMC has not been explored with 1) a reaching motor adaptation paradigm and 2) TMS applied at different time points during the preparation of a reach. Additionally, studies with right dPMC stimulation have also not explored whether TMS causes a virtual disruption of trajectory errors in reaching and have mostly focused on reaction time responses (Praeg *et al*., 2005). Considering that hemispheric differences have been found between the two regions, it could be argued that TMS to the right dPMC would result in different behavioural effects when compared to the findings that were illustrated for the left dPMC (chapter 8, experiment

6) which can be due to different subdivisions that have been noted within the left and right dPMC (Genon *et al*., 2017). This study is the first attempt to explore this.

11.2 Methodology

Participant details (e.g. N, age, gender, handedness) for this experiment is shown in table 3.2. Following RMT identification with functional measures (see section 3.2.2.2 and 3.6.2), the right dPMC was stimulated. Right dPMC location and the coil orientation used for stimulation is described in section 3.3.2.2.5 and also shown graphically in figure 3.3. The reaching paradigm is demonstrated in figure 3.5.

11.3 Data acquisition: MEPs and Kinematics

MEPs were only collected to identify RMT (section 3.6.2) and no MEPs were elicited or collected during right dPMC stimulation. Kinematic data were acquired throughout the experiment and analysed and quantified offline in MatLab 2017b (The MathWorks Inc, Natick MA, USA) (see section 3.6.1).

11.4 Statistical analysis: Kinematics

A two-way RMANOVA was performed for the kinematic variables whereby TIME, CONDITION and TIME*CONDITION interactions were explored. Sphericity assumptions were tested and post-hoc analysis was performed for the significant findings (section 3.7.1 describes this in further detail).

11.5 Results

11.5.1 Kinematics:

The RMANOVA revealed a significant main effect for TIME on movement onset and movement offset ($p < 0.05$) but not for maximum velocity, movement duration, summed error and maximum force ($p > 0.05$) (see table 11.1). A significant main effect of CONDITION was found for movement offset, summed error, movement duration and maximum force ($p < 0.05$) but not for movement onset and maximum velocity and (table 10.1). No significant interactions were found ($p > 0.05$) (table 11.1).

Post-hoc testing for TIME (table 11.2, figure 11.1[A-E]) revealed that movement onset significantly increased compared to T10 in both FAM reaching and FF reaching conditions ($p < 0.006$) but not during the WO condition. Movement offset was significantly increased at 250ms, 280ms and 310ms compared to T10 in the FAM condition ($p < 0.006$). Movement offset significantly increased at 130ms, 160ms,

220ms, 250ms and 310ms compared to T10 during the FF condition. Movement offset was not significantly changed in the WO condition compared to T10 (all $p > 0.006$).

Post hoc testing for CONDITION (table 11.2, figure 11.1[A-E]) with regards to movement offset showed that FF reaching was significantly increased compared to FAM reaching (at 130ms and 220ms $p < 0.016$). Movement offset in FF reaching was significantly increased compared to WO (at 100ms, 130ms, 160ms, 220ms, 280ms and 310ms $p < 0.016$). No significant differences were found for FAM vs. WO ($p > 0.016$). Summed error was significantly increased in FF reaching compared to FAM reaching only at 190ms ($p < 0.016$). No differences in summed error were revealed for WO vs. FF reaching, and WO vs. FAM reaching (all $p < 0.016$). Movement duration significantly increased in FF reaching compared to both FAM reaching (at 160ms and 220ms $p < 0.016$) and WO reaching (at 100ms, 100ms, 130ms, 160ms, 190ms, 220ms, 280ms and 310ms $p < 0.016$). There were no significant differences in movement duration when comparing FAM vs. WO responses (all $p > 0.016$). Maximum force was significantly increased in FF reaching ($p < 0.016$) compared to FAM and WO reaching which were not significantly different ($p > 0.016$).

Post-hoc testing results are further demonstrated in table 11.2 and figure 11.1[A-E].

Table 11.1. Results of the two-way RMANOVA:

	TIME			CONDITION			TIME*CONDITION INTERACTION		
	df(Error)	F	Sig.	*df*(Error)	F	Sig.	*df*(Error)	F	Sig.
Movement Onset (ms)	8 [96]	12.22	**< 0.001**	2 [24]	0.602	0.556	16 [192]	1.206	0.266
Movement Offset (ms)	8 [96]	4.531	**< 0.001**	2 [24]	10.37	**0.001**	16 [192]	1.411	0.140
Maximum Velocity ($m.s^{-1}$)	8 [96]	0.695	0.695	1.4 [16.1]	0.140	0.785	16 [192]	1.631	0.064
Duration (ms)	8 [96]	0.598	0.777	2 [24]	11.01	**< 0.001**	16 [192]	1.196	0.274
Summed Error (distance: cm)	2.6 [30.7]	1.11	0.355	2 [24]	3.554	**0.044**	16 [192]	0.838	0.642
Maximum Force (*N*)	8 [96]	0.822	0.585	1.1 [12.5]	135.60	**< 0.001**	16 [192]	0.535	0.926

Table 11.2. Post-hoc testing results: The table shows kinematic responses during FAM, FF and WO blocks of reaching when TMS was applied to the right dPMC at different time points. Values represent means and standard errors of the mean.

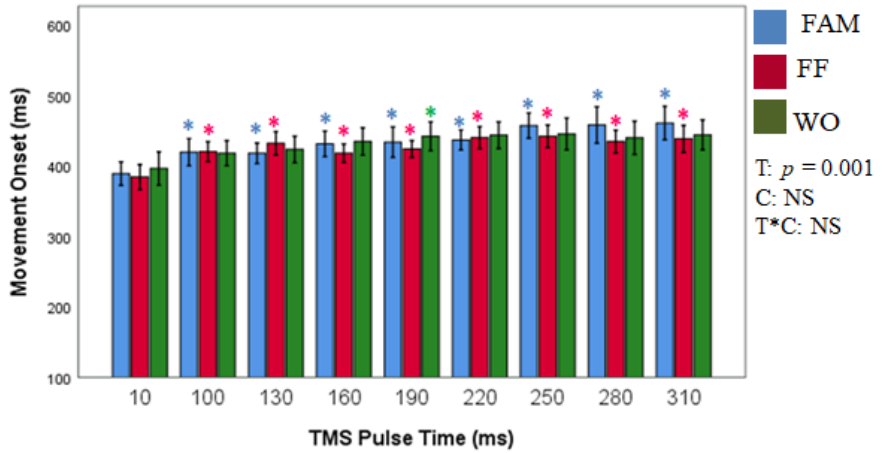
TIME	TMS: 10ms Mean [SEM]	TMS: 100ms Mean [SEM]	TMS: 130ms Mean [SEM]	TMS: 160ms Mean [SEM]	TMS: 190ms Mean [SEM]	TMS: 220ms Mean [SEM]	TMS: 250ms Mean [SEM]	TMS: 280ms Mean [SEM]	TMS: 310ms Mean [SEM]
CONDITION	Movement Onset (ms):								
FAM	389 [17]	419 [19] *	418 [15] *	431 [18] *	434 [22] *	437 [14] *	457 [18] *	458 [26] *	461 [24] *
FF	384 [18]	420 [14] *	432 [16] *	418 [13] *	424 [12] *	440 [16] *	442 [16] *	434 [16] *	438 [19] *
WO	396 [24]	418 [18]	423 [19]	434 [19]	442 [20] *	443 [19]	445 [23]	440 [24]	444 [21]
	Movement Offset (ms):								
FAM	1164 [32]	1194 [29]	1185 [28]	1204 [28]	1198 [30]	1204 [31]	1227 [32] *	1228 [33] *	1242 [35] *
FF	1198 [38]	1242 [38]✦	1266 [37] *■✦	1248 [35] *✦	1250 [39]	1264 [33] *■✦	1261 [46] *	1257 [38]✦	1257 [41] *✦
WO	1184 [32]	1174 [32]	1194 [34]	1201 [37]	1200 [32]	1197 [36]	1216 [35]	1194 [41]	1202 [29]
	Maximum Velocity ($m.s^{-1}$):								
FAM	0.31 [0.02]	0.31 [0.01]	0.32 [0.02]	0.31 [0.02]	0.31 [0.02]	0.32 [0.02]	0.32 [0.02]	0.31 [0.02]	0.31 [0.02]
FF	0.32 [0.02]	0.32 [0.02]	0.32 [0.02]	0.31 [0.02]	0.32 [0.02]	0.31 [0.02]	0.31 [0.02]	0.31 [0.02]	0.32 [0.02]
WO	0.31 [0.02]	0.32 [0.02]	0.32 [0.02]	0.32 [0.02]	0.32 [0.02]	0.32 [0.02]	0.32 [0.02]	0.32 [0.02]	0.32 [0.02]
	Movement Duration (ms):								
FAM	775 [29]	775 [25]	768 [27]	773 [24]	765 [24]	767 [28]	770 [29]	771 [25]	784 [24]
FF	814 [31]	822 [32] ✦	834 [33] ✦	829 [31] ■✦	826 [36] ✦	825 [27] ■✦	819 [36]	823 [32] ✦	818 [31] ✦
WO	788 [22]	756 [26]	771 [28]	766 [29]	758 [25]	754 [28]	771 [26]	754 [31]	758 [22]
	Summed Error (distance: cm):								
FAM	2.31 [0.30]	2.14 [0.33]	2.25 [0.32]	2.23 [0.27]	2.30 [0.39]	2.12 [0.28]	2.21 [0.31]	2.26 [0.30]	2.38 [0.34]
FF	2.70 [0.21]	2.73 [0.15]	3.44 [0.61]	2.95 [0.21]	2.81 [0.17] ■	2.88 [0.20]	2.90 [0.23]	2.75 [0.16]	2.89 [0.20]
WO	2.35 [0.31]	2.31 [0.27]	2.35 [0.29]	2.04 [0.21]	2.33 [0.28]	2.33 [0.28]	2.30 [0.26]	2.12 [0.21]	2.32 [0.27]
	Force (*N*):								
FAM	4.9 [0.2]	4.9 [0.1]	4.9 [0.1]	4.9 [0.1]	4.8 [0.1]	4.8 [0.1]	4.9 [0.1]	4.8 [0.1]	4.9 [0.1]
FF	10.6 [0.5] ■✦	10.6 [0.5] ■✦	10.5 [0.5] ■✦	10.4 [0.5] ■✦	10.5 [0.5] ■✦	10.4 [0.5] ■✦	10.4 [0.5] ■✦	10.5 [0.5] ■✦	10.6 [0.6] ■✦
WO	4.9 [0.2]	4.9 [0.2]	4.9 [0.2]	4.9 [0.2]	4.8 [0.2]	4.9 [0.2]	4.8 [0.2]	4.8 [0.2]	4.9 [0.2]

Symbols represent significance following post hoc testing:

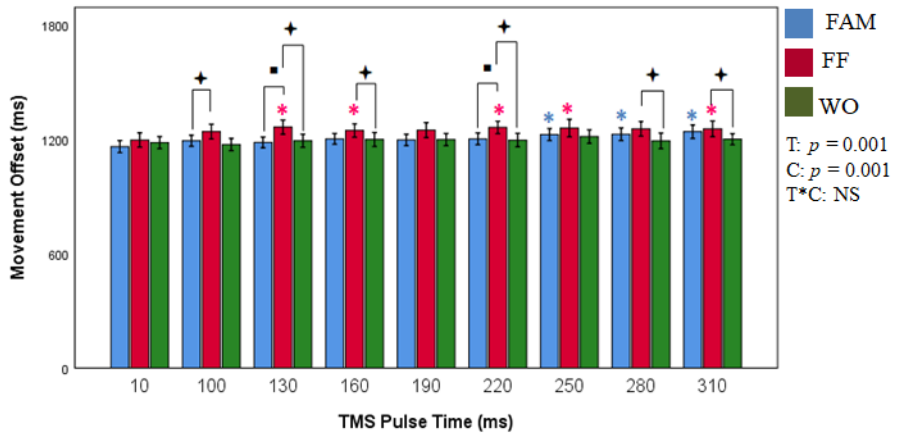
* = significant difference vs T10 for time in familiarisation blocks, * = significant difference vs T10 for time for FF blocks, * = significant difference vs T10 for time for WO blocks, ■ = significant difference between FAM and FF, ✦= significant difference between FF and WO, ▲ = significant difference between FAM and WO

Figure 11.1 [A-E]: Graphical presentation of the post-hoc testing results (based on table 11.2) for the significant kinematic variables:

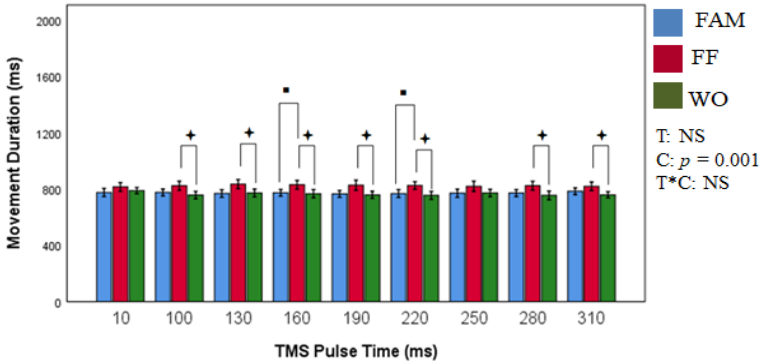
A) Movement onset (ms)



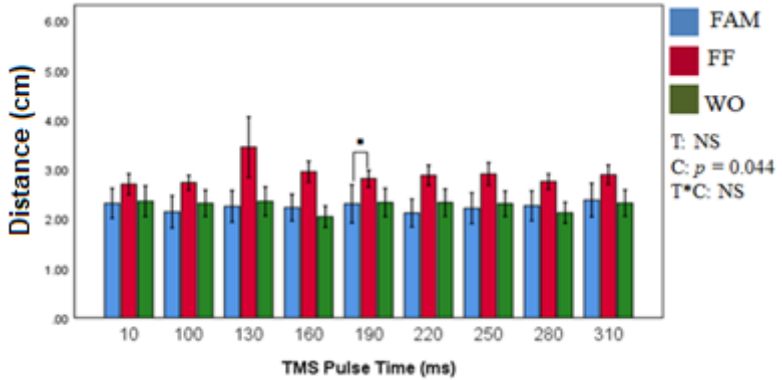
B) Movement offset (ms)



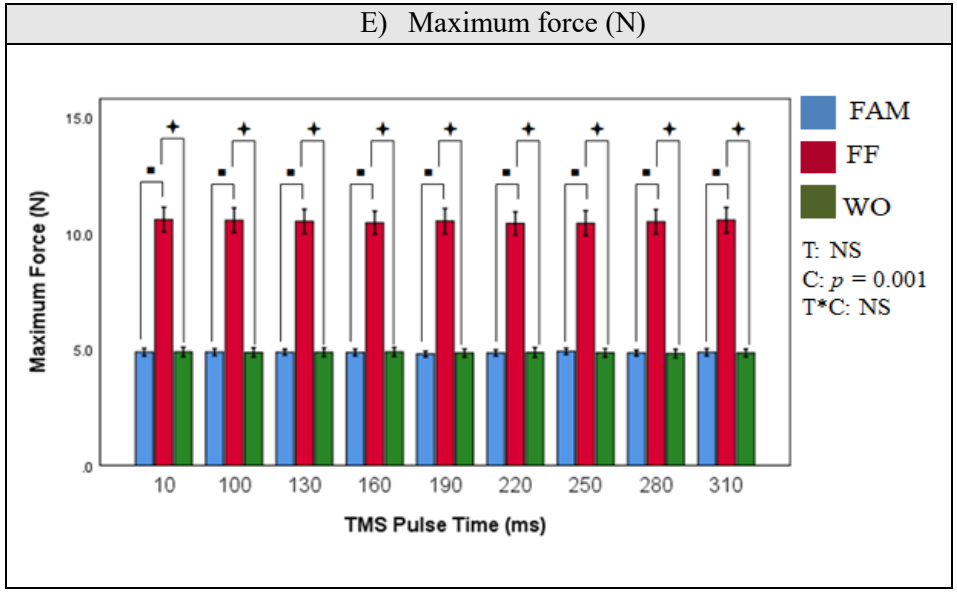
C) Movement duration (ms)



D) Summed error



E) Maximum force (N)



Symbols represent significance following post hoc testing:

* = significant difference vs T10 for time in familiarisation blocks, * = significant difference vs T10 for time for FF blocks, * = significant difference vs T10 for time for WO blocks, ■ = significant difference between FAM and FF, ✦= significant difference between FF and WO, ▲ = significant difference between FAM and WO

11.6 Discussion

The findings from this experiment demonstrated the ways in which SP-TMS to the right dPMC had an impact of right-arm reaching preparation behaviour. Although studies have shown that motor planning is affected when the right dPMC is targeted (Praeg, *et al*., 2005), other factors such as performance (e.g. summed error) during novel reaching preparation have not been extensively studied. This study therefore aimed to provide a novel insight into whether a virtual disruption (via TMS) to the right dPMC can have an impact on its function and impair kinematic behaviour during reaching preparation.

11.6.1 Kinematics

11.6.1.2 The role of the right dPMC regarding motor preparation:

The findings from this experiment demonstrated that TMS to the right dPMC significantly shifted movement onset responses in FAM and FF reaching. Shifts in responses were also noted in WO reaching but not to the extent as FAM and FF reaching (table 11.2). Movement offset was also found to be significantly affected with TMS as delays in responses were found during FAM and FF reaching, but not during WO reaching (table 10.2).

These findings are in line with results that have been obtained with SP-TMS protocols during visuo-spatial motor learning tasks. For example, Praeg *et al*., (2005) found that TMS to the right dPMC significantly impacted and delayed reaction times during motor learning which was not the case when a control region was stimulated. Although most studies have illustrated that the left dPMC plays an important role in motor preparation (Rushworth et al., 2003; Davare et al., 2006), this experiment revealed that the right dPMC also plays a role in motor preparation because TMS delayed reaching responses. Therefore it could be argued that preparation behaviours for reaching may not be restricted to only one hemisphere. A possible reason as to why TMS delayed responses can be attributed to distinct right dPMC sub-regions that have been reported to have specific functions and connections with other cortical structures that facilitate motor planning and preparation (Genon *et al*., 2017). For example, using structural-, resting- and functional-connectivity measures, Genon *et al*., (2017) found 5 right dPMC sub-regions that were connected to different cortical structures, including:

1) A rostral region connected to the prefrontal cortex
2) A central region connected to parietal structures
3) A caudal region linked to the motor circuitry
4) A dorsal region associated with cognitive and motor structures
5) A ventral region that was linked to visuo-motor structures

Genon *et al*., (2017) argued that different right dPMC connections assist different functional behaviours. For example, rostral connections with the prefrontal cortex aid cognitive functions such as memory (Jonides *et al*., 1993; Genon *et al*., 2017). On the other hand, dorsal and caudal right dPMC sub-regions and connections (with motor structures) have been suggested to facilitate motor planning and preparation (Genon *et al*., 2017). This is in line with fMRI studies that have found greater neural activity within this particular sub-region in motor planning and execution tasks (Picard and Strick, 2001; Genon *et al*., 2017). Studies in non-human primates have also supported this notion, with greater cellular activity noted in the caudal right dPMC sub-region during motor preparation (Boussaoud, 2001; Genon *et al*., 2017). The findings obtained for movement onset and offset were important in demonstrating the functional role of the right dPMC in movement preparation which have not previously been studied with motor adaptation protocols.

11.6.1.3 The impact of right dPMC TMS on reaching trajectories:

Although RMANOVA statistical testing revealed that TMS to the right dPMC had a significant effect on reaching trajectories (table 11.1), post-hoc testing did not reveal major significant differences between FF and FAM reaching conditions. There were also no significant differences in summed error regarding 1) FAM vs. WO reaching, and 2) FF vs. WO reaching (table 11.2).

This finding is in line with previous studies that have used TMS as a virtual disruption tool to explore right dPMC functioning. For instance, studies ranging from finger movement tasks to hand grip and lifting tasks have found that TMS to the right dPMC did not have a significant detrimental impact on motor performance (Schluter *et al*., 1998; Schluter *et al*., 2001; Davare *et al*., 2006). The reason as to why summed error was not significantly affected with right dPMC stimulation during preparation for novel reaching can be explained in terms of hemispheric functions relating to handedness (Schluter *et al*., 1998; Beck et al., 2009). For instance, Schluter *et al*., (1998)

implemented a TMS protocol during a hand motor task and their results showed that when the right dPMC was stimulated only left hand functions were disrupted, whereas left dPMC stimulation caused a disruption in both the left and right hand performance during the task. Functional MRI studies have also demonstrated similar results in a finger movement tasks of both hands, whereby neural activity in the right dPMC was heightened during left handed finger movement as opposed to left dPMC activity which was increased when finger movements were performed with either hand (Schluter *et al*., 2001).

Neuroimaging cerebral blood flow experiments have found enhanced right dPMC activity during complex sequential finger tasks (Sadato *et al*.,1996) and have therefore provided evidence for the role of the right dPMC in maintaining selective attention in complex tasks (Sarter, Givens and Bruno, 2001; Schubotz and von Cramon, 2003). It could be argued that if the reaching task in this experiment was based on reaching towards different targets, right dPMC activity would have been heightened (because participants may have had to sustain greater attention during reaching) and as a result TMS may have caused greater disruptions in reaching. Based on this assumption, the nature of the reaching task may have contributed to the lower impact on trajectory errors that were found in this study.

11.7 Conclusion:

Previous studies have mainly explored right dPMC function with TMS during sequential finger movement tasks as well as hand grip and lifting tasks, however this experiment provided novel findings into how TMS to the right dPMC has an impact on reaching preparation which has not previously been explored. The study revealed that TMS to the right dPMC shifted both movement onset and offset responses, and this is in line with findings from visuo-adaptation tasks. The study therefore provided an insight into the functional role of the right dPMC with regards to reaching preparation, which is a function that has been argued to be facilitated via right dPMC sub-regional connections with other cortical structures. The findings for summed error in this experiment were different in comparison to what was revealed when the left dPMC was stimulated (chapter 9, table 9.2). Summed error findings thus provided evidence for dPMC hemispheric differences in preparation for novel reaching. Considering that various regions in this thesis were impaired differently with TMS stimulation during

novel reaching, the final chapter of this thesis incorporates a systematic comparative analysis to compare novel reaching performance between all of the regions that were stimulated (left and right M1, SMA, left and right PPC, and left and right dPMC) to explore how they statistically differ in terms of the disruption caused. The final experimental chapter therefore highlights a model of the motor network, illustrating the relative influence of several cortical regions involved in novel motor performance.

