Investigating the Brain Mechanisms Involved in Learning Abstract Sensorimotor Mappings

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ABSTRACT

Myoelectric-computer interfaces (MCIs) provide a unique opportunity to study mechanisms of motor learning and adaptation as they allow the creation of abstract sensorimotor tasks disassociated from biomechanical constraints, and the manipulation of visuomotor mappings at the level of individual muscles. In addition, study of MCI use provides a useful basis for designing optimal prosthetics, by understanding how the motor system deals with new patterns of muscle co-ordination.

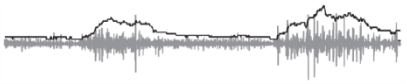
Here I used MCI tasks in order to examine subjects' ability to learn and adapt to abstract sensorimotor mappings.

In the tasks, subjects moved a 2D cursor controlled by electromyogram (EMG) recorded from between two and eight hand and forearm muscles. Each muscle was assigned a direction of action (DoA) and cursor position was determined using the vector sum of the EMG.

Subjects were able to quickly learn abstract mappings, and adapt successfully to rotations of the full muscle-DoA mapping (global) and rotations where subsets of the muscle-DoA relationships were perturbed (local). Adaptation was biased by naturalistic behaviour, but that did not impede subjects from solving the tasks. Strategies that subjects used to solve local adaptation tasks could be biased via tDCS of M1 and the cerebellum.

Global and local rotations were adapted to in different ways, with local adaptation lacking the after-effects associated with classical adaptation, indicating the creation of a new internal model for the adapted state, as opposed to alteration of a single one. tDCS affected these forms of adaptation in different ways, with stimulation of M1 predominantly affecting global adaptation and stimulation of the cerebellum predominantly affecting local adaptation.

In conclusion, I have demonstrated that the motor system can successfully learn and adapt to abstract motor tasks, with the underlying processes being dependent on M1 and the cerebellum in ways that have a structural dependence.



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Claire Schofield, March 2014

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LIST OF ABBREVIATIONS

3DI – Third dorsal interosseous

ADM – Abductor digiti minimi

APB – Abductor policis brevis

BMI/BCI – Brain machine/computer interface

CNS – Central nervous system

DoA – Direction of action

ECR – Extensor carpi radialis

EEG - Electroencephalogram

EMG – Electromyogram

FCR – Flexor carpi radialis

FDI – First dorsal interosseous

FDS – Flexor digitorum sublimis

fMRI – Functional magnetic resonance imaging

LTD – Long term depression

M1 – Primary motor cortex

MCI – Myoelectric controlled interface / Myoelectric-computer interface

MEP – Motor evoked potential

MNS – Median nerve stimulation

MVC – Maximum voluntary contraction

OCT – Optimal Control Theory

OFCT – Optimal Feedback Control Theory

PD – Preferred direction

PPC – Posterior parietal cortex

RMI – Re-mapping index

rTMS – Repetitive transcranial magnetic stimulation

RMI – Re-weighting index

SMA – Supplementary motor area

TD –Tuning depth

tDCS – Transcranial direct current stimulation

TMS – Transcranial magnetic stimulation

CHAPTER 1 - INTRODUCTION

In which I introduce the concepts and motivation behind the work presented in this thesis.

1.1 Introduction

Myoelectric-Controlled Interfaces (MCIs) allow the creation of abstract sensorimotor tasks, by which various questions relating to basic motor learning and adaptation, and the ultimate application of MCIs as prosthetic devices can be investigated. They act as a distinct experimental paradigm in relation to the current methods in the field of study, and therefore provide a novel means to study these questions.

In this section I introduce the three broad themes on which this work is based: Motor Learning and Adaptation, Brain Stimulation, and Brain-Machine Interfaces (BMIs) and MCIs.

1.2 Background and Concepts

1.2.1 Motor Learning and Adaptation

Motor Learning

At its most basic level, motor learning is the acquisition of the association between a given sensory stimulus and the corresponding motor action (Braun et al., 2010b).

However, several different processes can fall under this banner, and as a result motor learning can be described by three different computational approaches; supervised learning, reinforcement learning and unsupervised learning (Wolpert et al., 2001), the first of which is the most relevant for this thesis.

In supervised learning, a desired behavioural output exists, with the aim being to find the motor command that best results in that behaviour. The performance of the system can then be measured by the difference between the current and desired behaviours,

providing an error signal which is used to adjust the motor command. This form is also referred to as error-based learning (Mazzoni and Krakauer, 2006, Tseng et al., 2007).

In reinforcement learning, the relationship between the motor command and behaviour is characterised by a reward signal. It is distinct from supervised learning in that the measure that is maximised is the total reward for the duration of the task, meaning that an instantaneous 'target' is not required. Also, since reward is determined over the total task, all actions over that time frame impact upon it. This means that the credit assignment, or the determination of actions that result in a 'good' outcome, has a temporal component. Motor skill learning falls under this definition (Huang et al., 2011) (Izawa and Shadmehr, 2011).

Finally, in unsupervised learning the system has no desired behaviour and receives no measure of success. As such, unsupervised learning simply reinforces inputs that result in 'something' (a simple example being Hebbian learning, in which the strength of a connection between neurons is strengthened upon coincidental firing). Pure unsupervised learning will not necessarily result in learned representations that are in any way useful.

The nature of feedback provided is important to the type of learning that is utilised. For example, a cursor-based, visuomotor task could provide feedback of cursor location (allowing supervised learning) or simply acknowledgement that a target has been reached. In the latter case, the dominant learning type would be reinforcement learning.

Internal models

Our interaction with the world is based on accurate movements, which are guided by sensory feedback, be it visual, proprioceptive or otherwise. This allows us to adjust our behaviour to different environments we are presented with.

There are, however, limitations to error correction via sensory feedback alone. The most obvious are the delay between feedback and continued movement, and the noise present in the signal, both of which should lead to slow or unstable movements. But movements are generally fast and accurate, which implies the existence of prior knowledge about the environment known as an internal model (Kawato et al., 1987, Miall and Wolpert,

1996). An internal model is a neural process describing a relationship between a motor action and the effect on the environment. They can be updated based on sensory feedback, creating more accurate representations. Evidence for their existence (and adaptive capacity) is provided by after-effects following perturbation, as the system is using a model that is no longer appropriate for a perturbed environment (Wolpert et al., 1995, Shadmehr et al., 2010). Two forms of internal model have been described based on the direction of the transformation taking place: forward models and inverse models.

A forward model is so called as it describes the causal direction, determining the sensory consequences of a given motor command. It is based on a state estimate of the environment, then utilises an efference copy, an internal copy of the motor command generated by the motor system, in order to compare the relationship between predicted and actual outcome (Miall and Wolpert, 1996, Shadmehr et al., 2010).

Inverse models use a current state estimate to determine the motor command required in order to achieve a desired state (Wolpert and Kawato, 1998). Due to the delay between action and feedback, the feed-forward control that an inverse model provides is essential for accurate movement (Wolpert et al., 2001). Therefore while forward models describe a process by which motor control can be improved, inverse models are necessary for it to occur accurately at all.

Redundancy

The human motor system is highly redundant, with many under-determined degrees of freedom that can be used in multiple ways to achieve any particular goal. As a result, the inverse model is ill-posed, i.e. there is more than one solution to a given task. Nevertheless, kinematics and electromyogram (EMG) patterns are remarkably stereotyped across movement repetitions and subjects, for example, the bell-shaped velocity profile of reaching movements (Abend et al., 1982, Berardelli et al., 1996).

Therefore the motor system is faced with the task of finding the optimum in a large solution space, and there is evidence to show that it does so in a stereotyped manner. This question of how the motor system selects an appropriate solution to a given motor task is known as the degrees of freedom problem (Bernstein, 1967).

Optimal Control and Cost Functions

A major theory for the framework under which this takes place is Optimal Control Theory (OCT), which provides a powerful explanation for the behavioural consistency, in that natural movements achieve task goals while minimising a cost function (Todorov, 2006). For example, while the multiple muscles of the forearm could in principle generate wrist forces in many different ways, only the experimentally-observed pattern of cosine-tuning will also minimise overall effort (Fagg et al., 2002, Haruno and Wolpert, 2005). However, while a cost function may explain *why* a particular solution to an ill-posed motor task is optimal, it tells us nothing about *how* that solution is found within the high-dimensional space of possible movements.

Central to this theory is the need for a criterion that determines what is considered 'optimal' behaviour. One way to formulate this question mathematically is to postulate a 'cost function' over all behaviours, with the optimal behaviour being that associated with the minimum cost. The exact nature of such a cost function is still being debated (O'Sullivan et al., 2009), but various studies have accurately predicted the task dynamics of tasks such as eye saccades, reaching movements (Harris and Wolpert, 1998), adaptation to force fields (Emken et al., 2007) and bimanual co-ordination (Diedrichsen, 2007) using a cost function that simultaneously minimises error and effort (Ganesh and Burdet, 2013).

It should be noted that it is easy to fall into the trap of framing all natural behaviour as being 'optimal', based on what quantity is being optimized. It is therefore beneficial to define cost functions a priori (where this is possible), in order to avoid the possibility of back-engineering from observable behaviour (Krakauer, 2012). However, there is evidence that optimization is the cause of stereotyped behaviour. (Nagengast et al., 2009) showed that when confronted with a complex, unfamiliar task, subjects initially showed highly variable behaviour, eventually converging on almost identical solutions after training.

Optimal Feedback Control Theory

OCT was initially based around an optimal solution constructed from feed-forward commands (Flash and Hogan, 1985, Harris and Wolpert, 1998). Optimal feedback

control theory (OFCT) extended the theory by integrating the role of sensory feedback (Diedrichsen et al., 2010), and it is currently the leading suggestion for how optimal behaviour can be generated. OFCT states that the motor system uses a combination of a feed-forward predictive model and feedback error in order to drive corrective control. Therefore a prediction based on previous knowledge of the state of the world drives initial movement which can then be modulated using feedback (Diedrichsen et al., 2010). The system, then, can combine two streams of information (prediction and sensory feedback) in order to create a state estimate from which the motor command can be determined. It can be shown that optimal behaviour can be produced by a feedback control policy with a time varying gain (Shadmehr and Krakauer, 2008).

Due to redundancy, dimensions of movement can be classified into task-relevant and task-irrelevant. A consequence of OFCT is that the motor system will allow a certain amount of error, if those errors will not directly affect task success (Braun and Wolpert, 2007).

This can be illustrated simply by a typical motor action, for example picking up a bottle. Errors along the height of the bottle have less impact on the successful completion of the task, whereas errors along the width have higher penalties due to the smaller 'area of success'. Therefore the two dimensions can be considered as the task irrelevant and task relevant dimensions respectively. Task accuracy can then be improved by directing variability into the task-irrelevant dimension, or the uncontrolled manifold (Scholz and Schoner, 1999, Jackson and Nazarpour, 2012).

This leads directly to the concept of the minimum intervention principle, which states that only task relevant errors will be corrected by the internal feedback policy (Todorov and Jordan, 2002). Allowing a greater level of variability in task-irrelevant dimensions minimises both the energy cost and the signal dependent noise that would arise from greater expended effort. In practice, this is seen as trial-to-trial correlations in muscle activity, which have previously been explained as primitive muscle synergies, correlations that exist within the motor system as a result of hard wiring (Mussa-Ivaldi and Bizzi, 2000). In the example with the bottle, if the motor action that is carried out does not correlate with the intended final position, but does not impact the ability to successfully pick up the bottle, then the error will remain uncorrected by the feedback

policy. Since task-relevant dimensions often span multiple joints, optimal control policies are likely to act on multiple muscles in conjunction, i.e. muscle synergies.

This highlights one of the key issues of studying optimal control. Although OFCT successfully describes several key aspects of motor control, the problem of high dimensionality arising from OCT still remains; it has simply been shifted from learning an optimal inverse model to learning an optimal control policy. One suggestion is that movements are constrained to linear combinations of a small number of 'motor primitives' or synergies, perhaps hard-wired through evolution or development into spinal motor circuits (Tresch et al., 1999, d'Avella et al., 2003, Ting and Macpherson, 2005). Equipped with an appropriate set of primitives, motor learning is simplified to a low-dimensional search for a suitable combination that approximates optimal control. However, when applied to natural behaviour, predictions arising from optimal control and synergies are similar, making it difficult to disassociate the two ideas and hence properly explore the question of how the degrees of freedom problem is resolved.