Chapter 12

The comparative importance of different cortical regions in motor control and motor adaptation

12.1 Introduction

The purpose of this chapter was to compare the relative importance of cortical motor regions that were involved in motor control and motor adaptation. The main disruptive impact of TMS on reaching preparation were quantified by measuring the summed error of reaching trajectories and timing of reaching; both of which have been shown to be disrupted by TMS in previous chapters. Summed error, in particular has been reported to represent successful motor adaptation; with less errors indicating enhanced performance (Pizzamiglio *et al*., 2017a; Pizzamiglio *et al*., 2017b).

By exploring the impact of TMS on kinematics during upper-limb reaching, the functional role of different cortical areas in the motor network can be quantified. This has been supported by previous studies that have also used TMS protocols to explore the functional purpose of a region. For example, Della-Maggiore *et al*., (2004) found that TMS delivered to the left PPC during upper-limb novel reaching following movement onset impaired reaching trajectories. Other studies have illustrated that rTMS to the SMA had a negative effect on bimanual motor co-ordination performance, however this was not the case when the M1 was stimulated (Obhi *et al*., 2002). TMS protocols targeting the cerebellum during a finger reaching-to-point task resulted in distance-to-point estimation errors, therefore demonstrating the role of the cerebellum in planning and preparing movements (Miall *et al*., 2007).

Studies have reported increased neuronal firing in the dPMC during the encoding of kinematic parameters in a motor task (Alexander and Crutcher, 1990; Fu, Suarez and Ebner, 1993; Ward *et al*., 2007). However, the type of kinematic parameter encoded by the dPMC is currently unclear. Therefore, investigating kinematic factors separately between regions can help reveal the structures in the motor network that may play a more distinctive role in encoding a specific type of kinematic parameter. Additionally, researchers have demonstrated an insight into the cortical networks that underpin motor control in grasping and reaching behaviours. As well as PPC, SMA and PMC projections to the M1, there are a large range of connections which feed into these

structures to facilitate motor activity. For example, the DLPFC has been reported to be involved in motor related behaviours, ranging from movement selection to performance attentiveness and researchers have noted that it transmits organisation and planning information to the PMC to transfer to the M1 (Ehrsson *et al*., 2000; Kantak *et al*., 2012; Badoud *et al*., 2017). Network projections between the DLPFC and the pre-SMA have also been illustrated (Wang et al., 2005; Silva Moreira, Marques and Magalhaes, 2016; Kim *et al*., 2018). Additionally, areas such as the visual cortex (V1), somatosensory cortex (S1), basal ganglia (BG) all interact with the M1. The projections from the M1 also feed into regions such as the red nucleus (RN), and the vestibular network (VN) which in turn interact with the cortical signals descending towards the spinal cord, enabling motor behaviours such as reaching to take place (Scott, 2004). The role of these regions in reaching and grasping has been supported by lesion studies. For example, Whishaw, Gorny and Sarna (1998) found that RN lesions in mice disrupted both limb aiming behaviours and paw rotation during a skilled reaching task, thus providing evidence for RN function with regards to limb motor control (Whishaw and Gorny, 1996). Similarly, with regards to Huntington's Diseases (HD) which is a condition that arises from basal ganglia impairments (Reiner, Dragatsis and Dietrich, 2011), researchers have found that reaching performance during both normal and novel (force-field) reaching was accompanied by muscle jerks and error-feedback processing in HD patients compared to healthy controls (Smith, Brandt and Shadmehr, 2000). Figure 1.4B (adapted from Briggs *et al*., 2018) also provides a graphical demonstration of the various projections from different regions that facilitate motor execution for goal directed behaviour.

Furthermore, the fact that the same upper-limb arm reaching paradigm and TMS protocol (SP-TMS delivered at 110% RMT) was used across participants, direct hemispheric asymmetries between regions could be explored in this chapter. Hemispheric asymmetries have been previously reported by researchers, for example when participants performed hand movements Verstynen *et al*., (2005) noted greater neural activity in the left M1 during right hand movements compared to the right M1. Other studies have similarly found that right handed movement result in much greater neural activity in the left hemisphere compared to the right hemisphere (Cramer *et al*., 1999; Schlerf *et al*., 2014). Lesion studies also provide further evidence for hemispheric asymmetries between structures of the left and right hemisphere. For instance, damage

to the right dPMC has been associated with symptoms of ideomotor apraxia whereas damage to the left dPMC has been linked to dystonia (Schnider et al., 1997; Ceballos-Baumann and Brooks, 1998; Gross and Grossman, 2008; Wheaton et al., 2008; Beck et al., 2009). Asymmetries have been reported between different regions of the left and right hemisphere, but this has not been explored during a TMS robotic reaching paradigm, which is a novel element in this thesis.

In order to explore the comparative impact of TMS during upper-limb reaching, a three factorial mixed ANOVA was performed. A novel canonical model was then built based on the differential effects of TMS across regions. The overall purpose of this chapter was to demonstrate the relative importance of the role played by each region in motor control and motor adaptation.

12.2 Methodology

All of the experimental data from chapters 4 – 11 were pooled together for this chapter, and this is further explained in section 3.2. Participant demographics for this chapter are outlined in table 3.2. As previously mentioned throughout the chapters, TMS intensity was set for each region individually for the participant's via functional measures (i.e. left M1, right sided BB MEP – and set at 110% RMT). Figure 3.3 demonstrates the coil orientation and location used for the stimulation of the different regions (canonical brain figures adapted from an MRIcron template – Rorden and Brett, 2000). TMS was always delivered at 110% of RMT. The reaching task that was explored in this chapter was based on the motor adaptation protocol outlined in experimental chapters 5 – 11 and is shown in figure 3.5.

12.3 Data acquisition: Kinematics

The only type of data analysed in this chapter were kinematic parameters which were quantified in Matlab 2017b (The MathWorks Inc, Natick MA, USA) (see section 3.6.1).

12.4 Statistical analysis: Kinematics

Section 3.7.3 describes the statistical analysis that was undertaken for this chapter. Following the three-factorial mixed ANOVA (SPSS 23, IBM) that was undertaken for each kinematic variable, the following statistical tests were performed:

1) A one-way between-subjects ANOVA was performed for significant REGION kinematic variables ($p < 0.05$) (collapsed for TIME factor [by averaging TMS pulse times across participants]). Post hoc testing included Independent t-tests

for: Left M1 vs. left PPC, SMA, right M1, left dPMC, right dPMC and right PPC; Left PPC vs. SMA, right M1, left dPMC, right PPC and right dPMC; SMA vs. left PPC, right M1, left dPMC, right PPC and right dPMC; Right M1 vs. left PPC, left dPMC, right PPC and right dPMC; Right PPC vs. left dPMC, right dPMC; Left dPMC vs. right dPMC; (significance set at $p < 0.002$).

2) A one-way repeated measures ANOVA was performed for significant CONDITION kinematic variables, with maximum velocity, movement duration, summed error and maximum force collapsed for TIME factor by averaging TMS pulse times across participants. Post hoc testing included paired Student's t-test: FF vs. FAM, FF vs. WO and FAM vs. WO (significance set at $p < 0.016$).
3) A one-way repeated measures ANOVA was performed for significant TIME kinematic variables, followed by paired Student's t-test (vs. T10) (significance set at $p < 0.006$).
4) Significant interactions found in the mixed ANOVA are graphically presented in the results section.

Overall, data are presented as mean values, ± the standard error of the mean (SEM) (REGION, CONDITION and TIME).

12.5 Results

12.5.1 Kinematics

12.5.1.1 Mixed ANOVA findings:

The results of the three-factorial mixed ANOVA (table 12.1) revealed a significant effect for REGION on summed error ($p < 0.05$) but not movement onset, movement offset, maximum velocity, movement duration and maximum force ($p > 0.05$). There was a significant effect for CONDITION on movement onset, movement offset, maximum velocity, movement duration, summed error and maximum force ($p < 0.05$). A significant effect was found for TIME on movement onset and movement offset ($p < 0.05$) but not maximum velocity, movement duration, summed error and maximum force ($p > 0.05$). A significant interaction for REGION*CONDITION was found for movement onset, maximum velocity and summed error ($p < 0.05$) but not movement offset, movement duration and maximum force ($p > 0.05$). The findings also revealed a significant REGION*TIME interaction for movement onset and movement offset ($p < 0.05$) but not maximum velocity, movement duration, summed error and maximum

force. No significant interactions for CONDITION*TIME and REGION*CONDITION*TIME were found (for all kinematic variables $p > 0.05$).

12.5.1.2 One way ANOVA and post-hoc testing findings for REGION:

The one-way between-subjects ANOVA (table 12.2A) revealed a significant effect for summed error for FF, FAM and WO reaching between regions stimulated (all $p < 0.05$) (TMS blocks).

Post-hoc testing (table 12.2B and figure 12.2[C-E]) for summed error (REGION factor) during FAM reaching was significantly greater for left M1 stimulation compared to right M1, left dPMC, right PPC and right dPMC stimulation ($p < 0.002$) but not left PPC and SMA stimulation ($p > 0.002$). With regards to FF reaching, summed error was significantly greater during left M1 stimulation compared to SMA, right M1, left dPMC, right PPC and right dPMC stimulation ($p < 0.002$) but not when compared to left PPC stimulation ($p > 0.002$). Summed error during WO reaching was significantly greater with left M1 stimulation when compared to all other regions ($p < 0.002$). With regards to FAM reaching summed errors, there was no significant difference between left PPC stimulation compared to SMA stimulation ($p > 0.002$), however summed error was significantly greater during left PPC stimulation compared to right M1, left dPMC, right PPC and right dPMC stimulation (all $p < 0.002$). Summed error during FF reaching was significantly greater with left PPC stimulation compared to SMA, right M1, left dPMC, right PPC and right dPMC stimulation. WO reaching summed errors with left PPC stimulation was significantly greater when compared to right M1, right PPC and right dPMC stimulation ($p < 0.002$) but not when compared to SMA and left dPMC stimulation responses ($p > 0.002$). FAM summed error responses with SMA stimulation was significantly greater compared to right M1, left dPMC and right dPMC responses ($p < 0.002$) but not compared to the right PPC ($p > 0.002$).

Summed error during FF reaching with SMA stimulation was significantly greater compared right PPC and right dPMC stimulation ($p < 0.002$). However, there were no significant differences in FF summed error when comparing the SMA to the right M1 and left dPMC ($p > 0.002$). With regards to WO responses, summed error was significantly greater during SMA stimulation compared to right M1, left dPMC, right PPC and right dPMC stimulation. Summed error FAM responses during right M1 stimulation was significant greater compared to right PPC stimulation ($p < 0.002$), but

not when compared to the left dPMC and right dPMC ($p > 0.002$). FF summed error responses were only significantly greater with right M1 stimulation when compared to right PPC and right dPMC stimulation ($p < 0.002$), but not when compared to the left dPMC. WO responses were not significantly different between the right M1 and the left dPMC, right PPC and right dPMC ($p > 0.002$). Summed error during FAM and FF reaching with left dPMC stimulation was significantly greater compared to right PPC and right dPMC stimulation ($p < 0.002$), but this was not the case with WO reaching ($p > 0.002$). No significant differences were found in FAM, FF and WO reaching when comparing right PPC and right dPMC summed error responses ($p > 0.002$).

12.5.1.3 One way ANOVA and post-hoc testing findings for CONDITION:

Although the overall N (94) was larger in this analysis, the results obtained for CONDITION corroborate the results that were found in the previous experimental chapters. See section 5.5.2 (left M1), section 6.6.1 (left PPC), section 7.5.1 (SMA), section 8.5.1 (right M1), section 9.5.1 (left dPMC), 10.5.1 (right PPC) and section 11.5.1 (right dPMC) for results. A summary of the significant findings are illustrated in table 12.3A.

12.5.1.4 One way ANOVA and post-hoc testing findings for TIME:

The results obtained for TIME reflect what was found in the previous experimental chapters (5 – 11). See section 5.5.2 (left M1), section 6.6.1 (left PPC), section 7.5.1 (SMA), section 8.5.1 (right M1), section 9.5.1 (left dPMC), 10.5.1 (right PPC) and section 11.5.1 (right dPMC) for results. The summative results for TIME are illustrated in table 12.3B.

12.5.1.5 Significant interaction effects:

A significant REGION*CONDITION interaction was found for movement onset, maximum velocity and summed error ($p < 0.05$) but not movement offset, movement duration and maximum force ($p > 0.05$). Therefore, significant parameters were not collapsed for time, and these results are graphically demonstrated in figures 12.4[A-C].
A significant REGION*TIME interaction was found for movement onset and movement offset ($p < 0.05$) but not for maximum velocity, movement duration, summed error and maximum force ($p > 0.05$). These were not collapsed for time because of the significant TIME factor within the interaction.
REGION*TIME interactions are demonstrated in figures 12.5[A-B].

Table 12.1. Results of the three-factorial mixed ANOVA for TMS blocks of reaching:

	Movement onset (ms)			**Movement offset (ms)**			**Maximum velocity (m.s^{-1})**			**Movement duration (ms)**			**Summed error**			**Maximum force (N)**		
	Df (Error)	F	Sig.	*Df* (Error)	F	Sig.	*Df* (Error)	F	Sig.	*Df* (Error)	F	Sig.	*Df* (Error)	F	Sig.	*Df* (Error)	F	Sig.
R	6 [87]	0.290	0.940	6 [87]	0.632	0.704	6 [87]	0.591	0.736	6 [87]	1.506	0.186	6 [87]	5.883	**< 0.001**	6 [87]	0.983	0.442
C	1.9 [163.0]	18.81	**< 0.001**	2 [12]	13.80	**< 0.001**	2 [12]	13.43	**< 0.001**	2 [12]	42.30	**< 0.001**	1.5 [124.0]	78.85	**< 0.001**	1.2 [96.4]	1491.6	**< 0.001**
T	4.8 [416.7]	104.61	**< 0.001**	6.5 [558.2]	52.91	**< 0.001**	5.3 [453.2]	0.689	0.638	6.7 [578.4]	1.169	0.320	6.0 [517.6]	1.126	0.346	4.9 [420.2]	1.107	0.355
R*C	11.3 [163.0]	1.865	**0.046**	11.5 [165.6]	1.457	0.149	11.3 [163.2]	2.225	**0.015**	11.8 [171.0]	0.888	0.558	8.6 [124.0]	2.685	**0.008**	6.7 [96.4]	0.499	0.825
R*T	28.8 [416.7]	1.613	**0.025**	38.5 [558.2]	1.456	**0.040**	31.3 [453.2]	0.475	0.994	38.9 [578.4]	0.650	0.954	35.7 [517.6]	1.430	0.054	29.0 [420.11]	0.524	0.982
C*T	11.6 [1002.0]	1.579	0.095	12.2 [1057.6]	1.632	0.076	6.7 [579.3]	0.847	0.544	11.8 [1020.3]	1.285	0.223	9.1 [784.7]	0.980	0.455	5.3 [457.6]	0.820	0.541
R*C*T	69.2 [1002.0]	0.756	0.930	73.0 [1057.6]	0.842	0.823	49.0 [579.3]	0.563	0.987	70.4 [1020.3]	0.738	0.947	52.2 [784.7]	1.211	0.147	31.6 [457.6]	0.417	0.998

Table 12.2A. REGION specific summed error values (mean [± SEM]) for the different reaching conditions, followed by a one-way between subjects ANOVA for summed error (collapsed for TIME):

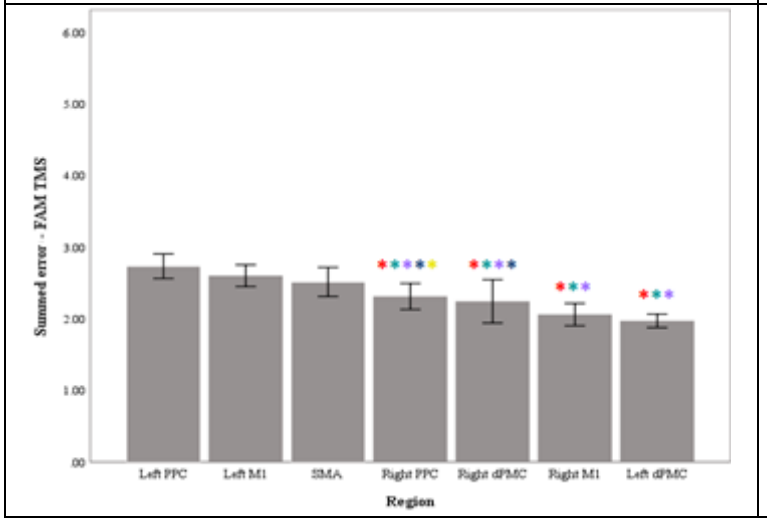
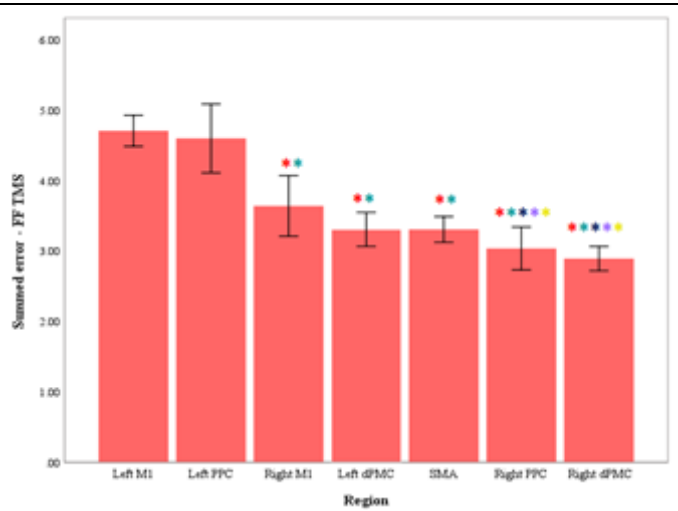
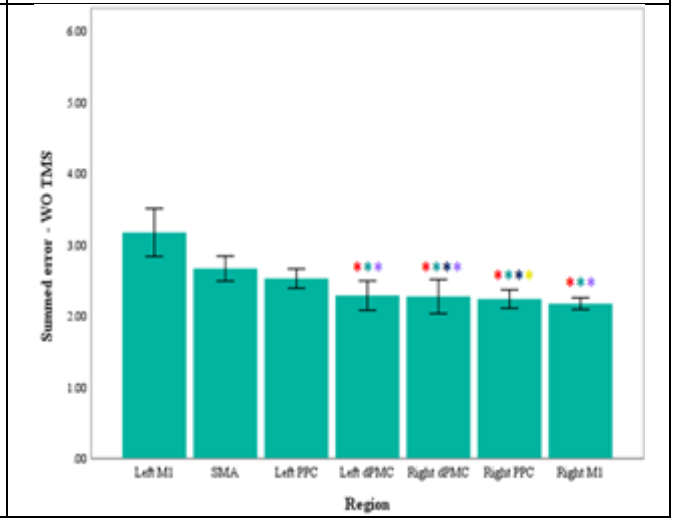
	Summed error - TMS		
REGION	FAM	FF	WO
Left M1	2.60 [0.20]	4.71 [0.38]	3.17 [0.38]
Left PPC	2.73 [0.21]	4.60 [0.53]	2.53 [0.20]
Left dPMC	1.97 [0.12]	3.31 [0.30]	2.29 [0.23]
SMA	2.52 [0.23]	3.31 [0.22]	2.66 [0.21]
Right M1	2.06 [0.17]	3.64 [0.49]	2.17 [0.13]
Right PPC	2.31 [0.18]	3.04 [0.30]	2.24 [0.13]
Right dPMC	2.24 [0.30]	2.89 [0.17]	2.27 [0.24]

	One-way ANOVA (between subjects design) TMS (collapsed for TIME)		
	Df [Error]	F	Sig.
FAM	6 [87]	2.25	**0.046**
FF	6 [87]	5.50	**< 0.001**
WO	6 [87]	3.04	**0.009**

Table 12.3B: Post hoc testing results for summed error TMS (collapsed for TIME) (REGION main factor):

REGION				
		Summed error – TMS		
Comparisons		FAM (Sig.)	FF (Sig.)	WO (Sig.)
Left M1 Vs.	Left PPC	0.071	0.609	0.071
	SMA	0.150	**< 0.001**	0.150
	Right M1	**< 0.001**	**< 0.001**	**< 0.001**
	Left dPMC	**< 0.001**	**< 0.001**	**< 0.001**
	Right PPC	**< 0.001**	**< 0.001**	**< 0.001**
	Right dPMC	**< 0.001**	**< 0.001**	**< 0.001**
Left PPC Vs.	SMA	0.005	**< 0.001**	0.005
	Right M1	**< 0.001**	**< 0.001**	**< 0.001**
	Left dPMC	**< 0.001**	**< 0.001**	**< 0.001**
	Right PPC	**< 0.001**	**< 0.001**	**< 0.001**
	Right dPMC	**< 0.001**	**< 0.001**	**< 0.001**
Left dPMC Vs.	Right PPC	**< 0.001**	**0.002**	**< 0.001**
	Right dPMC	**< 0.001**	**< 0.001**	**< 0.001**
SMA Vs.	Right M1	**< 0.001**	0.009	**< 0.001**
	Left dPMC	**< 0.001**	0.975	**< 0.001**
	Right PPC	0.004	**0.001**	0.004
	Right dPMC	**< 0.001**	**< 0.001**	**< 0.001**
Right M1 Vs.	Left dPMC	0.173	0.008	0.173
	Right PPC	**0.002**	**< 0.001**	**0.002**
	Right dPMC	0.005	**< 0.001**	0.005
Right PPC Vs.	Right dPMC	0.211	0.132	0.211

Figure 12.1 [C-E]: A graphical illustration of post-hoc testing results for summed error TMS responses between regions for different reaching conditions

C. FAM	D. FF	E. WO
		

Symbols represent:

Significant difference between left M1 and other cortical regions stimulated = *

Significant difference between left PPC and other cortical regions stimulated = *

Significant difference between left dPMC and other cortical regions stimulated = *

Significant difference between SMA and other cortical regions stimulated = *

Significant difference between right M1 and other cortical regions stimulated = *

Table 12.3A. One-way ANOVA findings for CONDITION main factor in TMS blocks:

	CONDITION					
	Movement onset (ms)	**Movement offset (ms)**	**Maximum velocity ($m.s^{-1}$)**	**Movement duration (ms)**	**Summed error (distance: cm)**	**Maximum force (N)**
Left M1	✓	✓	✓	✓	✓	✓
Left PPC	✓	✘	✓	✓	✓	✓
Left dPMC	✘	✓	✓	✓	✓	✓
SMA	✓	✘	✓	✓	✓	✓
Right M1	✓	✓	✓	✓	✓	✓
Right PPC	✓	✓	✘	✓	✓	✓
Right dPMC	✘	✓	✘	✓	✓	✓