The solution then, is to use abstract tasks unrelated to naturalistic movement. Since only those primitives appropriate for natural behaviours will be selected, control would be expected to become less optimal as tasks depart from this ethological repertoire, meaning that abstract tasks are an ideal way in which to investigate the differences in predictions between optimal control and synergies. In particular, it is useful to examine adaptation/learning after changes to the environment. The use of abstract adaptation tasks to examine questions of redundancy is looked at in Chapter 3.

Motor adaptation

Adaptation is the trial-to-trial modification of movement based on error feedback. Specifically it does not require learning a new pattern of muscle activation, but rather re-mapping well learned movements to a new spatial goal (Krakauer, 2009). The definition by (Martin et al., 1996) adds three necessary criteria to this. First, that the action is a specific 'movement' whose parameters are adjusted, second, that the adaptation is gradual and finally that an after-effect is present on returning to the original mapping.

In terms of studying motor adaptation, there are two widely used experimental paradigms. The first is visuomotor perturbation, in which the visual consequences of a motor action are altered, but the action performed remains the same. An example would be changing the relationship between cursor position and hand position in a task where subjects must use a joystick to direct a cursor to a target (Krakauer et al., 1999, Krakauer et al., 2000, Anguera et al., 2007). Prism adaptation, in which subjects are instructed to wear goggles that distort the visual field (Luaute et al., 2009), also falls under this definition.

The second is force field adaptation, in which a physical perturbation is introduced, leading to disruption of both the visual and proprioceptive consequences of a motor action. This is generally achieved using manipulandums (robotic arms), which can be used to produce variable forces (Shadmehr and Mussaivaldi, 1994), adjustments in weight (Krakauer et al., 1999), or other means of producing changes in force.

Perturbation results in error, one that is initially corrected through feedback. The error occurs because the internal model being used for feed-forward control is inappropriate for the perturbed environment. With practice, the feed-forward control adapts to the perturbation, thus removing the error. This adaptation requires active movement, as demonstrated very early on in the field in experiments by Held using passive conditions – where subjects are presented with a visuomotor displacement, but do not generate a movement. No after-effects are seen as subjects lack the sensory prediction error and hence cannot predict the sensory consequences, hence adaptation of an internal model requires active generation of movements (Held and Freedman, 1963).

The after-effect is representative of the retention of the acquired transformation (Bock et al., 2005, Hadipour-Niktarash et al., 2007), with that retention occurring due to the alteration of the original internal model in response to movement errors. Whether an after-effect is present can indicate whether the internal model that is being used has been adjusted (and therefore no longer exists in its original form), or been rejected altogether in favour of a new one. Obviously under many circumstances learning occurs without interference with previously learned behaviour, suggesting multiple internal models can be acquired and updated in a modular fashion according to the context in which errors occur (Miall, 2002, Imamizu and Kawato, 2009). However, the factors that determine whether learning proceeds via adaptation of an existing model or the creation

of a new one, and the brain areas responsible for these processes remain unclear (Karniel and Mussa-Ivaldi, 2002, Tanaka, 2010). This is a focus of the work in Chapter 5.

There are various adaptation effects that cannot be explained as the result of a single process. Spontaneous recovery is the re-emergence of an adapted movement after that movement has been washed out, anterograde interference is the detrimental effect of a learned action on the learning of a new action (Krakauer et al., 2005) and savings is the ability of previous learning to speed current learning even after the prior effects have been washed out (Kojima et al., 2004). (Smith et al., 2006) showed that these effects could be accounted for by a simple two-state model in which adaptation is the combination of two processes acting on different timescales. The nature of their model is expanded upon in Chapter 7.

This idea that adaptation can be broken down into contributions of multiple processes fits with previous research suggesting that distinct neural regions contributed in different ways to motor adaptation. Specifically, that primary motor cortex (M1) is more involved in the retentive aspects and the cerebellum is critical for successful error reduction. This was tested directly by (Galea et al., 2011) in a study designed to double disassociate the roles of M1 and the cerebellum. The relative contributions of M1 and the cerebellum to motor adaptation are looked at further in Chapters 4-5.

Structural learning

It is a commonly cited aspect of motor adaptation when discussing redundancy that the potential exploration space for motor effectors is far too big for the optimum to be easily located. As such, various theories are proposed under which the motor system uses certain constraints in order to determine which areas of the space should be prioritised (the concept of muscle synergies would be an example of this). One such theory is the concept of biased exploration, or using prior experience of similar environments in order to create the conditions for the initial exploration. This can be considered as the construction of a lower dimensional parameter space, in which the path followed by the effectors is determined via the prior learning.

Structural learning is the concept that prior learning can be generalized in order to facilitate learning of similar tasks, in essence the learning of an underlying structure (exemplified by the idea of a parameter space). In terms of sensorimotor learning, it has been proposed that the motor system has the capability to extract common features from variable environments and hence be able to achieve more efficient learning and adaptation in novel tasks (Braun et al., 2010a).

(Braun et al., 2009) showed that exposure to randomly varying visuomotor tasks with a consistent underlying structure biased learning towards that structure (thus facilitating learning of tasks with the same structure).

The idea of previous structure biasing future adaptation was previously discussed by (Ganesh et al., 2010). In the study, subjects were given a choice of solutions and tended towards the one that had most recently been successful, regardless of whether that solution was sub-optimal or not. The authors characterised this as a form of motor memory, where the central nervous system (CNS) uses to most recent correct solution without concern for global optimization.

There are two particularly relevant points here. The first, the idea of task performance being based on previously successful solutions, is looked at in Chapter 5. The second is the idea that the CNS does not prioritise global optimization once a successful solution has been found. The task in (Ganesh et al., 2010) biased the finding of that solution by trials where subjects were forced into a given state, followed by free trials. Subjects chose the most recent solution experienced regardless of whether that solution was optimal and whether they had experienced the optimal solution previously.

The motor cortex and motor learning

Previous human studies have suggested that M1 is involved in retention of newly acquired visuomotor perturbations (Richardson et al., 2006, Hunter et al., 2009). In particular, (Hadipour-Niktarash et al., 2007) found that transcranial magnetic stimulation (TMS) of M1 detrimentally impacted retention of a novel visuomotor perturbation, but not the acquisition of the adapted state. (Muellbacher et al., 2002) showed that low frequency repetitive TMS (rTMS) disrupted retention of a ballistic finger abduction task, a finding supported by (Baraduc et al., 2004). The latter also

found that rTMS did not affect retention of a force-field variation of the task, suggesting that motor learning of novel dynamics in a more distributed manner (with the authors highlighting the cerebellum and its theorised role in internal model creation as particularly relevant).

However, it has been suggested that the nature of the task is related to the effect of stimulation. (Saucedo Marquez et al., 2013) showed a task specific effect of anodal tDCS over M1 where a sequential finger tapping task benefitted during learning, and a force task benefitted only in retention.

The cerebellum and motor adaptation

The cerebellum has been shown to play an important role in motor adaptation (Diedrichsen et al., 2005, Tseng et al., 2007), with lesioned patients showing highly impaired adaptive control (Chen et al., 2006, Bastian, 2011) and an inability to learn internal models (Smith and Shadmehr, 2005). Cerebellar activation has been shown in multiple fMRI studies of visuomotor adaptation tasks (Imamizu et al., 2000, Graydon et al., 2005, Anguera et al., 2010). Further to this, the excitability of the cerebellum changes over the course of adaptation, indicating consolidation via synaptic long term depression (Jayaram et al., 2011).

The cerebellum has also been proposed as important for the formation of internal models (Ramnani, 2006, Ito, 2008). This leads to the question of whether multiple distinct internal models are held within the cerebellum, an idea supported by (Imamizu et al., 2003), in which distinct regions of cerebellar activity were observed in response to learning two novel visuomotor mappings. The modular theory has a computational model in the form of MOSAIC (Modular Selection And Identification Controller) (Wolpert and Ghahramani, 2000, Haruno et al., 2001), which illustrates context dependent model switching. In a meta-analysis of various cerebellar studies, (Bernard and Seidler, 2013) found distinct regions of activation for multiple types of motor learning tasks, further supporting this theory.

1.2.2 Brain Stimulation

Two main stimulation techniques have been used in the work presented in this thesis, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Both techniques can increase or decrease excitability in target brain areas by changing the stimulation parameters (Reis et al., 2008). In this section, I describe these techniques and some of the relevant work.

TMS

TMS is a non-invasive stimulation technique in which a magnetic pulse is used to stimulate a given cortical region, inducing neuronal action potentials (Groppa et al., 2012).

The general parameters that determine the effect of the stimulation are as follows:

I. The shape of the coil. Coil shape is chosen with respect to where the area being targeted is located within the brain. For example, figure-8 coils provide a highly targeted pulse, at a relatively shallow level – appropriate for targeting the motor cortex.
II. The nature of the pulse. There are three types of stimulation; single-pulse, in which pulses are separated by several seconds, paired pulse, in which two pulses are delivered within a short time of each other and repetitive stimulation, in which pulses are delivered in a train.

Single pulse TMS of the motor cortex can be used to elicit responses in muscles that receive input from the stimulated area (Barker et al., 1985). These motor evoked potentials (MEPs) can be recorded via surface electrodes and used to assess a given pathway.

Paired pulse stimulation is generally used to inhibit or facilitate a given area (based on the strength of the two pulses and the interval between them) or investigate interactions between different areas. Repetitive stimulation can be used to either increase or decrease the excitability of a target area, depending on the frequency of the stimulation. rTMS can be used to produce long-lasting effects that persist after the stimulation

period has ended. In the work described here, only single-pulse stimulation was used, although several studies referred to in the text used other techniques.

tDCS

tDCS is the use of a small electrical current run between two electrodes placed on the surface of the head in order to stimulate a target region. One electrode is placed over the relevant region, with the other acting as a return electrode in order to correctly direct the flow of current. Electrode montages used here are described in the relevant chapters.

tDCS differs from TMS in that instead of causing rapid depolarization in order to induce action potentials, it modifies neuronal activity via polarization of the resting membrane potential (Creutzfeldt et al., 1962, Nitsche et al., 2008). The stimulation is polarity specific, meaning that the excitability of the target region can either be increased (via membrane depolarization) or decreased (membrane hyperpolarization) depending on the direction of the current flow (Nitsche and Paulus, 2001). The exact neurobiological mechanism by which this effect occurs is not as yet fully understood (Medeiros et al., 2012), although it has been proposed to be a result of alterations of resting membrane potentials, resulting in changes in spontaneous discharge rates and activation of NMDA receptors (Liebetanz et al., 2002).

tDCS also has an effect that is persistent, lasting beyond the stimulation time. How long is persists is dependent on the length of time the stimulation lasts, with there being a window of time in which the persistence of the effect rapidly increases compared to the stimulation time. A stimulation time of 7 minutes will result in an effect persisting for ~10-15 minutes, 10 minutes results in ~30 minutes persistence and 15 minutes will result in persistence of the effect for ~1hr (all persistence times start from the end of the stimulation period) (Nitsche et al., 2008).

Finally, the current density (which determines the strength of the induced electrical field) determines efficacy. Stronger currents result in stronger effects (Nitsche and Paulus, 2000, Iyer et al., 2005), but generally studies utilising tDCS do not go above a current density of 0.08 mA/cm^2 (equivalent to a current of 2mA running through a 5cmx5cm electrode). This has been determined as a safe level for human studies (Nitsche et al., 2003a).

While tDCS does alter the excitability of the target region, that region is not necessarily the sole area affected. As such, care must be taken when interpreting results from tDCS experiments that focus on behaviour as opposed to the physiological effect on the targeted region (Nitsche et al., 2008).