Table 12.2B. One-way ANOVA findings for TIME main factor in TMS blocks:

	TIME	
	Movement onset (ms)	**Movement offset (ms)**
Left M1	✓	✓
Left PPC	✓	✓
Left dPMC	✓	✓
SMA	✓	✓
Right M1	✓	✓
Right PPC	✓	✓
Right dPMC	✓	✓

Symbols represent:

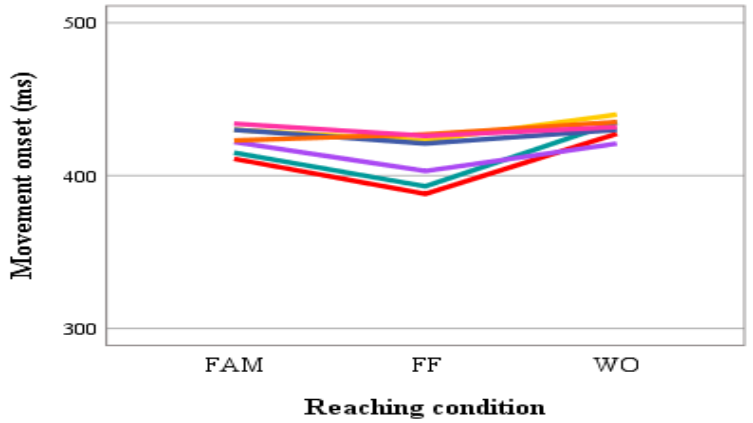
✓ = Significant ANOVA results ($p < 0.05$)

✘ = Non-significant ANOVA results ($p > 0.05$)

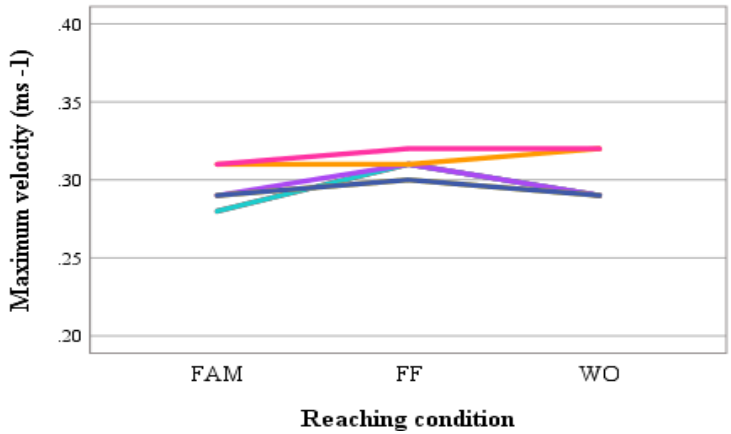
Figure 12.4 [A-C]. Graphical illustration of REGION*CONDITION interaction effects in TMS blocks:

REGION*CONDITION

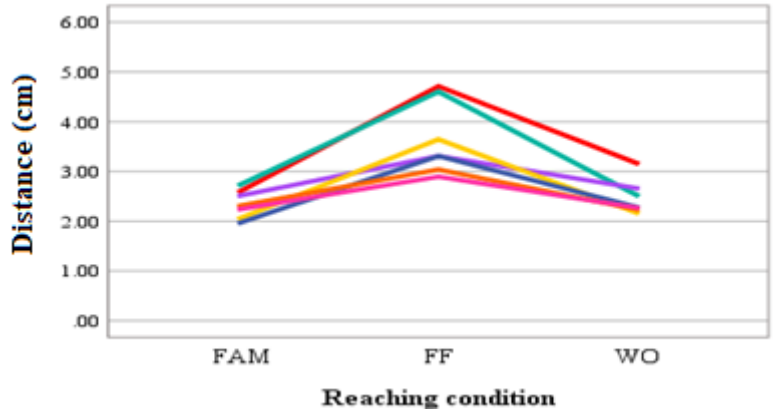
A) Movement Onset (ms)



B) Maximum velocity (m.s^{-1})



C) Summed error (cm)



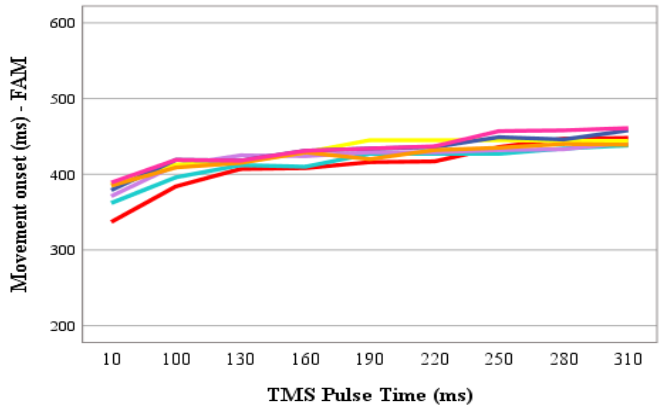
Regions colour coded as:
Left M1, **left PPC**, **left dPMC**, **SMA**, **right M1**, **right PPC** and **right dPMC**

Figure 12.5 [A-B]. Graphical illustration of REGION*TIME interaction effects in TMS blocks:

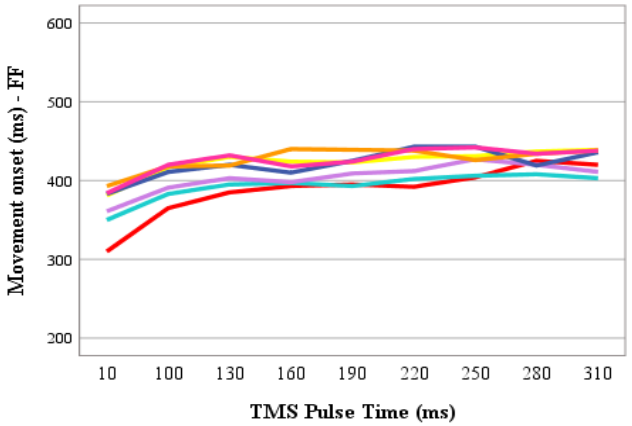
REGION*TIME

A) Movement onset (ms)

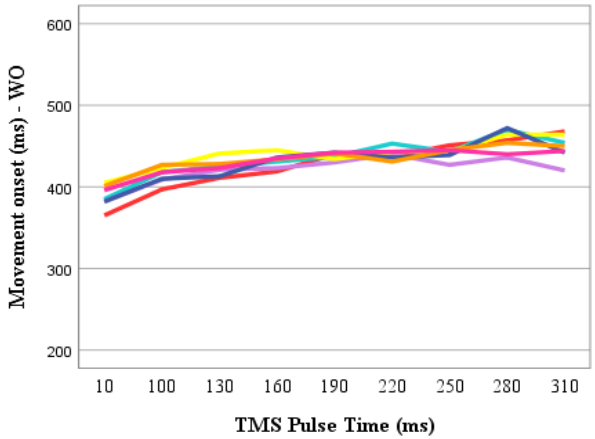
FAM



FF

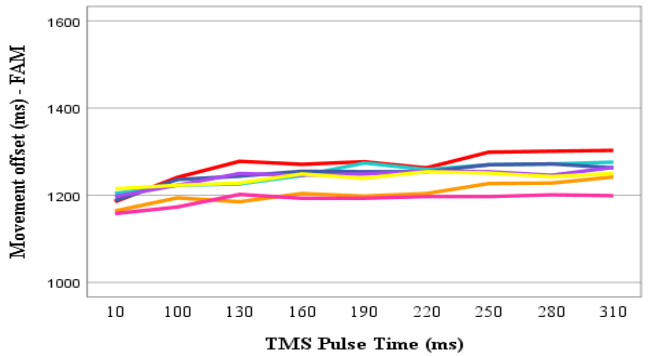


WO

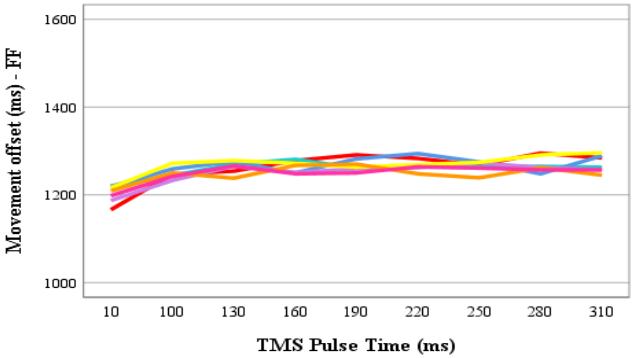


B) Movement offset (ms)

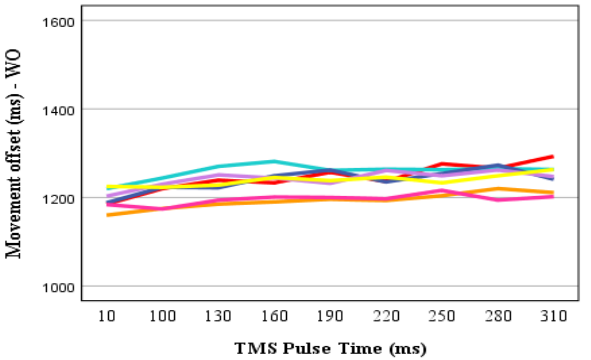
FAM



FF



WO



Regions colour coded as:
Left M1, **left PPC**, **left dPMC**, **SMA**, **right M1**, **right PPC** and **right dPMC**

12.6 Discussion:

Previous studies exploring the impact of TMS on preparation for upper-limb reaching have not targeted a variety of regions using robotic methods but have rather targeted one or two regions using different types of reaching paradigms (such as pointing-to-reach tasks) and TMS protocols (rTMS and twin-coil methods). Throughout the motor adaptation paradigms in this thesis (chapters 5 – 11) the same reaching task and TMS protocol (SP TMS, 110% RMT, and TMS delivered randomly at different time points of reaching preparation) was undertaken. The use of consistent paradigms enabled direct kinematic comparisons between different cortical regions in this chapter. Overall, this final chapter provided a novel insight into the different levels of influence across regions of the motor network and demonstrated that TMS-based disruption to different cortical structures had a varied impact on motor control (FAM) and motor adaptation (FF) as measured by summed error and some interactions for timing of reaching.

12.6.1 Kinematics:

12.6.1.2 Region specific relative influence defined by summed error

The main finding from this experimental chapter was that TMS had a region-specific impact on motor control and motor adaptation because summed error was significantly different between regions across the different reaching conditions (FAM, FF and WO). Post hoc testing revealed the relative importance of a regions role in preparation for reaching, for example, TMS to the left M1 and the left PPC resulted in greater summed error responses during FF reaching when compared to all other regions. Based on this finding, it could therefore be inferred that based on this comparative chapter that the left M1 and left PPC play a greater role in the preparation for motor adaptation during upper-limb reaching compared to other regions in the motor network, such as the SMA, left and right dPMC and right PPC. These findings are in line with studies that have similarly demonstrated the important role of left M1 and left PPC in reaching behaviours. For example, Cavina-Pratesi, Connolly and Milner (2013) found that patients with optic ataxia due to left PPC lesions had arm reaching deficits, but not reaching-to-grasp deficits. TMS studies have also shown that virtual disruptions to the

left PPC compared to a control area (e.g. the occipital lobe) following movement onset resulted in impaired reaching trajectories (Della-Maggiore, *et al*., 2004). This experiment provided a novel finding because it demonstrated that the left PPC is not only involved in reaching execution (as previously demonstrated by Della-Maggiore, *et al*., 2004) but also reaching preparation and TMS to the left PPC during reaching preparation can result in reaching trajectories that resemble a model of optic ataxia. Left M1 stimulation also had a significant detrimental impact on reaching during motor adaptation. As well as suggesting an obvious direct role of left M1 in right arm reaching, this could have been due to TMS affecting other cortical structures (such as the cerebellum) (via trans-synaptic transmission) that facilitate M1 functioning for motor output (Chouinard *et al*., 2003; Richardson *et al*., 2006). Direct TMS disruption of cerebellar regions and their possible roles in motor adaptation would support this avenue of future work and the use of double-coil TMS induced disruption of cerebello-M1 connection function during motor adaptation.

Although TMS to the left M1 and left PPC resulted in a greater disruption to reaching preparation compared to other regions (e.g. the SMA), we should be cautious and not de-emphasise the role of the SMA particularly when experimental findings from previous chapters in this thesis (chapter 7) demonstrated its given role in movement preparation. This is supported by studies that have undertaken different motor protocols. For instance, in an fMRI motor imagery and execution task, Kasess *et al*., (2008) found that the SMA caused a suppression in movement planning and preparation which resulted in inhibited M1 activity (Kim *et al*., 2018). Studies in PD patients have also provided evidence for the importance of the SMA in motor preparation and execution (Chung *et al*., 2018). The SMA is strongly connected with the basal ganglia and has been found to be disrupted in PD patients (Jenkins *et al*., 1992; Haslinger *et al*., 2001; Chung *et al*., 2018). For instance, imaging studies have revealed reduced cerebral blood flow in the SMA of PD patients whilst they were performing a motor task with a joystick (Playford *et al*., 1992; Chung *et al*., 2018). Patients with PD also have increased neuronal desynchronisation during movement preparation, before movement onset (Rowland *et al*., 2015; Chung et al., 2018). Based on this notion, it can be argued that TMS effected reaching preparation because it disrupted communication between cortical networks that are connected with the SMA including the basal ganglia.

Furthermore, the role of the SMA and left dPMC should not be disregarded because this comparative chapter revealed that TMS to these two regions during motor adaptation resulted in significantly greater summed error responses compared to other regions, such as the right PPC during preparation for FF reaching. Researchers have argued that that the SMA and PMC play an important role in facilitating the 'Bereitschaft (readiness) potential' in a motor task during movement preparation (Deecke and Kornhuber, 1987; Di Russo *et al.,* 2005; Nguyen, Breakspear and Cunnington, 2014; Verleger et al., 2016). For example, by using a dipole EEG analysis method in a finger flexion task, Di Russo *et al*., (2005) revealed that the SMA and PMC produce these potentials prior to movement onset. Lesion studies have also shown that patients with SMA lesions have impaired Bereitschaft potential features (Deecke *et al*., 1978; Di Russo *et al*., 2005) thus providing further evidence for the role of the SMA in "pre-movement potential" generation. Therefore, it can be suggested that in this study TMS disrupted the Bereitschaft potential process, thereby causing increased SMA and left dPMC-based summed error responses. However, it has been argued that the impact of the SMA in facilitating the Bereitschaft potential depends on the type of motor task being performed (Praamstra *et al*., 1996). For example, when subjects performed fixed vs. freely selected movements with a joystick, Praamstra *et al*., (1996) reported that the movement potentials eliciting the Bereitschaft potential in the SMA were less affected when subjects performed fixed movements compared to freely selected movements. Furthermore, the complexity of a motor task has also been found to influence the Bereitschaft potential (Shibasaki and Hallett, 2006), a notion supported by Simonetta *et al*., (1991) who concluded that sequential movements compared to simple movements led to both larger and earlier Bereitschaft potential onset (Shibasaki and Hallett, 2006). Similar findings were illustrated by Benecke *et al*., (1985). Shibasaki and Hallett (2006) also noted that the speed of a movement, specifically faster motions were associated with a later Bereitschaft potential onset. Based on such studies, it could be argued that the reason as to why TMS did not severely affect SMA functioning was due to the nature of the task, i.e. simple, fixed reaching movements took place compared to complex sequential movements. Furthermore, studies have also shown that the Bereitschaft potential can arise from other regions depending on the task performed. For example, Wheaton, Shibasaki and Hallett (2005) explored how movement related cortical potentials are affected during everyday motor tasks in right handed participants.

Their findings revealed that the Bereitschaft potential developed from the left parietal cortex during movement planning and preparation (Shibasaki and Hallett, 2006). Considering this, it could be suggested that in this thesis TMS had a greater impact on the left PPC because the Bereitschaft potential firstly developed from the parietal cortex and then the medial-frontal areas (Wheaton, Shibasaki and Hallett, 2005; Shibasaki and Hallett, 2006). Therefore, a number of factors ranging from task complexity to physiological features (e.g. the Bereitschaft potential) can help explain why some regions were more severely impacted with TMS compared to others.

Furthermore, resting-state fMRI studies have demonstrated the importance of different connecting pathways in the motor circuit that facilitate motor function. For instance, studies in stroke patients with upper-limb impairment have shown that increased functional connectivity between the affected M1 (i.e. ipsilesional hemisphere) and areas such as the SMA and frontal lobe resulted in enhanced motor recovery (Park *et al*., 2011; Auriat *et al*., 2015). Other important connecting pathways include the ipsilesional M1 and the contralesional dPMC (Bestmann et al., 2010; Auriat *et al*., 2015). For instance, a TMS-fMRI (dual-coil) study conducted by Bestmann *et al*., (2010) in stroke patients revealed that a decrease in inhibition from the affected dPMC to the unaffected dPMC was associated with greater motor deficits. Based on these studies, it could be argued that TMS to one specific region had a distinct effect on the networks associated with that region, which provides an explanation for the varied region-specific impact of TMS.

The fact that TMS had differential effects in motor control and motor adaptation provides evidence for the task specific properties of different nodes in the motor network (Buchel, Coull and Friston, 1999; Wei *et al*., 2018) which has been supported by neuroimaging studies. For example, in an fMRI motor task where participants were instructed to perform: 1) right ankle movement, 2) agonist muscle movement and 3) movement with pressure-stimulation, Wei *et al*., (2018) found that agonist muscle movement compared to both right ankle movement and pressure-stimulation resulted in the greatest and most dispersed activity in in areas ranging from the thalamus to the left M1. Agonist muscle activity also takes place in motor adaptation protocols (Pizzamiglio *et al*., 2017b). It can therefore be argued that in this experiment TMS may have disrupted the spread of cortical activity related to agonist muscle movement, thereby resulting in increased trajectory reaching errors.

12.6.1.3 Evidence for hemispheric asymmetries during motor adaptation

Post hoc testing results for summed error (table 12.2B) provides evidence for hemispheric asymmetries because some cortical structures between the left and right hemisphere responded differently during motor adaptation. This was particularly evident for the left PPC vs. the right PPC. These results are in line with lesion-studies that have also demonstrated asymmetries between regions. For example, researchers have reported that damage to the right PPC can result in spatial neglect whereas damage to the left PPC can result in right-handed defects during reaching (Perenin and Vighetto, 1988; Husain and Nachev, 2007; Koch *et al*., 2011; Andersen et al., 2014). Such studies have therefore highlighted separate functional roles of the two regions, with the right PPC involved in visual/spatial attention and the left PPC involved in visually guided reaching (Della-Maggiore *et al*., 2004; Koch *et al*., 2011). The results for summed error support literature findings regarding the greater functional role of the left PPC (compared to the right PPC) in 1) visually guided-reaching and 2) novel reaching behaviours.

12.6.1.4 Regions and conditions impacted for maximum velocity (REGION*CONDITION)

As well as the region-specific impact on summed error, a significant REGION*CONDITION interaction was found for maximum velocity (table 12.1 and figure 12.4[A-C]. The findings revealed that regions such as the right dPMC and right PPC were highly impacted with TMS for maximum velocity during motor control [FAM and WO reaching] but not so much during motor adaptation [FF reaching]. This was not the case for other regions such as the left PPC, left M1, SMA, right M1 and left dPMC. Studies in non-human primates have revealed that the dPMC plays a critical role in encoding kinematic parameters of a movement (Alexander and Crutcher, 1990; Fu, Suarez and Ebner, 1993; Ward *et al*., 2007), based on this it can be suggested that when TMS is delivered to the dPMC, it will have an impact on parameters such as velocity. However, it is important to note that TMS to the left dPMC did not impact on motor control, but rather during motor adaptation and this can be due to the functional asymmetries that have been reported between the left and right dPMC. For example, greater neural activity has been noted in the left dPMC compared to the right dPMC during the learning phase of a motor task (Hardwick *et al*., 2013). Furthermore, it has

been argued that the left dPMC in contrast to the right dPMC facilitates movement selection, this has been supported by both left dPMC virtual disruption studies and clinical population studies as subjects were found to perform poorly during response selection tasks (Halsband *et al*., 1993; Mochizuki *et al*., 2005; Kantak *et al*., 2012; Hardwick *et al*., 2013). Considering these studies, it could be argued that TMS will have a greater impact in regions that play a more functional role in the learning of a new motor task, which is in line with what was found in this experiment (e.g. left dPMC was impacted more with TMS during MA compared to FAM and WO reaching).

12.6.1.5 Limitations to consider

This chapter revealed a region-specific influence for summed error particularly for the left M1 and left PPC compared to other regions that were targeted. However, this can be considered as a limitation of the experimental approach that was undertaken to disrupt normal processing during the preparation phase of reaching. For example, it could be argued that if partipants had performed complex tasks, including sequential movements towards different reaching targets compared to fixed movements towards one target, TMS to areas such as the SMA and dPMC may have had a more detrimental impact on summed error responses during reaching preparation (based on findings from Simonetta *et al*., 1991 and Praamstra *et al*., 1996). This notion has also been supported by Shibasaki *et al*., (1993). In a finger movement protocol using PET imaging methods, they revealed that task complexity increased cerebral blood flow in the SMA and M1 because the demanding nature of the task affected the components associated with movement-related cortical potentials (Shibasaki and Hallett, 2006). Therefore, if this study were to be replicated, altering the nature of the reaching task would be an important factor to take into account, i.e. making the task more demanding for the subject. However, there is a trade off between making the task more difficult and avoiding fatigue. Nonetheless, shortening the reaching paradigm could provide a solution in ensuring subject comfort during a complex and fatiguing motor task. Nonetheless, it important to not under emphasise the role of other regions that were targeted with TMS because 1) previous chapters revealed that TMS did have an impact on other structures targeted during preparation for novel reaching and, 2) table 12.2A revealed larger summed error responses during FF vs. FAM reaching for all regions, thus demonstating each regions' important functional role in movement preparation.

Furthermore, using a combination of methods could have led to more in depth findings regarding the neurophysiological impact of TMS during reaching preparation. For instance, if TMS-EEG or TMS-fMRI was employed, observing cortical potentials (with EEG) or cerebral blood flow (with fMRI) could have helped establish the network effects of TMS across different structures, particularly when considering that TMS does not only have a direct affect on the area that is being stimulated, but it also has an impact on regions connected with the stimulated area (Ruff, Driver and Bestmann, 2009). If this study was repeated it would be useful to employ additional imaging methodologies in conjuction with TMS. Mixed methodologies would enable different statistical analysis to be carried out. For example, neural activation patterns could be correlated with different performance measures (e.g. summed error) during preparation for novel reaching (Ruff, Driver and Bestmann, 2009), therefore both causal and correlational inferences could be drawn with regards to the results obtained (Ruff, Driver and Bestmann, 2009).