The effect of tDCS on cortical excitability is well established, the subsequent effect of the modulated activity on motor function and performance less so.

tDCS and the motor cortex

The details in the preceding section are specifically linked to M1 (although stimulation of other areas gives similar values) (Nitsche et al., 2008). M1 is the most common target for tDCS studies (Medeiros et al., 2012), and as such there is an increasing body of work concerning the effects of stimulation on motor performance and learning (although less so on motor adaptation).

In particular, multiple studies have linked M1 stimulation to effects on retention. M1 anodal tDCS has been shown to increase retention of a motor skill between sessions on separate days, without affecting the acquisition rate during those sessions (Reis et al., 2009) and to improve motor memory retention of simple thumb movements (Galea and Celnik, 2009).

tDCS and the cerebellum

tDCS of the cerebellum has been shown to have a polarity dependent, target specific effect on cerebellar excitability with an effect that lasts up to 30 minutes beyond the stimulation period. Again, the mechanism by which this occurs is currently unknown, but has been theorised to be a result of modulation of activity along the cerebello-thalamus-cortex pathway mediated by Purkinje cells (Galea et al., 2009). tDCS of the cerebellum is less well studied than that of M1, and as a result the parameters of stimulation and their relationship to excitability effects and their duration are yet to be fully quantified (Grimaldi et al., 2013).

The cerebellum has an inhibitory effect on the motor cortex (cerebellar-cortical inhibition, or CCI), one that can be demonstrated via the inhibitory effect on MEP amplitude in M1 when preceded by a cerebellar conditioning stimulus (Ugawa et al., 1995, Pinto and Chen, 2001). Effects on M1 excitability lasting beyond the cerebellar stimulus duration have been demonstrated with rTMS, although the exact nature of this effect is as yet unclear as studies have reported both increased (Oliveri et al., 2005) and decreased (Fierro et al., 2007) M1 excitability. Electrode position appears to play an important role in the exact effects of the stimulation, with three different setups appearing in the literature. The stimulating electrode is consistently placed approximately 3cm lateral to the inion with the reference electrode being placed either in the same position on the contralateral side of the head (Ugawa et al., 1991), over the ipsilateral deltoid muscle (Ferrucci et al., 2008) or over the ipsilateral buccinator muscle (Galea et al., 2009). Importantly, with the electrodes placed in the latter of these montages, tDCS modulates cerebellar excitability in a site specific manner, with no measured associated effects in M1 excitability. This is in contrast to the first, in which activation of M1 via cerebellar structures was reported (Iwata et al., 2004). Since the studies here focus on disassociating the roles of M1 and the cerebellum, I used the electrode montage described by (Galea et al., 2009) for all of the following experiments.

tDCS of the cerebellum during adaptation experiments has demonstrated a facilitation of the adaptive process with anodal stimulation, and the corresponding decrease with cathodal stimulation (Galea et al., 2011, Jayaram et al., 2012). The Galea study in particular showed a specific effect on adaptation to a visuomotor rotation task, with anodal and cathodal stimulation increasing and decreasing the rate of adaptation respectively. Both studies showed no effect on the retentive aspects of adaptation (i.e. the rate of de-adaptation).

1.2.3 BMIs and MCIs

BMIs

Brain-machine interfaces (BMI) use recorded output from cortical neurons in order to control an external device (Fagg et al., 2007). The technology has clinical applications in neuromotor prostheses – with the possibility of restoring motor function to patients

with paralysis or missing limbs (Kuiken et al., 2007, Song et al., 2008). However, BMI control is slow, non-intuitive and inaccurate, making its application to a clinical situation currently somewhat limited (Fetz, 2007).

The common BMI implementation over the past few years is a biomimetic approach, in which decoding algorithms are used to infer movement parameters from neural signals. These parameters can then become the input for an external effector, examples being robotic arms or computer cursors (Serruya et al., 2002, Taylor et al., 2002, Carmena et al., 2003). In spite of the increasing complexity of decoding algorithms in recent years, BMI control remains slow and clumsy when compared to natural movements. The lack of processes such as online error correction means that movements consist of discrete sections, not the smooth trajectories of natural movements (Velliste et al., 2008). The lack of multiple feedback modalities has also been highlighted as an issue, with proprioception especially been noted as something that current BMI technology fails to emulate (O'Doherty et al., 2009). Therefore, there needs to be significant improvement before real-world clinical applications can be considered the norm and not the exception.

There is a second issue, related to the nature of movements themselves. It has been argued that BMI decoders, in order to be usable over the long term, must be able to adapt on-line and emulate the various processes of learning, adaptation and optimization that take place within the motor system. This has already begun to be addressed in some studies (Li et al., 2011, Carmena, 2013), but remains an area that requires work.

A possible alternative is focusing on the adaptive ability of the brain, as opposed to the decoder. This is referred to as the biofeedback approach, in which subjects are asked to utilise a decoding algorithm that is not necessarily related to natural movement. This form of control differs from normal motor control in that it bypasses the standard pathways that mediate volitional movement (Fetz, 2007) – meaning subjects must acquire a new internal model of how to achieve a desired outcome. Therefore the original question within the field was whether it was possible to learn arbitrary mappings between the recorded neural signal and feedback (Fetz, 1969). It was initially shown that monkeys could be trained to volitionally control neighbouring motor cortical neurons within a timescale of minutes. This was later extended to disassociation from what the motor system would typically do, by showing that subjects can disassociate

neural signals controlling muscles that would typically be co-activated if given feedback that dictates that this is necessary (Fetz and Finocchio, 1971).

The conceptual difference between the biomimetic and biofeedback approaches is a difference of what the BMI is in relation to the subject. The biomimetic BMI can be considered a prosthesis, as its intended function is to replace what has been lost, while the biofeedback BMI can be thought of as a tool, something that will require a certain amount of learning in order to use to its full capability, but will provide a greater level of adaptability in the long term (Jackson and Fetz, 2011).

The question with this approach is thus, do humans have the ability to learn abstract mappings in an efficient way? Can we create prosthetics that go beyond the traditional 'replication' of a lost limb and provide greater utilisation, or rehabilitation implementations? It is necessary to understand learning processes in order to design a decoding algorithm that is easy to learn vs. easy to initially operate. The overall aim of this work is to study those mechanisms in detail, looking at how subjects adapt to perturbations, what forms of feedback they can utilise successfully, and other underlying functions. To achieve this, I am using a myoelectric-computer interface (MCI).

MCIs

MCIs, instead of using neuronal activity, use EMG recordings from muscles for the basis of control. MCIs can be considered an approximate emulation of BCIs, and can be used to test similar ideas without the invasive recordings that are generally necessary for BCI use (Tian and He, 2003) (although non-invasive BCIs do exist, using electroencephalogram (EEG) data, the same level of neural decoding algorithms have not been achieved (Cincotti et al., 2008)). However, there are also likely to be differences in their operation and use, and hence clinical application, meaning that the study of MCIs in and of themselves is beneficial. In addition, the nature of MCIs as abstract motor tasks with a non-invasive setup provides a unique opportunity to study underlying mechanisms of motor learning.

The use of an MCI to study these mechanisms has three particular advantages that I wish to highlight. The first is the fact that it has near limitless potential for creation of

novel neuromotor mappings. Traditional motor learning tasks are limited in the sense that the actions subjects are required to perform are frequently used in day to day life, meaning a significant portion of learning data is simply not accessible. The MCI then, has the potential to look at movements that are well outside the ethological repertoire. This in turn allows exploration of both the fundamental components and limitations of motor learning without being constrained by the biomechanical and anatomical properties of the limb (Jackson and Nazarpour, 2012). The second advantage is the ability to not only measure how a subject completes a task, but also to define the optimal way in which they should complete it. MCIs provide the ability to precisely define the mapping between motor commands and effectors. Optimal control theory makes specific predictions about muscle tuning functions when optimising accuracy in the presence of signal dependent noise (Harris and Wolpert, 1998, Todorov, 2002). As such, we can define the combination of muscle activations that lead to the optimal outcome in terms of task learning and adaptation to perturbations, giving a very precise measure of how subjects reach optimality. The final specific advantage is the ability to create perturbations that only affect a subset of participating muscles. This is again in contrast to typical motor tasks, where the perturbation generally only affects the overall execution. For example, in a standard motor task even if a perturbation only affects a single joint (itself difficult to achieve), multiple muscles act on each joint and there is no way to restrict how subjects use those muscles.

There is also a potential for clinical application of MCIs as prosthetic limbs. Current models, however, much like BMIs, lack the speed and accuracy of natural movements. As a result, their improvement relies on an understanding of motor control strategies than can be utilised by the patient in order to learn a new paradigm of control. This provides an additional clinical motivation for the work undertaken here.

In terms of previous MCI work, there are a few key studies I wish to highlight. Firstly, (Radhakrishnan et al., 2008) used an MCI to show that subjects were capable of learning abstract sensorimotor mappings, using both naturalistic and non-naturalistic muscle-cursor relationships. The work here is based on the paradigm described in that study. Secondly, a series of studies using a cyberglove, where joint angles are recorded from multiple points on the hand, and used to control the position of a cursor (Mosier et al., 2005). Although not exactly the same as an MCI, the paradigms share the underlying concept of abstract relationships between motor command and behavioural

output. With the cyberglove work, subjects learned a mapping between finger co-ordination patterns and cursor position, in contrast to (Radhakrishnan et al., 2008) where each recorded muscle was assigned an individual direction. (Liu and Scheidt, 2008) showed that online feedback of cursor position was necessary for learning of abstract mappings, a finding supported by (Radhakrishnan et al., 2008) who also showed that visual feedback was sufficient for learning. (Liu et al., 2011) further showed that subjects had the capability to adjust novel finger co-ordination patterns in response to rotational or scaling distortions of an original mapping (over a timescale of days).

Finally, several further studies have used myoelectric tasks in order to change the relationship between recorded muscle activity and the effect on the task. (de Rugy et al., 2012) found that co-ordination of wrist muscles relied on habitual rather than optimal usage when subjected to artificially altered limb biomechanics. In contrast, (Nazarpour et al., 2012) found that task-specific synergies in hand muscles emerged based on high level task constraints, as would be predicted by optimal control. (Berger et al., 2013) found that mappings compatible with identified muscle synergies in the forearm showed faster adaptation than incompatible mappings.

In summary, some aspects of MCI use have been previously investigated, but the full potential of abstract sensorimotor mappings and specifically adaptation between abstract mappings has not been explored.

1.3 Aims

This work has two overall motivations, the first being a basic science to approach to questions regarding motor adaptation using the MCI as a study tool, the second being an investigation of the use of an abstract tool such as the MCI with the aim of providing information regarding ability and limitations with the ultimate use of potential clinical application (understanding of the mechanisms of sensorimotor adaptation being vital for designing effective rehabilitation strategies (Bastian, 2008)). Therefore the main aim of this work is to use MCI based tasks to explore various questions concerning the nature of motor learning and adaptation. The specific questions I wish to examine are as follows:

- To what extent do synergistic relationships between muscles govern adaptation to an abstract MCI task?
- How do subjects adapt to perturbations of varying structure? Is their use of adaptation strategies affected by the locality of perturbed muscles, or the space in which the task is conceptualised?
- How are M1 and the cerebellum involved in adapting to locally varying, abstract adaptation tasks?

Therefore the thesis proceeds as follows. In Chapter 2 I describe the setup of the MCI and the basic structure of the experiments in the following chapters. In Chapter 3 I look at perturbations of varying structure and the effect of the relationships between utilised muscles on the nature of adaptation. In Chapter 4 I use tDCS to examine the effect of changing excitability of M1 and the cerebellum on motor strategy use. In Chapter 5 I look at the effect of perturbation structure on future adaptation, and the underlying adaptation processes involved in differently structured perturbations. In Chapter 6 I use TMS and median nerve stimulation (MNS) to create artificial immediate perturbations of cursor position to an MCI task. Finally, in Chapter 7, I use modelling techniques to look at some of the effects described in Chapter 5.

CHAPTER 2 - MATERIALS AND METHODS

In which I describe the experimental and analysis methods used in the following chapters.

Participants: All subjects were naive to the experimental objectives, had no history of neurological disorders and gave written informed consent. All studies presented here were approved by the local ethics committee at Newcastle University (Ethics approval number: 000023-2008).