Moreover, it is important to consider the sample population that was studied in this thesis; individuals aged 18 – 40. A future consideration would be to develop the study by recruiting other groups of participants, including middle aged and older aged adults (e.g 55+ years). This would be interesting to explore because studies employing TMS protocols have demonstrated that neuroplasiticity in the M1 is reduced in older adults (Fathi *et al*., 2010; Porto *et al*., 2015). This notion is supported by Fathi *et al*., (2010) as their findings concluded reduced MEP amplitude responses in older aged subjects compared to both younger and middle-aged subjects. They argued that the reduced plasticity in older adults could be attributed to impaired cortical networks between the basal-ganglia and motor circuits (e.g. the M1, SMA and sensorimotor regions). In addition to recruiting older adults, recuiting patients with neurological impairments could also help expand the findings of this study. For example, the comparative chapter in thesis revealed the importance of the left PPC, and chapter 6 also demonstrated that a patient-like model of optic ataxia was created with the virtual lesion TMS approach (as the results were similar to clinical findings from Pisella *et al*., 2000). Therefore, directly studying motor adaptation in patients (such as those with optic ataxia) could help: 1) provide a comparison group for analysis purposes (i.e. healthy group vs. patient group), 2) explore the strength of TMS as a virtual lesion tool, and 3) further investigate the hypothesis regarding the role of the left PPC for the preparation of novel reaching.

Overall, if the studies in this thesis were to be replicated a number of factors would be considered, ranging from implementing a more complex motor reaching paradigm to employing other imaging methods in conjuction with TMS. In addition to this, it would also be interesting to explore other sample-populations, such as older-aged adults or clinical patients with neurological impairments. Despite these limitations, novel findings were illustrated, and the relevance of these findings with regards to future directions (e.g. in the field of neurorehabilitation and neurocompuational models) are discussed in chapter 13.

12.7 Conclusion:

This experiment provided novel findings by demonstrating the comparative impact of TMS to various nodes of the motor network. The main findings revealed a statistical difference in summed error between different cortical regions. More specifically, areas such as the left M1 and left PPC were found to play a significant role in motor adaptation compared to other regions such as the SMA, right M1, left dPMC, right PPC and right dPMC. Based on these findings it can be argued that damage to areas including the left M1 and left PPC may result in greater impairments during upper-limb reaching during motor adaptation, which is line with patient studies (e.g. stroke and traumatic brain injury patients). Furthermore, the fact that TMS had a varied impact on different regions provides evidence for the notion that different areas of the motor network play a different functional role in motor control and adaptation. This was illustrated by the interactions that were found, whereby the right dPMC and right PPC were highly impacted for maximum velocity during motor control and motor adaptation whereas other regions were only highly impacted during motor adaptation. Functional asymmetries that have been found between regions of the two hemispheres explains why TMS affected some regions more than others. Overall, this final chapter begins to build a unique and novel model for studying the motor network during a range of tasks including reaching and as a function of healthy ageing or disease whereby the regions may operate in compensatory roles resulting in a different pattern or signature of region-specific importance.

Chapter 13

Final conclusion and Future directions

This thesis outlined a novel approach in studying the network nodes in the motor circuit during an upper-limb robot-mediated reaching tasks. The approach taken to explore behavioural responses using TMS protocols in this thesis was novel because it was the first attempt to describe the different behavioural effects (kinematic responses) of SP-TMS delivered to a number of cortical structures at nine different time points during the preparation phase of a reach with a robot-mediated force-field paradigm. The overall results that were obtained in this thesis were also novel as the findings identified regions of the motor circuit that play a more functional role in novel reaching. For instance, both individual chapters (chapter 5 and 6) and the final comparative chapter revealed that the left M1 and left PPC were similarly and most significantly disrupted with TMS during novel reaching.

These findings have a wide range of future implications, one of which includes its application in brain machine interfaces (BMI) in the field of neurorehabilitation. BMI's are based on obtaining brain signals, interpreting them into commands which are then transferred to devices to perform actions (Shih, Krusienski and Wolpaw, 2012). BMIs have therefore been used to control functions in patients with impairments (McFarland and Vaughan. 2016) by providing the brain with channels based on cortical activity (Ranjangam *et al*., 2016; Shih, Krusienski and Wolpaw, 2012). BMI applications have been used to help assist functional recovery among clinical populations, ranging from patients with stroke to those with multiple sclerosis (Shih, Krusienski and Wolpaw, 2012; Ramos-Murguialday *et al*., 2019). Ramos-Murguialday *et al*., (2019) reported that BMI training in stroke patients to assist upper-limb movement (i.e. the paretic arm) with a robotic device resulted in an increase in a clinical outcome measure, Fugl-Meyer score, therefore demonstrating its effectiveness in the field of neurorehabilitation and aiding functional recovery. The use of TMS with a virtual disruption approach has helped researchers identify regions that are important for particular functions (Bolognini and Ro, 2010; Carmena and Cohen, 2012) and due to this stimulation methods have been implemented in the BMI field (Reis *et al*., 2009; Carmena and Cohen, 2012). The final chapter of this study demonstrated the functional role of the left M1 compared to

other regions of the motor network (e.g. right PPC and right dPMC) in novel motor behaviours. The role of the ipsilateral M1 should also not be ignored, as findings from this thesis demonstrated its importance in novel reaching. Therefore, the data from both the left M1 and right M1 can be used as a BMI signal source to aid functional recovery in stroke patients (Carmena, *et al*., 2003; Schroeder and Chestek, 2016; Hatsopoulos and Suminksi, 2011).

BMI approaches are not only confined to assisting motor recovery but also cognitive recovery (Hauschild *et al*., 2012) and this is important in terms of the left PPC findings in this thesis. For instance, studies in non-human primates have shown that extracted PPC signals increase performance rates, specifically reaching trajectories and this can be important in helping assist patients with left PPC lesions such as those with optic apraxia (Hauschild *et al*., 2012). Overall this thesis has demonstrated regions that are involved in novel reaching that can be used as a site for signal extraction for BMI approaches (Ranjangam *et al*., 2016; Andersen *et al*., 2014).

The findings from this thesis also revealed that although the SMA, right M1, left dPMC and were not as disrupted as the left M1 and left PPC, their roles in preparation for novel reaching should not be de-emphasised, as the individual experimental chapters revealed their role in novel reaching too. For instance, with regards to the SMA, the findings from chapter 7 demonstrated that reaching trajectories were significantly impaired in FF reaching compared to FAM and WO reaching (albeit, not at all time time points). Additionally, the results from chapter 9 illustrated significant disruptions at all time points when TMS was delivered to the left dPMC. These findings are relevant within the neurorehabilitation field because they have helped provide further evidence regarding the importance of left dPMC- and SMA- M1 connectivity in aiding functional recovery among stroke patients. For example, studies have shown that rTMS delivered to the intact hemisphere of stroke patients enhanced neural communication between the affected SMA and M1, which led to improved motor performance when patients performed paretic hand movements (Grefkes *et al*., 2010; Liew *et al*., 2014). Therefore, the results from this thesis demonstrated the critical role of regions in the motor circuit (other than the M1 and left PPC) that facilitate motor preparation and execution.

Moreover, Huang and Krakauer (2009) reported that the use of robotic protocols in healthy participants have helped researchers gain an understanding into the mechanisms

of motor control and motor learning. Based on this notion, it could be argued that this thesis demonstrated an insight into methodological factors that are important in the field of neurorehabilitation. For example, the findings highlighted that subjects were able to optimise their reaching following four blocks of no-TMS motor adaptation reaching trials (which is in line with motor adaptation research - Pizzamiglio et al, 2017a; Pizzamiglio et al., 2017b). Therefore, implementing and expanding such motor protocols in the field of neurorehabilitation can be considered, particularly when taking into account that researchers such as Patton *et al*., (2006) have demonstrated that resistive robotic tasks compared to assistive tasks resulted in better therapeutic outcomes in stroke patients. However, the principles of neuroplasticity during motor adaptation remain under-researched and some have argued that demanding and complex motor learning tasks facilitate neuroplasticity compared to repetitive motor adaptation tasks (Turner et al., 2013). Therefore, whether this particular model can be used for motor recovery among patients can be questioned. Nonetheless, further investigations into methodological factors in motor protocols (such as, the type of motor task undertaken, the duration of the task and number of sessions) can help build the foundations for new research within the field neurorehabilitation (Huang and Krakauer, 2009).

Furthermore, the main findings from the right M1 revealed that TMS had an disruptive impact on reaching trajectories particularly during force-field reaching compared to normal reaching (FAM and WO) (figure 12.2D and table 12.2A). This finding confirmed what previous researchers have noted regarding right M1 function during ipsilateral reaching (right arm) and that the right M1 also undergoes modulations of activity during right arm reaching (Van den Berg, Swinnen and Wenderoth, 2011). This result is not only useful for BMI neurorehabilitation applications (i.e. in stroke patients where the contra-lesional hemisphere becomes important in guiding ipsilateral functions - Dancause *et al*., 2006; Ganguly *et al*., 2009) but the finding can also be applied within neuro-computational models regarding data-based virtual lesions that have been incorporated into patient models (for example, stroke patients). Using TMS to create patient models via a virtual disruption can help researchers overcome many of the challenges faced when investigating the effects of lesions on functional connectivity in clinical populations (Sliwinska, Vitello and Devlin, 2014). For example, Sliwinska, Vitello and Devlin (2014) reported that the use of TMS: 1) has greater degrees of

accuracy and specific structures can be explored compared to patients lesions studies whereby the damage affects a wide range of structures, and 2) the same subjects can be used to explore the effects of TMS in different regions (i.e. greater degree of control vs. heterogeneous stroke lesion patients). Based on these notions, the data in this thesis can help gain a deeper understanding into how neural networks operate following disrupted functional activity.

It is important to note that findings from this thesis also revealed that TMS to some regions, such as the right PPC and the right dPMC was not so impactful. This could have been due to the methodology that was undertaken. For example, in this thesis only right handed subjects were recruited and studies have shown that TMS to the right dPMC effects left handed functions compared to right handed functions (Schluter *et al*., 1998). Similarly, the right PPC has been found to be involved in planning left handed reaching movements only compared to the left PPC which has been involved in planning both right and left handed movements (Schluter *et al*., 2001; Oliveira *et al*., 2010). In addition to this, imaging studies have revealed that 1) sequential motor tasks and 2) complex motor tasks affect the right dPMC and right PPC as both regions play a role in maintaining selective attention (Poster and Peterson, 1990; Sadato *et al*., 1996; Malhotra, Coultard and Husain, 2009) whereas a simple motor adaptation task was used in this thesis. Therefore, the future directions of this research would include providing a deeper insight on the function of the right dPMC and right PPC by refining methodological factors, including the motor task undertaken (i.e. using a complex task rather than simple task) and recruiting a different sample population (i.e. both right and left handed subjects). Such research findings can help demonstrate how handedness contributes to motor preparation and execution, and the differences with regards to how cortical regions interact in both left- and right-handed subjects during novel reaching.

Nonetheless, the studies in this thesis were novel as previous researchers that have explored the behavioural effects of TMS have mainly investigated behavioural responses following movement onset compared to exploring responses prior to movement onset (i.e. motor preparation) (*Della-Maggiore et al., 2004).* In addition to this, most researchers have employed; 1) paired-pulse TMS and rTMS paradigms to explore the functional role of cortical regions in motor tasks (Gerloff *et al*., 1997; Serrienet *et al*., 2002; Steyvers *et al*., 2003; Nachev, Kennard and Husain, 2008; Mars *et al*., 2009; Chouinard and Paus, 2010) and 2) different motor paradigms such as visuo-

motor adaptation tasks, finger sequencing tasks, 'point' reaching and 'grasp' reaching tasks (Gerloff et al., 1997; Culham, Cavina-Pratesi and Singhal, 2006; Lee and Van Donkelaar, 2006; Miall et al., 2007) compared to a novel SP-TMS, robotic induced arm reaching perturbation paradigm which was used in this thesis.

Overall, in this thesis a novel TMS mapping method was introduced to create virtual disruptions of different regions in the motor network in order to explore the functional role of different structures in upper-limb motor control and motor adaptation. Despite novel findings illustrating the pivotal role of regions such as the left and right M1, left PPC, SMA and left dPMC which can be implemented in the field of neurorehabilitation (e.g. BMIs) and also in neurocomputational patient models, there are future considerations to take into account. For example, other regions of the motor network can also be targeted such as the cerebellum and the DLPFC as these two structures have been argued to play a key role in encoding kinematic parameters and facilitating motor responses (Overduin, Richardson and Bizzi 2009; Badoud *et al*., 2017). In addition to this, it would be important to perform a "control" protocol of a NO-TMS paradigm in order to make direct comparisons of TMS virtual-disruption during reaching vs. no TMS during reaching over the course of the same number of trials. Moreover, developing a more demanding motor protocol could also help reveal the importance of regions such as the right PPC and right dPMC in motor control and motor adaptation, as the functioning of these two regions were not as effected with TMS compared to other regions that were targeted. Therefore: 1) stimulating further putative cortical regions in the motor circuit, 2) obtaining control findings with a NO-TMS protocol, and 3) modifying the adaptation protocol could help further refine our understanding of the regions involved in motor control and adaptation.

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Appendix 1. Ethical approval:

EXTERNAL AND STRATEGIC DEVELOPMENT SERVICES
uel.ac.uk/qa
Quality Assurance and Enhancement

13 June 2016

Dear Pegah Mohajer Shojaii,

Project Title:	**The Neural Mechanisms of Motor Learning in Healthy Adults Using Neuroimaging Technologies**
Principal Investigator:	**Professor Duncan Turner**
Researcher:	**Pegah Mohajer Shojaii**
Reference Number:	**UREC 1516 108**

I am writing to confirm the outcome of your application tothe University Research Ethics Committee (UREC), which was considered by UREC **on Wednesday 18 May 2016.**

The decision made by members of the Committee is **Approved**. The Committee's response is based on the protocol described in the application form and supporting documentation. Your study has received ethical approval from the date of this letter.

Please note the UREC Application Form for ethical approval has been revised. For future applications please use the revised application form which can be found on:
https://uelac.sharepoint.com/ResearchInnovationandEnterprise/Pages/Ethics.aspx

The Committee would like to commend you on the presentation of this application for ethical approval.

Should you wish to make any changes in connection with your research project, this must be reported immediately to UREC. A Notification of Amendment form should be submitted for approval, accompanied by any additional or amended documents:
http://www.uel.ac.uk/wwwmedia/schools/graduate/documents/Notification-of-Amendment-to-Approved-Ethics-App-150115.doc

Any adverse events that occur in connection with this research project must be reported immediately to UREC.

Docklands Campus, University Way, London E16 2RD
Tel: +44 (0)20 8223 3322 Fax: +44 (0)20 8223 3394 MINICOM 020 8223 2853
Email: r.carter@uel.ac.uk

Approved Research Site

I am pleased to confirm that the approval of the proposed research applies to the following research site.

Research Site	Principal Investigator / Local Collaborator
University of East London	Professor Duncan Turner

Approved Documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
UREC application form	2.0	3 June 2016
Participant Information Sheet	2.0	3 June 2016
Consent Form	2.0	3 June 2016
Annexe 3 – Medical Questionnaire	2.0	3 June 2016
Annexe 4 - recruitment advertisement	2.0	3 June 2016

Approval is given on the understanding that the UEL Code of Practice in Research is adhered to.

The University will periodically audit a random sample of applications for ethical approval, to ensure that the research study is conducted in compliance with the consent given by the ethics Committee and to the highest standards of rigour and integrity.

Please note, it is your responsibility to retain this letter for your records.

With the Committee's best wishes for the success of this project.

Yours sincerely,

Catherine Fieulleteau
Research Integrity and Ethics Manager
University Research Ethics Committee (UREC)
Email: researchethics@uel.ac.uk

Appendix 2. Participant information sheet and consent form:

University of East London

Stratford Campus: School of Sport, Health and Bioscience,
London,
E15 4LZ

University Research Ethics Committee

If you have any queries regarding the conduct of the programme in which you are being asked to participate, please contact:

Catherine Fieulleteau, Research Integrity and Ethics Manager, Graduate School, EB 1.43
University of East London, Docklands Campus, London E16 2RD
(Telephone: 020 8223 6683, Email: researchethics@uel.ac.uk).

The Principal Investigator(s)

1) Director of studies:

Professor Duncan Turner,

Address:

AE5.23, School of Health, Sport and Bioscience,
University of East London,
Stratford Campus,
Romford Road,
London,
E15 4LZ,

(Telephone: **0**20 8223 4514, Email: d.l.turner@uel.ac.uk)

2) Investigator/PhD student:

Pegah Mohajer Shojaii

(Email address: p.shojaii@uel.ac.uk)

Consent to Participate in a Research Study

The purpose of this letter is to provide you with the information that you need to consider in deciding whether to participate in this study.

Project Title

The Neural Mechanisms of Motor Learning in Healthy Adults Using Neuroimaging Technologies

Project Description

Research aim: This research project will aim to explore the neural mechanisms of motor adaptation through a motor learning task with a computerized robot.

Procedure:

The motor learning task will require you to sit in a customised chair, facing a screen. Here, you will be asked to make arm reaching movements in a particular direction, with your arm placed in a device connected to the robot. The robot will then apply force-fields which can influence the output of your arm reaching movement.

Whilst you carry out this task, your muscle activity (EMG) and motor evoked potentials (MEPs) will be recorded through surface electrodes placed on your arm muscles, and also through a safe neuroimaging method, known as transcranial magnetic stimulation (TMS).

Risks:

There are no medical risks involved in the study:

All the methods that will be used in this research have already been established in the Neurorehabilitation Unit over the last 10 years and we do not foresee any technical or health and safety issues. We have tested over 200 subjects over 10 years with no adverse events in all studies.

Study length:

The experiment will take approximately two hours and a half to complete.

Confidentiality of the Data

As this project will have 12-15 participants, the risk of your data being identified is increased, however anonymity steps will be taken in order to ensure your privacy. For example, you will be given a participant number, and your data will be stored under that number. Your consent form and medical questionnaire will be stored separately. After the PhD project has been complete, your data will be stored in the research lab for >10 years.

Location

The research will be carried out in a Neurorehabilitation Unit (NRU), located in the Stratford campus of the University of East London, within the School of Health, Sport and Bioscience (HSB).

Remuneration

You will receive a £20 Amazon voucher after completing the experiment.

Disclaimer

You are not obliged to take part in this study, and are free to withdraw at any time during tests. Should you choose to withdraw from the programme you may do so without disadvantage to yourself and without any obligation to give a reason.

UNIVERSITY OF EAST LONDON

Consent to Participate in a Programme Involving the Use of Human Participants.

The Neural Mechanisms of Motor Learning in Healthy Adults Using Neuroimaging Technologies

Researchers:

The principle investigator: Professor Duncan Turner (BSc, PhD)

Investigator/PhD student: Pegah Mohajer Shojaii (BSc, MSc)

	Please tick as appropriate: YES	NO
I have the read the information leaflet relating to the above programme of research in which I have been asked to participate and have been given a copy to keep. The nature and purposes of the research have been explained to me, and I have had the opportunity to discuss the details and ask questions about this information. I understand what is being proposed and the procedures in which I will be involved have been explained to me.		
I understand that my involvement in this study, and particular data from this research, will remain strictly confidential as far as possible. Only the researchers involved in the study will have access to the data. *(Please see below)*		
I understand that maintaining strict confidentiality is subject to the following limitations: If the sample size is small, or focus groups are used state that that this may have implications for confidentiality / anonymity. My confidentiality will be maintained unless a disclosure is made that indicates that I or someone else is at serious risk of harm. Such disclosures may be reported to the relevant authority.		
I will be pseudo-anonymised in publications that will arise from the research.		

I am aware that the proposed methods of publication dissemination of research findings, includes: - Peer reviewed journals - Non-peer reviewed journals - Peer reviewed books - Publication in media or website - Conference presentation - Internal report - Promotional report and materials - Dissertation/Thesis - Presentation to participants or relevant community group		
I give permission for your team to use the data in future research.		
I give permission to be to be contacted for future research studies by your team.		
It has been explained to me what will happen once the programme has been completed.		
I understand that my participation in this study is entirely voluntary, and I am free to withdraw at any time during the research without disadvantage to myself and without being obliged to give any reason. I understand that my data can be withdrawn up to the point of data analysis and that after this point it may not be possible.		
I hereby freely and fully consent to participate in the study which has been fully explained to me and for the information obtained to be used in relevant research publications.		

Participant's Name (BLOCK CAPITALS) ……..

Participant's Signature ……..

Investigator's Name (BLOCK CAPITALS) ……..

Investigator's Signature ……

Date: …….

Appendix 3. Medical questionnaire:

Project title: The Neural Mechanisms of Motor Learning in Healthy Adults Using Neuroimaging Technologies

Medical Questionnaire

This questionnaire is designed for the purpose of understanding if you have any conditions that may result in excluding you from the research being conducted. All the data supplied in this questionnaire will remain private and confidential.

Date:
Participant Number:

Date of birth:
Gender: M / F
Handedness: Right / Left

Do you take any medication or recreational drugs? Y / N
If yes, state below:

How many units of alcohol do you consume per week on average:

Have you had any surgeries in the past?
If yes, state below:

Do you have a history of head or spinal injury (e.g concussion, car crash whiplash):

Do you have any chronic illness? Y / N
If Yes, state below:

Do you have any neurological disorders (e.g. stroke, spinal cord injury, colour blindness, dyslexia, Parkinson's or Alzheimer's disease, epilepsy/seizures, family history of these)?
Y / N
If Yes, state below:

Do you have a psychiatric history (e.g. schizophrenia, bipolar disorder, depression, obsessive compulsive disorders, panic disorder, family history of these)? Y / N
If Yes, state below

Do you have a cardio-respiratory Disease (asthma, angina, high blood pressure, respiratory distress)?
Y / N
If yes, state below:

Do you have a musculoskeletal condition: (bone fracture, muscle or ligament tear)? Y / N
If yes, state below:

Do you have any metal or electrical implants (e.g. pacemakers, intracranial plates, skeletal pins, vascular clips)? Y / N
If yes, state below:

If you are a woman are you pregnant or experiencing altered menstrual cycles? Y / N
If yes, state below:

END OF QUESTIONNAIRE