2.1 Electromyogram (EMG) Recording Setup

Subjects were seated in with their hands secured palm down inside gloves attached to flat arm rests. EMG was recorded using surface electrodes positioned over hand and forearm muscles, amplified (1-5k), high-pass filtered at 30Hz (Neurolog NL824/820, Digitimer) and sampled at 5kHz (PCI-6071E, National Instruments). Custom Delphi (Borland) software running on a PC rectified and smoothed (with a 400 ms rectangular window) the EMG from each muscle to obtain myoelectric control signals. Subjects were first told the specific movements which would activate each recorded muscle and instructed to make comfortable contractions of each in turn at a level that they would be able to repeat many times. This level (typically corresponding to 10-20% of maximum voluntary contraction, verified offline) was used to normalise the control signal of each muscle.

2.2 The MCI

Two types of tasks were used, with differing types of perturbation; Rotation tasks, in which the relationship between muscle activation and cursor movement was rotated, and displacement tasks, in which the cursor position was perturbed along one axis of muscle activation.

2.2.1 Rotation tasks

Cursor control

The myoelectric control signals determined the instantaneous position of a yellow cursor displayed on computer monitor in front of the subject. Muscles were assigned a direction of action (DoA). The set of DoAs for a given experiment were equally distributed to cover 360° from the centre of the screen in order to give subjects full access to the 2D screen space. The 2D cursor position **x**, was determined by the sum of unit vectors aligned to the DoAs for each muscle, scaled by the control signal obtained from the rectified, smoothed EMG:

$$\mathbf{x} = \sum_{m} E_m . \mathbf{R}(\theta_m) . \hat{\imath}$$

Eq. 2.1

where E_m, θ_m are the control signal and DoA for muscle m, **R** is a rotation matrix and **î** is a unit vector aligned to the polar axis. Control signals were scaled such that activation of a single muscle at 100% of the comfortable contraction level (10-20% of the MVC of that muscle) would take cursor to the edge of the screen, while relaxing all of the muscles brought it back to the centre. A single trial began with the appearance of a (red) peripheral target centred at 70% of the distance to the screen edge.

The selection of the muscles used as controlling effectors was determined by the structure of the task in each case. Three basic task structures were used for rotation tasks:

1) Single hand – six muscles.

2) Bimanual – eight muscles, the same four used in each hand.

3) Bimanual – six muscles, three in each hand selected randomly from the four muscles used in 2).

Subjects were told beforehand that the relevant muscles would control the movement of the cursor, but were not given any clues as to the nature of the DoA-muscle mapping.

Table 2.1 shows the muscles used for each type.

Right Hand	1	2	3	Left Hand	1	2	3
FDI	●	●	●	**FDI**		●	●
APB	●	●	●	**APB**		●	●
ADM	●	●	●	**ADM**		●	●
FDS		●	●	**FDS**		●	●
3DI	●			**3DI**			
ECR	●			**ECR**			
FCR	●			**FCR**			

Table 2.1 – Muscle assignments for each task type. 1 – Unimanual, 2- 8 muscle, bimanual, 3 – 6 muscle, bimanual.

Targets were presented psuedorandomly in blocks of either eight or twelve positions (dependent on the experiment, detailed in the relevant chapters). A single block consisted of all possible target positions presented in a random order.

Performance measurement

Two types of task were used; success-based and score-based. For the former, subjects were required to move the cursor to the target and maintain an overlap continuously for one second. Success was indicated with an auditory tone after which the target returned to the centre of the screen.

In the score-based design, subjects were given a two second movement period followed by a one second hold period. The transitions between periods were indicated by an auditory tone. Subjects were instructed that they should hold the cursor in target in order to gain the best possible score. Following the hold period, they were then given a score between 0 and 100. If d(t) is the distance to the target at time t during the hold period (length T), with target radius r, then score can be calculated using Equation 2.2.

$$Score = \frac{100\%}{T}\int_0^T s(t)\,dt$$

$$where\ s(t) = \begin{cases} 0\ if\ d(t) \geq r) \\ \dfrac{r - d(t)}{r} if\ d(t) < r \end{cases}$$

Eq. 2.2

The progression of a single trial in the rotation task is shown in Figure 2.1.

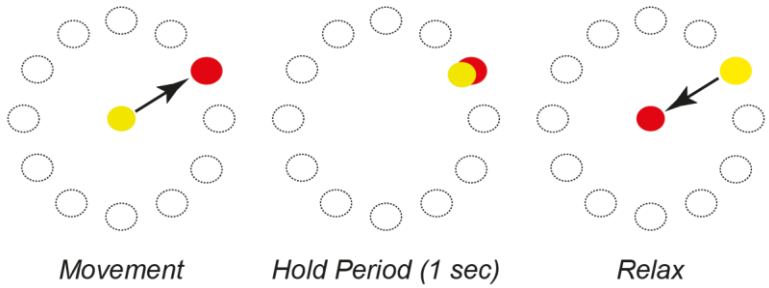


Figure 2.1– Single trial (Rotation task)

A single trial consisted of the appearance of a target, indicated by an auditory tone. In success-based experiments, subjects moved the cursor to the target and held it in position for 1 second (the hold period). In score-based experiments, subjects had 2 seconds in which to move the cursor to the target, and received a score based on their success in holding the cursor in place during the 1 second hold period. In both cases, subjects then had to relax to return to the centre and trigger the next trial.

Perturbations

After subjects were trained on an initial mapping, the mapping would be rotationally perturbed. Rotations consisted of one of two forms, referred to as either a Global or Local rotation. In a Global rotation, all of the muscle DoAs were rotated by the same amount, whereas in a Local rotation, a subset consisting of half of the DoAs were rotated, while the remaining half remained constant. All of the rotation tasks can be

classified as one of these two forms (although further structure may be applied within this definition, these occasions are discussed in the relevant chapters).

2.2.2 Displacement tasks

This task used control signals from two distal muscles, E_1, E_2, with orthogonal DoAs oriented diagonally to the screen co-ordinates *(x, y).* As such, instantaneous position was given by:

$$x(t) = \frac{1}{\sqrt{2}}[E_2(t) - E_1(t)]$$

Eq. 2.3

$$y(t) = \frac{1}{\sqrt{2}}[E_1(t) + E_2(t)]$$

Eq. 2.4

Targets appeared in one of three positions, shown in Figure 2.2, with the task set so that the central target could be reached by contracting both muscles to approximately 45% of maximum contraction level. Targets were ellipses that were either vertically or horizontally oriented with respect to screen co-ordinates.

The task followed a similar structure to the score-based rotation task, with a single trial consisting of a target appearance followed by a one second movement period and a one second hold period. Scores were only dependent on the proportion of the hold period spent inside the target.

The task also involved stimulation induced perturbations to the target position, which will be explained in the relevant chapter (Chapter 6).

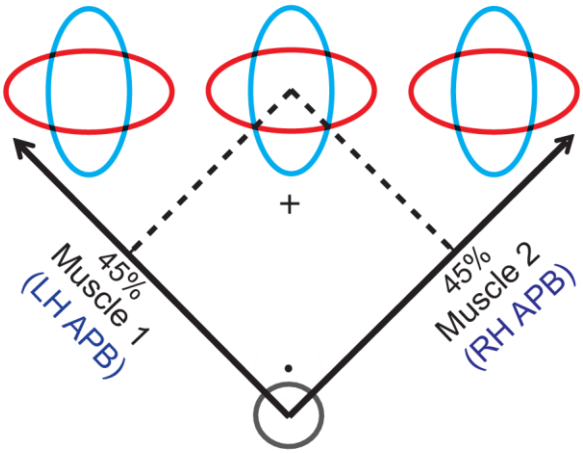


Figure 2.2 – Trial Structure (Displacement task)

Two muscles (APB in left and right hands) act along orthogonal axes oriented diagonally to the screen co-ordinates. Elliptical targets appear in one of three potential locations, and are either horizontally or vertically oriented. Approximately 45% of maximal voluntary contraction simultaneously in both muscles will take the cursor to the centre of the screen.

2.2.3 Task Structure Terminology Quick Reference

Trial: A single trial experienced by the subject where the cursor must be moved to a target appearing on a computer screen.

Period: The internal structure of a single trial consists of two periods, the movement period and the hold period. In the score-based task the movement period begins at the appearance of the target and lasts for one or two seconds, then is immediately followed by the one second hold period. In the success-based task, the movement period again begins at the appearance of the target, but lasts until the beginning of the successful hold period, defined as successfully holding the cursor in target for one second.

Block: A set of trials consisting of all possible cursor positions for that experiment (8 or 12 depending on the experiment). In all graphs presented here, data points represent the averaged value for a single block, thus eliminating effects caused by target position (for example, bias towards a certain direction created by a given random mapping).

Phase: The set of blocks in which the DoA mapping is consistent. A perturbation of that mapping would indicate the end of a phase.

Group: Used to refer to a set of blocks within the context of a phase.

Condition: A sequence of phases with an overarching structure that is completed by the subject with no interruptions (e.g. global rotation condition).

Task: A set (usually two) of conditions completed by a single subject.

Experiment: All data from a group of subjects that have all completed the same task.

2.3 EMG Analysis

2.3.1 Behavioural measures

In the success-based task, performance was quantified on a trial-by-trial basis by the movement time, defined as the temporal interval between the appearance of the peripheral target and the beginning of the continuous 1-s hold period at that target required to complete the trial (as in (Radhakrishnan et al., 2008)). In the score-based task, performance was quantified by score as given in Equation 2.2.

In addition, in the success-based task the directional error of movements was recorded. This was measured at the first time instant within each trial that the cursor crossed a circle with radius equal to half the distance to the peripheral targets. Directional error was defined as the angle subtended at the screen centre by the two vectors describing cursor and target location (Figure 2.3). The circular mean of this angle was calculated over blocks of consecutive trials that included one of each possible target location. Mathematically, the average directional error for a block of trials is given by the angle relative to the polar axis of a linear vector sum:

$$\boldsymbol{\varepsilon} = \sum_{t} \mathbf{R}(-\varphi_t).\mathbf{x}_t$$

Eq. 2.5

where φ_t is the angle of target t and $\mathbf{x}_t$ is the instantaneous position of the cursor for that target as it crosses the halfway line. If the cursor on average moves in the direction of

the target, then **ε** will have a value of 0°. (Note that the magnitude of the vector **ε** does not reflect the magnitude of the error but rather its consistency across trials).

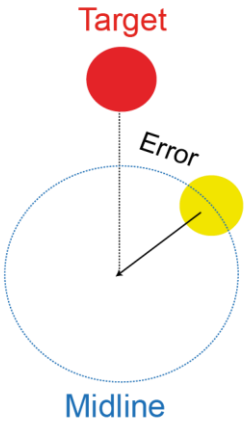


Figure 2.3 – Error definition

Error is defined as the angle between the target and the point at which the cursor first crosses the midline.

2.3.2 Muscle tuning

For the success based task, muscle tuning was assessed at the same time-point as directional error (i.e. the first time in the trial that the cursor was halfway to the target distance). For the score based task, values were averaged across the hold period.

The tuning function for each muscle *m* as a function of target *t* was defined as the instantaneous/averaged control signal obtained from the rectified, smoothed EMG, denoted $E_{m,t}$. Previously, it was found that such tuning functions can be approximated by cosine functions characterised by two parameters: the *tuning depth* (TD; the difference between the maximal and minimal muscle activity), and the *preferred direction* (PD; the direction for which the muscle is maximally active) (Radhakrishnan et al., 2008). Since the target directions are equally distributed, least-squares estimates of the TD and PD can be obtained by a simple linear sum of unit vectors directed towards each target, scaled by the muscle activity for that target. Thus, the preferred direction vector $\mathbf{p}_m$ given by:

$$\mathbf{p}_m = \sum_t E_{m,t}.\mathbf{R}(\varphi_t).\hat{\imath}$$

Eq. 2.6

has a direction aligned to the PD, and a magnitude proportional to the TD. It is convenient to define a second vector $\mathbf{q}_m$ as the PD vector for each muscle relative to its DoA, θ_m:

$$\mathbf{q}_m = \mathbf{R}(-\theta_m).\mathbf{p}_m$$

$$= \sum_t E_{m,t}.\mathbf{R}(\varphi_t - \theta_m).\hat{\imath}$$

Eq. 2.7

such that if the PD of a muscle is aligned to its DoA then $\mathbf{q}_m$ will have an angle of zero. Note that since $\mathbf{R}(\varphi_t - \theta_m).\hat{\mathbf{i}}$ is just the reflection of $\mathbf{R}(\theta_m - \varphi_t).\hat{\mathbf{i}}$ in the polar axis then it follows from the linearity of Equations 2.6 and 2.7 that:

$$\boldsymbol{\varepsilon} = \sum_t \mathbf{R}(-\varphi_t).\sum_m E_{m,t}.\mathbf{R}(\theta_M).\hat{\imath}$$

$$= \sum_t \sum_m E_{m,t}.R(\theta_m - \varphi_t).\hat{\imath}$$

$$= \sum_m \mathbf{q}'_m$$

Eq. 2.8

where $\mathbf{q'_m}$ is the reflection of the PD vector relative to the DoA. In other words, the vector $\boldsymbol{\varepsilon}$ describing average directional error is composed of independent contributions from each muscle that depend on the extent to which their PD differs from their DoA. This vector decomposition thus provides a straightforward way to quantify the contribution of particular subgroups of muscles to the overall adaptation of behaviour during perturbations.

In the data presented here, TD is scaled relative to subjects' comfortable contraction level.

2.3.3 Adaptation strategies

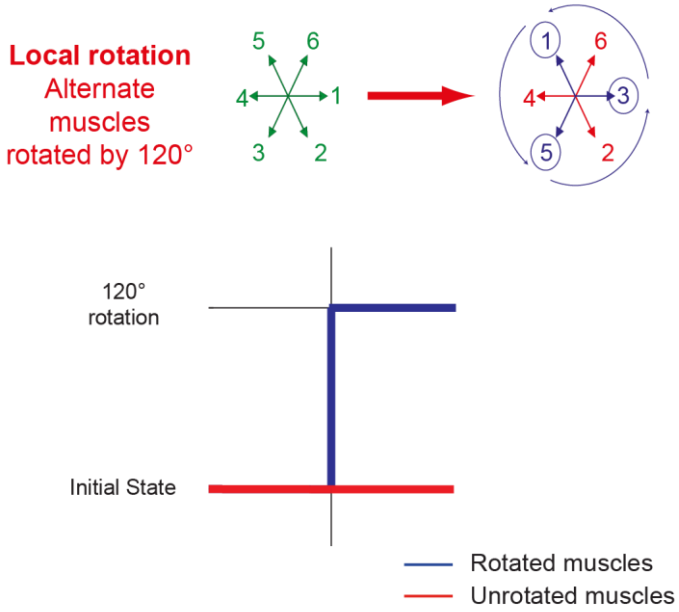


Figure 2.4 – Local Rotation Example

A local rotation affects a subset of muscles. Here, the DoAs of 3 muscles in a six muscle mapping are rotated by 120°. The figure shows both the change in mappings and the DoAs of the two groups of muscles over time.

Local rotation perturbations affecting the DoAs of a subset of muscles (Figure 2.4) will result in directional errors during movement and, as subjects learn to correct for this, we expect to see changes in the measured PDs or TDs of muscle tuning functions. However, since there are more muscles than cursor dimensions (i.e. the task is ill-posed) there are multiple strategies that could be used to compensate. A previous study using a BMI paradigm in monkeys identified three possible adaptation strategies termed re-aiming, re-weighting and re-mapping (Jarosiewicz et al., 2008, Jackson and Fetz, 2011), which are illustrated schematically in Figure 2.5.

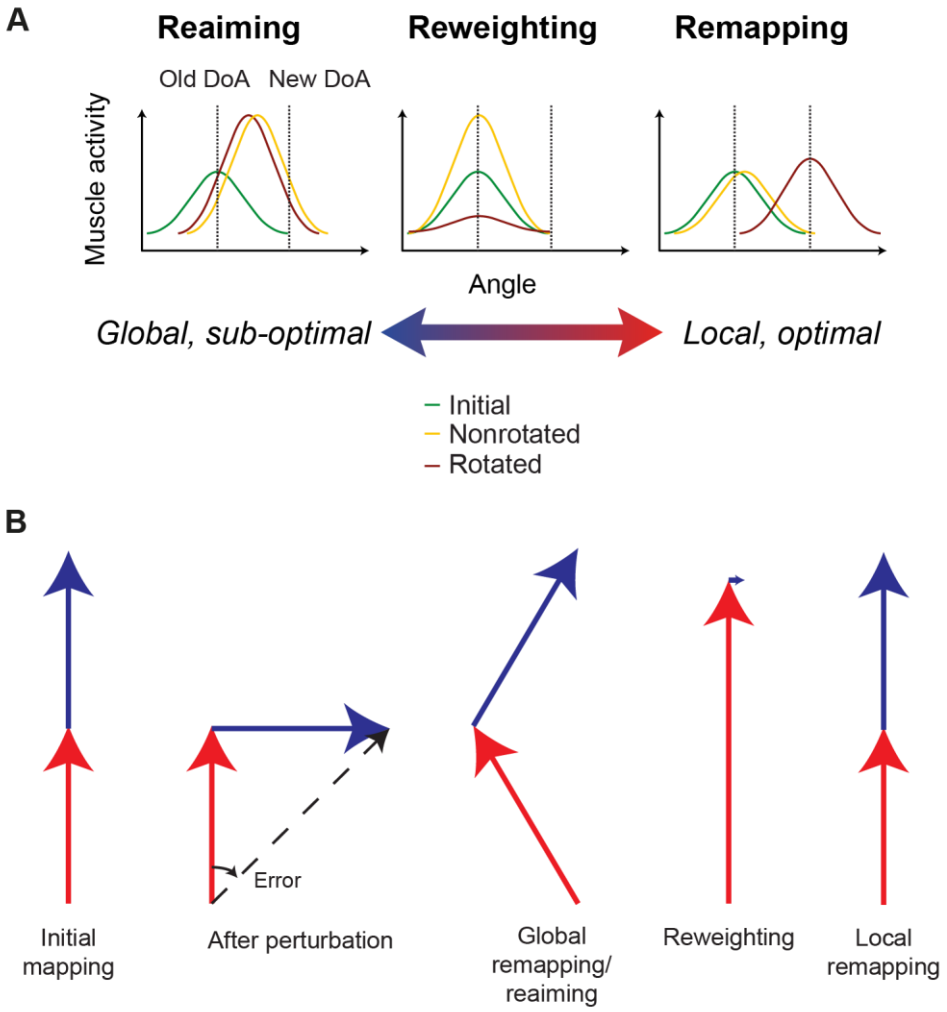


Figure 2.5 – Adaptation Strategies represented as tuning curves and vectors

A: Adaptation strategies represented as tuning curves.

B: Adaptation strategies represented as vectors.

Re-aiming results in a shift in both non-rotated and rotated muscles, and an increase in amplitude. Re-weighting results in an increase in amplitude in non-rotated muscles, and a corresponding decrease in rotated muscles. Remapping results in a shift in the rotated muscles, and thus no changes in amplitude.

Re-aiming (or global remapping) describes aiming towards an imaginary target that is rotated from the actual target by an angle equal and opposite to the perceived error. Effectively, this means that the PDs of all muscles (relative to the actual target) rotate equally to compensate for the perturbation. Note that while this strategy corrects the directional error produced by a local rotation, the resulting PDs of neither rotated nor

non-rotated muscles align with their actual DoAs. As a result, the TD of all muscles must increase after the perturbation to produce the same overall cursor displacement.

Re-weighting describes the strategy by which subjects reduce the TD of those muscles with DoAs that have changed, and instead rely more on muscles unaffected by the perturbation. In this case there is no change of PD, but the TD of non-rotated muscles must increase after the perturbation to produce the same amplitude of movement.

Local remapping entails selective changes to the PDs of only those muscles that have rotated. As a result, the PD of all muscles aligns to their corresponding DoA following the perturbation, and therefore their TD is unchanged.

While all three strategies will successfully compensate for the applied perturbation, they differ in terms of the total muscle activity involved in acquiring targets. Previously it was found that subjects aim to minimise overall effort (sum-squared muscle activity) consistent with the minimisation of inaccuracies resulting from signal-dependent noise (Harris and Wolpert, 1998). Under an effort cost, re-aiming and re-weighting are sub-optimal since only remapping distributes effort evenly amongst muscles that are used appropriately for their DoA. In fact, the three strategies described above reflect extremes of a spectrum of strategies ranging from sub-optimal global compensations to optimal remapping reflecting the local structure of the perturbation. Therefore, to quantify the particular strategy used by subjects, I defined two indices based on the empirically-determined PD and TD of rotated and non-rotated muscles. First, a re-mapping index (RMI) measured the extent to which the change in PD of rotated and non-rotated muscles reflected the local structure of the perturbation:

$$Remapping\ index = \frac{\Delta PD_{rotated} - \Delta PD_{non-rotated}}{\Delta DoA_{rotated}}$$

Eq. 2.9

where a value of 0 represents purely global remapping, and a value of 1 represents purely local remapping.

Second, a re-weighting index (RWI) measured relative changes in TD between rotated and non-rotated muscles:

$$Re - weighting\ index = \frac{TD_{non-rotated} - TD_{rotated}}{TD_{non-rotated} + TD_{rotated}}$$

Eq. 2.10

where a higher value (up to 1) represents a greater level of re-weighting towards the non-rotated muscles.

2.4 Stimulation Techniques

2.4.1 tDCS

Transcranial direct current stimulation (tDCS) was utilised in the experiments described in Chapters 4 and 5.

tDCS was applied using 5cm x 7cm electrodes encased in sponges soaked in saline solution, in line with the majority of other studies (generally the size of electrodes is between 25cm^2 and 35cm^2) (Nitsche et al., 2003a).

Motor cortex stimulation

For M1 stimulation, the active electrode was placed over either the left or right motor cortex (found by measurement – 5 cm lateral to the vertex (O'Shea et al., 2013)) with the reference electrode placed over the contralateral forehead.

The current was set at 1mA (to give a safe current density of 0.029 mA/cm^2 (Nitsche et al., 2008, Bikson et al., 2009)). Duration of stimulation was 8-10 minutes depending on the experiment. This has been shown to produce persistent effects lasting between 15 minutes to ~1 hour following stimulation (Nitsche et al., 2005).

Cerebellar stimulation

For stimulation of the cerebellum, the active electrode was placed 3 cm lateral to the inion, and the reference electrode placed over the ipsilateral buccinator muscle ((Galea et al., 2011)).

Current was set to 2mA (current density of 0.057 mA/cm^2), with previous work having demonstrated a clear effect at this level (Ferrucci et al., 2008, Galea et al., 2009), and duration of stimulation was between 8 and 15 minutes depending on the experiment.

2.4.2 TMS

Single pulse transcranial magnetic stimulation (TMS) was given using a figure-eight coil. Coil placement was found for M1 by finding the maximum MEP for APB.

Further details of TMS usage are discussed in the relevant chapter (Chapter 6).

2.4.3 MNS

Median nerve stimulation was utilised in the experiments detailed in Chapter 6. The median nerve is a mixed nerve, relaying efferent commands to the thumb and afferent inputs received from the hand. Stimulation was delivered through surface electrodes over the wrist (cathode placed distally) via a DS7A (Digitimer) stimulator. The stimulus itself consisted of a single, monophasic pulse with a width of 0.2ms. This setup is similar to the one described in (Nazarpour et al., 2012).

2.5 Graphs and Statistics

Two slightly differing forms of analysis have been used here. The first I will refer to as the Vector Analysis. Here, for each data point, the components of the population vector based on the overall activity of all contributing muscles are produced for each subject (as described in Chapter 2.3.2). The average overall vector is then calculated and the resulting PD and tuning depth values are taken from those average vectors. This analysis benefits from taking vector magnitude into account when determining average

PD, as it gives weight to consistent solutions as opposed to random behaviour (although importantly is not affected by the success of those solutions, i.e. there is no analytical bias towards a particular behaviour). The downside of this method is that statistical tests cannot be performed using the results, due to individual subject values being collated early in the analysis. Therefore a second method, referred to as Scalar Analysis was used. Here, subject population vectors were kept separate until the last step of calculation, allowing comparative statistical tests to be performed. The net effect is that all graphs shown are based on the Vector Analysis and resulting statistics are based on the Scalar Analysis. It is important to note that there is little difference between the two methods, but using Vector Analysis makes the effects I am highlighting clearer to understand when presented in graphical form, hence the use of both.

All statistical tests referred to in the text are paired t-tests unless otherwise stated. All paired comparisons are between the same subject doing different conditions, or separate muscles within the same subject. All errors referred to in the text and depicted on graphs are standard error of the mean.

CHAPTER 3 - ADAPTATION TO GLOBAL AND LOCAL PERTURBATIONS

In which I describe the results of a series of experiments looking at how subjects adapt to perturbations of varying structure in an abstract motor task.

3.1 Introduction

The question of how the motor system resolves the redundancy problem has not yet been fully answered. The explanations tend to fall into two camps, 1) the idea that high level constraints such as effort minimization provide the basis upon which the motor system determines optimal behaviour, and 2) the concept of motor primitives that act as low-level, hard-wired constraints, reducing the exploration space required for a given task to be solved. However, it is difficult to disassociate these two ideas, as motor primitives are likely to have evolved to reflect optimal behaviour. As a result, when studying movements within the ethological repertoire, predictions made by optimal control theory will likely match those made on the basis of hard-wired synergies (Valero-Cuevas et al., 2009, Nazarpour et al., 2012). In order to avoid this problem, I used a myoelectric-computer interface to create novel, abstract motor tasks which are disassociated from biomechanical constraints.

(Radhakrishnan et al., 2008) used an MCI task in which the activity of multiple muscles was mapped directly to cursor position. Surprisingly, they found that after training under both intuitive and non-intuitive mappings, hand muscles exhibited cosine-tuning (Todorov, 2002) that was optimal for their (arbitrary) action on the cursor, suggesting that the distal musculature is not constrained to a low-dimensional space of hard-wired motor primitives.

There remains possible a weaker interpretation of motor primitives as priors that bias the search for optimal solutions, rather than fixed constraints on behaviour. This form of organisation would be advantageous in facilitating adaptation to environmental changes where the general structure of natural behaviours is preserved (e.g. relationships between synergistic muscles), without preventing further optimisation at the level of individual muscles during more complex tasks. I speculated that such a role for

primitives might be revealed in the course of adaptation between abstract mappings, depending on their structural relationship (Braun et al., 2010b).

Using an MCI, one can create motor tasks in which the adaptation differs in structure. This is achieved by using a set of muscles to control a cursor, then perturbing either all of those muscles (a global rotation) or a subset (a local rotation). Further structure can be created within the context of a local rotation via the localization of the perturbed muscles. For example, in a bimanual task the subset can consist of either all of the muscles in a single hand, or half of the muscles within each hand. Due to task redundancy, in all local rotations the resultant movement errors can be corrected by different strategies ranging from sub-optimal, global compensation (re-aiming) to optimal, local remapping (as described in Chapter 2.3.2).

Therefore, the aims in this chapter are as follows:

1) To compare adaptation to a global and local rotation using muscles located within a single hand.

2) To compare adaptation between a local rotation where the perturbed muscles are localized in a single limb, and one where they are spread across limbs.

3) To look at adaptation to a perturbation in which there is no overall rotation affecting the cursor, and therefore certain adaptation strategies cannot be used.

3.2 Methods

3.2.1 Experiment 3.1: Adaptation to global and local perturbations

Ten right-handed subjects (7 male, ages 18-30) completed two conditions of myoelectric-control trials in a single session, separated by a short break of no more than 5 minutes. Each condition comprised three phases of 96 trials designated *Learn, Adapt,* and *Washout*. At the beginning of each condition the mapping of six muscles (of the right hand) to six DoAs was chosen at random (a different random mapping was chosen for each condition and each subject). After the *Learn* phase, the mapping was perturbed according to either a global or local rotation (Figure 3.1A). The global rotation comprised a 60° rotation of all the DoAs in the same direction. The local rotation

consisted of a 120° rotation of every other muscle. In each case, the perturbation was applied from the first trial of the *Adapt* phase and continued until the first trial of the *Washout* phase whereupon the original mapping was restored (Figure 3.1B). Each subject experienced one global rotation condition and one local rotation condition with opposite directions of initial perturbation. The order of the global/local conditions and the direction (clockwise/anticlockwise) of each were counterbalanced across subjects.

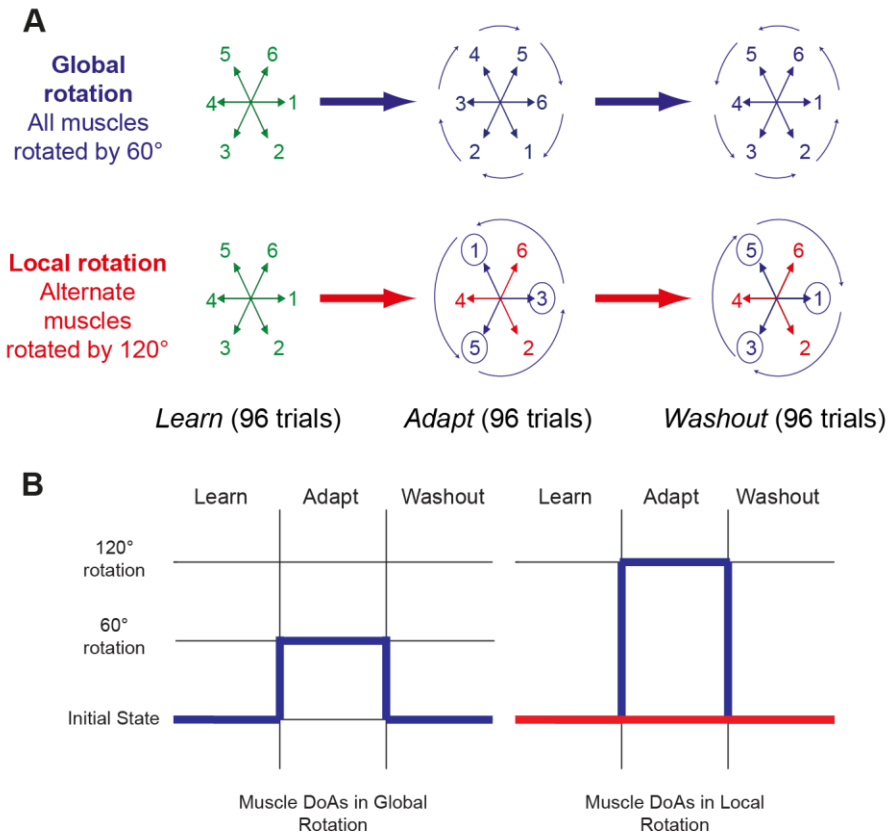


Figure 3.1 – Structure for Experiment 3.1

A – Experiment 3.1 consists of two conditions, a global rotation and a local rotation taking place in a single hand. Each condition consists of three phases, where the figure shows the general structure for each condition and phase.

B – The perturbation structure for Experiment 3.1 depicted in terms of state changes. The global rotation follows the blue line. The local rotation consists of two sets of effectors, one following the blue line and the other, the red.

Twelve equally distributed peripheral target locations were used in Experiment 1: six were in directions aligned to the muscle DoAs and six were in between. The presentation of targets was pseudo-random, such that each target position appeared once in each block of 12 trials.

3.2.2 Experiment 3.2: Adaptation to locally varying perturbations across limbs

Twelve subjects (8 male, ages 18 – 31) performed a bimanual task controlled by four muscles in each hand. Subjects again completed two conditions consisting of three phases of 96 trials each, but here designated *Learn, Adapt1* and *Adapt2*. Experiment 3.2 used only local rotations; the two conditions differed according to whether these were Within Hand or Across Hand perturbations. At the beginning of the *Learn* phase, muscles were randomly allocated to DoAs according to the following rules: for the Within Hand condition, consecutive DoAs alternated between right and left hand muscles, while in the Across Hand condition, the muscle allocation switched between hands for every second DoA (Figure 3.2A). At the beginning of the *Adapt1* phase, a local rotation was applied (90° rotation of every other DoA). Due to the arrangement of DoAs, for the Within Hand condition this affected only muscles of the same hand, while for the Across Hand condition this affected two muscles in each hand. At the beginning of *Adapt2*, a second local rotation was applied. The direction of this perturbation was opposite to the first, and affected those muscles that had not been rotated during *Adapt1* (Figure 3.2B). The order of Within/Across Hand conditions and the direction of initial rotation were counterbalanced across subjects. In addition, two further aspects of each condition were counterbalanced. For the Within Hand condition, the order of perturbations affecting the right and left hands was balanced across subjects. In the Across Hand condition, depending on which muscles were rotated, the local rotation would either preserve the adjacency of pairs of muscles within the same hand, or separate these pairs; the order of these two types of perturbation was also counterbalanced. Eight peripheral targets were used in Experiment 2 positioned in directions that bisected neighbouring DoAs. The presentation of targets was pseudo-random, such that each target position appeared once in each block of 8 trials.

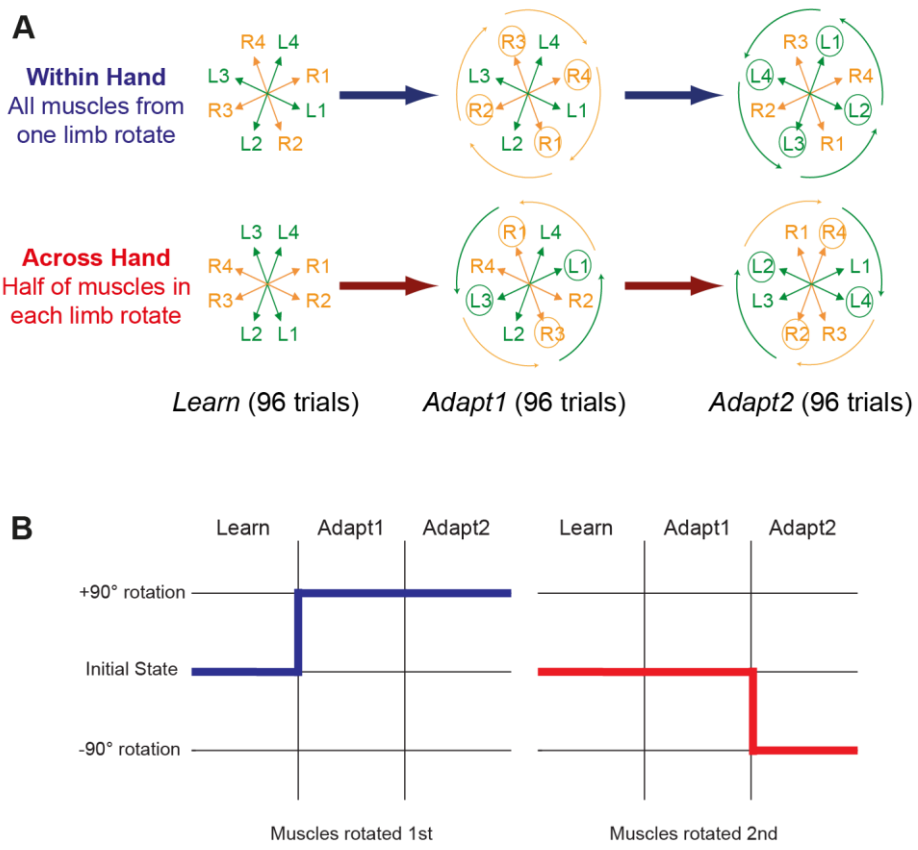


Figure 3.2 – Structure for Experiment 3.2

A – Experiment 3.2 consists of two conditions (both local rotations), a Within hand rotation in which muscles are grouped by hand and an Across hand rotation where the groups are split over the two hands. Each condition consists of three phases, where the figure shows the generalized structure for each condition and phase. The initial mapping structure is different between the two conditions, to allow for the following rotation structure.

B – The perturbation structure for Experiment 3.2 depicted in terms of state changes. In the Within hand condition, muscles are separated between the two rotation structures by hand. In the Across hand condition, half of the muscles in each hand follow each line.

3.2.3 Experiment 3.3: Global vs. local symmetric rotations

Twelve subjects (7 male, ages 18-31), performed a bimanual task controlled by three muscles in each hand. Those three muscles were chosen randomly from the four used in experiment 3.2, and the sets of muscles in each hand did not necessarily match (for example, an arrangement consisting of APB, ADM and FDS in the right hand, and 1DI, APB and ADM in the left hand was possible). The task was designed in this way in

order to make the DoA-muscle mapping as non-intuitive as possible, and to reduce the bias introduced by cross-hand correlation. DoAs were distributed in a LRLRLR pattern.

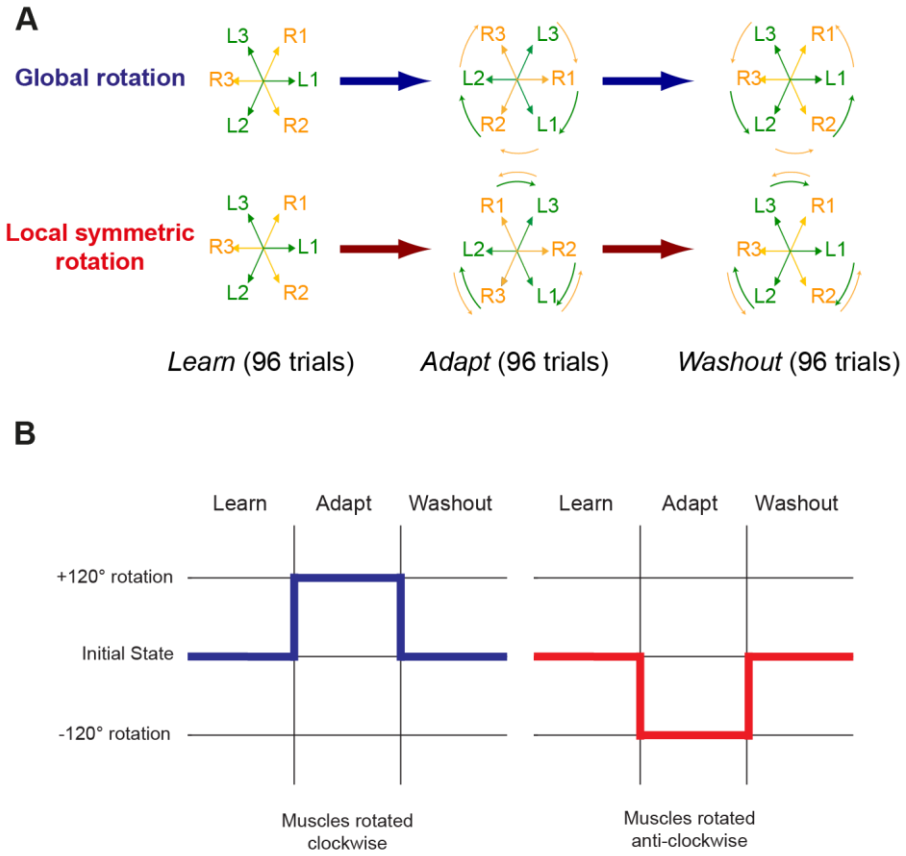


Figure 3.3 – Structure for Experiment 3.3

A – Experiment 3.3 consists of two conditions, a global rotation in which all muscles are rotated and a local symmetric condition in which the muscles in each hand are rotated in opposing directions. Each condition consists of three phases and the figure shows the generalized rotation structure for each condition and associated phases.

B – In terms of state changes, the global rotation follows the same structure as depicted for the global rotation in Figure 3.1B. In the local rotation, the muscles in one hand follow the blue line, while the other hand follows the red line.

Subjects completed two conditions in the same arrangement as in Experiment 3.1 (i.e. *Learn*, *Adapt*, and *Washout* phases*)*. Subjects again performed a global and a local rotation. The global rotation was simply a 60° rotation of all DoAs (as shown in Figure

3.3A). In the local rotation, all DoAs were again rotated by 60°, but in opposite directions by hand (Figure 3.3). This created a symmetric rotation in which all remapped DoAs differed from their original setting, but there was no absolute change on the cursor position. Subjects were counterbalanced for the condition that was completed first and the directions of rotations. Targets were presented under the same conditions as in experiment 3.1.

3.2.4 Experiment 3.4: Score-based MCI task

The aim of this experiment was to test the score-based version of the rotation task, as described in Chapter 2.2.1. As such, individual trials followed the format described there. Eight subjects (5 male, ages 22-33) performed a bimanual task using four muscles on each hand. The task structure was the completion of two conditions, each consisting of three phases of ninety-six trials in a *Learn*, *Adapt*, *Washout* format. The rotation structure was the same as Experiment 3.2, with subjects completing one condition with a Within Hand rotation and the other with an Across Hand rotation. Targets were presented under the same conditions as Experiment 3.2.

3.2.5 Data Analysis - Correlation structure of muscle use

Further to the analysis of the PD and the TD discussed in Chapter 2, the correlation structure between the muscles used was also investigated for experiments 3.1 and 3.2. The linear correlation between the activity profiles of all possible pairs of muscles was used to calculate a correlation matrix, which was then averaged across subjects. Consistent patterns of correlation between specific muscles then indicate tendencies for subjects to co-activate these naturalistic synergies (Radhakrishnan et al., 2008). Since the mapping of muscles to cursor position is randomised between subjects, any structure observed in this matrix will not reflect constraints imposed by the specific task arrangement. The effect of this structure on adaptation during the local rotation was further analysed by distinguishing between synergies that were either preserved or broken by the perturbation. Each non-rotated muscle was flanked by two muscles with adjacent DoAs; the muscle with the higher correlation to the non-rotated muscle was defined as the synergist. Depending on the direction of the local rotation, there was a

50:50 chance that after the perturbation the synergist would still have an adjacent DoA to the non-rotated muscle (in which case the synergy was preserved), or that it would be rotated away and thus no longer be adjacent to the non-rotated muscle (in which case the synergy was broken) (Figure 3.4). The non-rotated muscles were thus divided according to whether they formed part of synergies that were preserved or broken, and the average PD was compiled separately for each group.

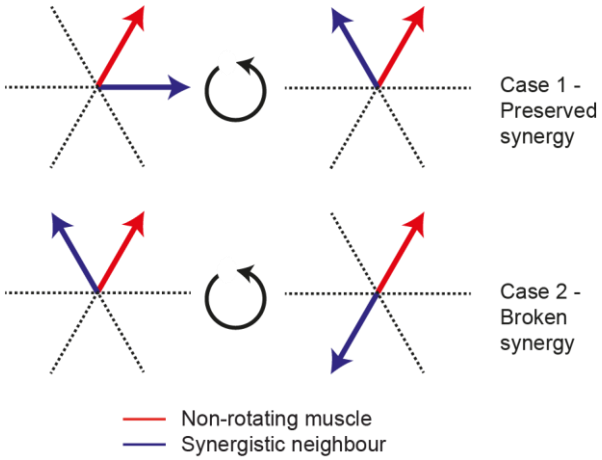


Figure 3.4 – Definitions of preserved/broken synergy based on correlated muscle activity

Each non-rotated muscle has two neighbours in the initial mapping, one of which will rotate over it, and one of which will rotate away. Non-rotated muscles are classified by which of the neighbours has the highest correlation co-efficient, i.e. which pairing can be considered to be more 'synergistic'. In Case 1, the synergistic neighbour rotates over the non-rotated muscles, resulting in a preserved synergy, as the two still benefit from co-activation. In Case 2, the synergistic neighbour rotates away, meaning that the synergy has been broken co-activation is no longer beneficial to successful performance of the task.

3.3 Results

3.3.1 Experiment 3.1: Adaptation to global and local perturbations

The setup was a unimanual task where the DoA mapping of six muscles was perturbed in either a global (all DoAs rotated by 60°) or local (half of the DoAs rotated by 120°) fashion. The aim was to look at subjects capabilities to adapt to both forms of perturbation and to look for the use of specific adaptation strategies being utilised for the local perturbation.

Behavioural data

As reported previously (Radhakrishnan et al., 2008), subjects rapidly acquired accurate control of a myoelectric cursor using a randomised arrangement of muscles. Figure 3.5A shows the mean raw trajectories for the final block of the Learn phase, the first block of the Adapt phase, the final block of the Adapt phase and the first block of the Washout phase. The Learn phase trajectories are clear, in most cases moving directly to the relevant target. In contrast, the starting Adapt phase trajectories are more clustered around the centre, with a deviation from the appropriate target caused by the DoA rotation. Figure 3.5B shows this more clearly, depicting the mean block trajectory aligned to the topmost target. The trajectories for the final blocks of the Learn and Adapt phases are close to the central line, while the trajectory in the first block of the Adapt phase shows the rotation induced error. The Washout phase trajectory then shows the error in the opposing direction on the return to the initial mapping, with this value being greater under the global rotation compared to the local rotation.

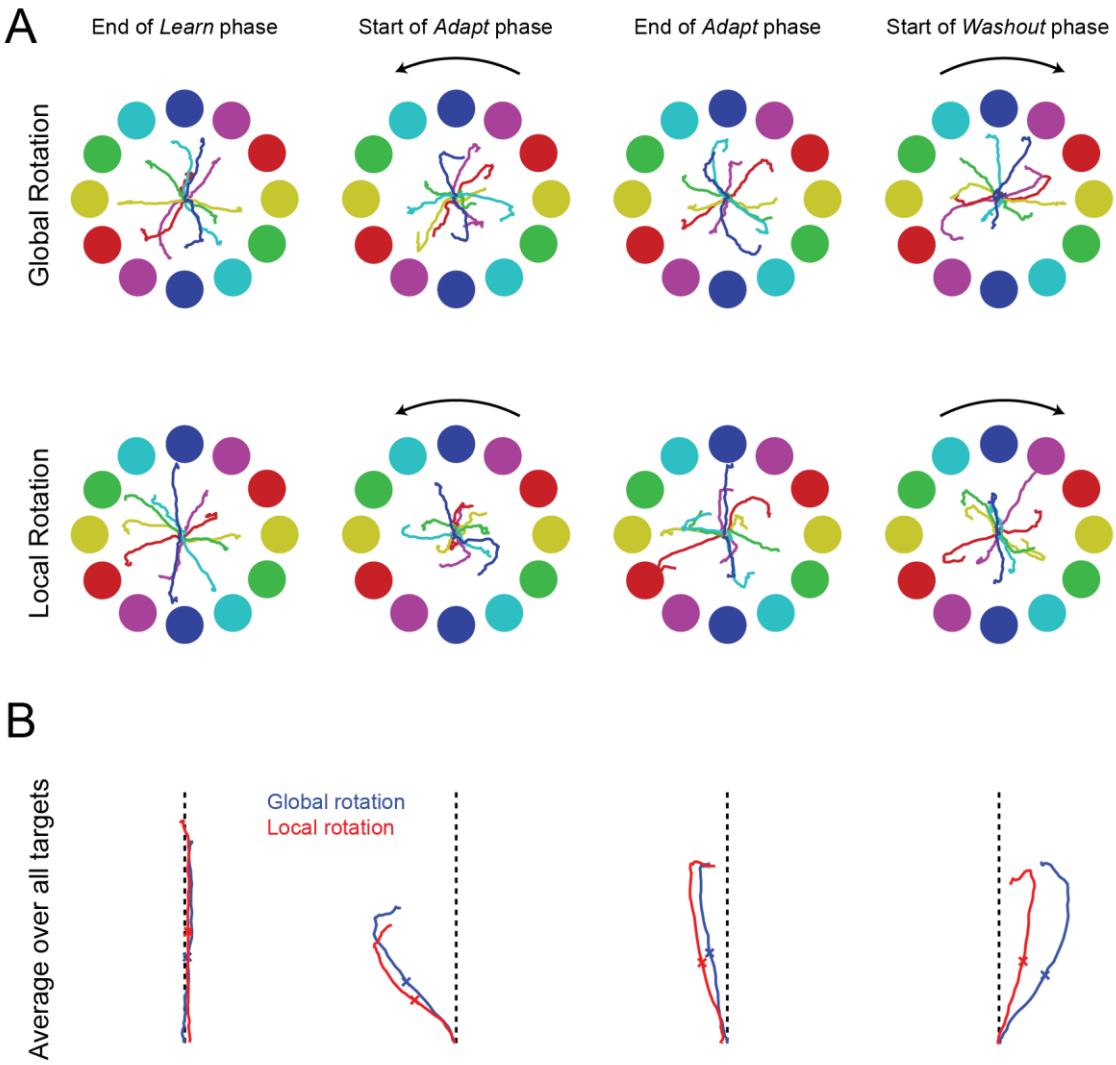


Figure 3.5 – Raw trajectories of cursor movements

A: The mean raw trajectories for individual trials within performance of global and local rotations. Each graph shows a set of 12 trials corresponding to a single block. Trajectories represent 250ms of movement, centred on the movement point.

B: Averaged raw trajectories for single blocks, aligned to the topmost target. The movement point is represented by an x. The misalignment between the trajectories and the central line is representative of movement errors caused by the rotation. The increased after effect present under a global rotation (as opposed to a local rotation) is evident in the average trajectory for the start of the Washout phase.

The increasing accuracy of control is further evidenced by the decreasing time taken to successfully reach the peripheral targets during the Learn phase of Experiment 3.1 (Figure 3.6A). Performance was perturbed following both global and local rotations leading to a transient increase in average movement times in the first block of trials during the Adapt phase which was marginally greater after local rotation (13.6 ± 3.9 s) compared with the global rotation (9.1 ± 1.1 s). However, this trend did not reach significance ($p=0.25$, $t(9)=1.21$). Movement times reduced progressively during the Adapt phase, and continued to decrease during the subsequent Washout phase.

To examine the progress of adaptation in more detail and look for evidence of after-effects during the Washout, the average directional error was calculated early in each trial when the cursor was halfway to the peripheral target (Figure 3.6B). Since there is little chance at this point to respond to feedback of cursor movement, these errors reflect predominantly the feed-forward execution of an inappropriate motor plan. Both global and local rotations produced a consistent error in the direction of the rotation which declined during the Adapt phase. It is important that although the structure of these perturbations differed at the level of individual muscles, each produced an average rotation of overall cursor position of 60°. Nevertheless, there was a non-significant trend for larger errors in the first block of trials in the Adapt phase following a local rotation (46.1 ± 17.1°) versus a global rotation (24.5 ± 8.5°; $p=0.14$, $t(9)=1.58$). A clear after-effect was observed in the first block of the Washout phase in the global rotation condition (-46.8 ± 10.6°). Interestingly, this was significantly larger than the small after-effect seen in the local rotation condition (18.4 ± 7.0°; $p = 0.03$, $t(9)=2.6$).

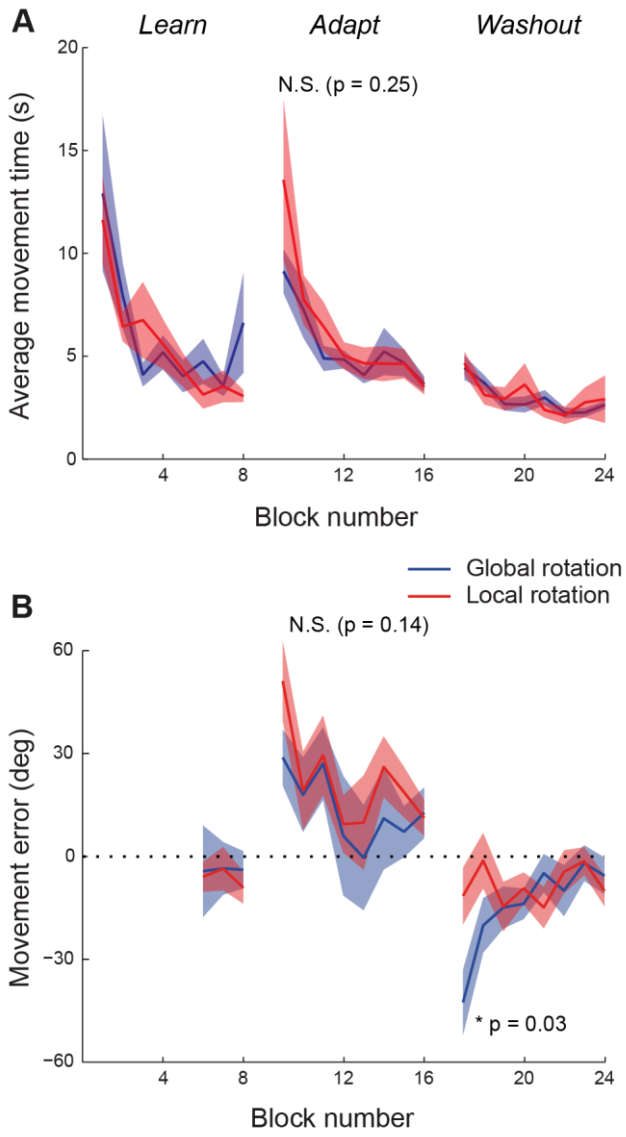


Figure 3.6 – Experiment 3.1: Movement times and Error

A – Movement times for both conditions, defined as the time taken from trial onset to the beginning of the successful hold period. Each data point represents the averaged movement time for that block of 12 trials. Both conditions show similar reductions in movement time over the course of each phase, with the (non-significant) exception of the first block of the Adapt phase, where the average movement time for the local perturbation is slightly higher.

B – Error is defined as the angle between the point where the cursor first crosses the midline and the target location. Errors for both conditions show a similar perturbation and resultant reduction in the Adapt phase, but diverge in the Washout phase (p=0.03), with a larger after-effect observed in the Global rotation condition.

Evolution of muscle tuning functions during global and local adaptation

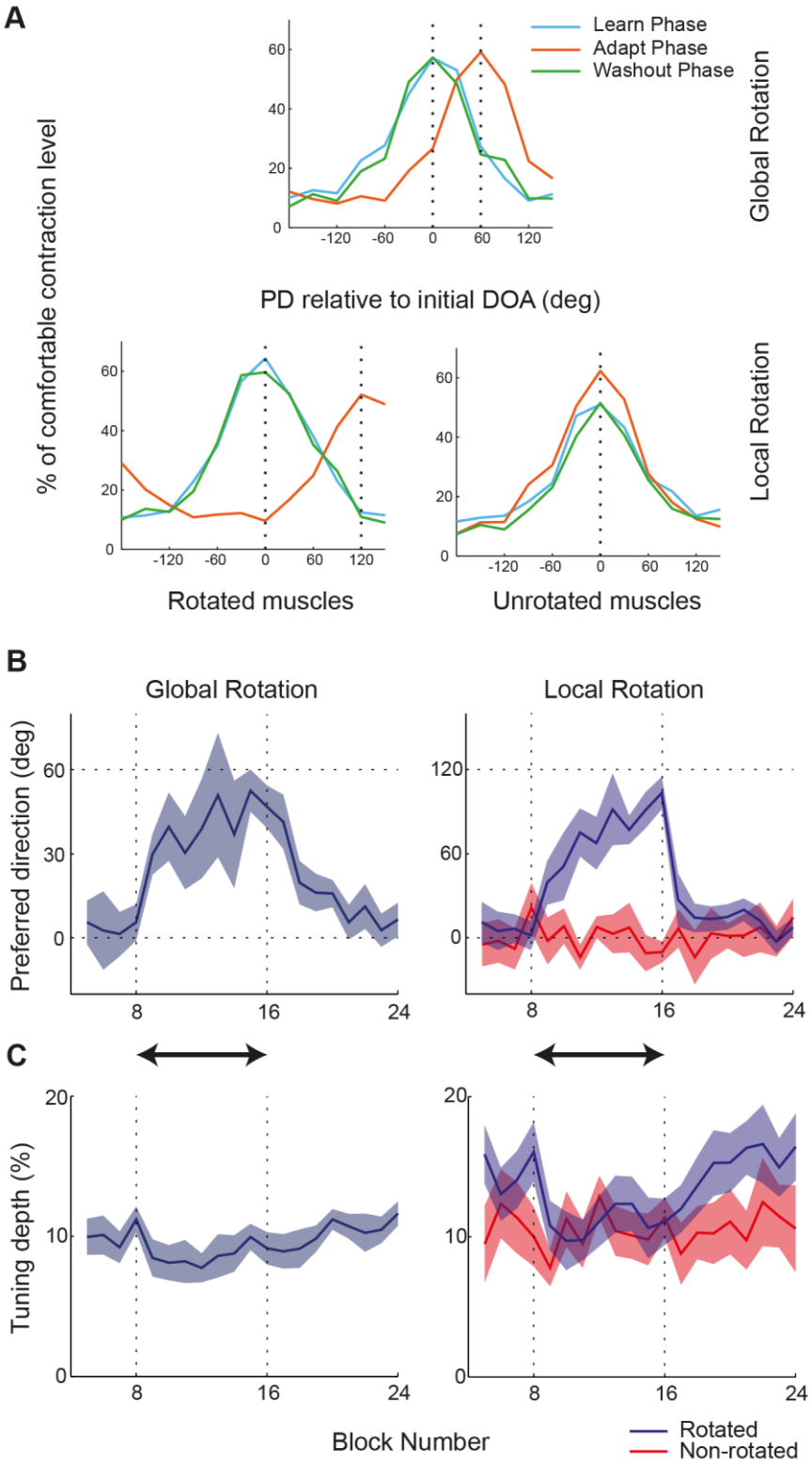


Figure 3.7 – Experiment 3.1: Tuning curves, PD and TD

A – Tuning curves averaged over all muscles and all subjects for Experiment 3.1. In the Global rotation condition the curve shifts to align with the new DoA during the Adapt phase and returns to 0 in the

Washout phase. During the Adapt phase in the Local rotation condition, the rotated muscles shift to the new DoA and there is evidence of increased activity in the non-rotated muscles.

B – PD for Experiment 3.1. The PDs of rotated muscles shift progressively towards their new DoAs and the PDs of the non-rotated muscles are unchanged, indicating little global re-aiming.

C – TD for Experiment 3.1. Decreased tuning depth during the Adapt phase in the rotated muscles indicates re-weighting (although the two sets of muscles do not have equal values initially).

Figure 3.7A shows tuning functions averaged across all muscles during the global rotation, and compiled separately for rotated and non-rotated muscles during the local rotation. These tuning curves were quantified for each block of trials by two metrics; PD and TD (see Chapter 2.3.1). Figure 3.7B shows the evolution of these metrics from the end of the Learn phase through the Adapt and Washout phases. Successful adaptation to the global rotation during the Adapt phase is revealed by the shift in relative PD to reflect the new DoA, thus resulting in a progressive reduction in directional errors. The slow return of the PD to the original DoA in the Washout phase reflects the after-effect of this adaptation.

During the local rotation there was predominantly evidence for an optimal local remapping strategy; the PDs of rotated muscles shifted progressively towards their new DoAs while the PDs of non-rotated muscles remained unchanged. Also present was the slight reduction in the TD of rotated muscles, indicative of partial use of a reweighting strategy utilised during the first half of the Adapt phase (Figure 3.7C). During the Washout phase, the PD of rotated muscles returned quickly to the original DoA consistent with the absence of after-effects in directional errors.

After-effects as a result of improved optimization

A possible explanation for the absence of after-effects following the local rotation perturbation is the use of a less optimal adaptation strategy, i.e. a focus on re-weighting would mean that the muscles with unchanged DoAs would continue to be the ones being used, and hence no after-effect would be seen. If a high after-effect is correlated with an adaptation strategy during the Adapt phase that gives more weight to DoAs that have changed between phases and a low after-effect with a strategy that gives more

weight to DoAs that remain constant, this would result in a lack of after effect following the return to the initial mapping. In the case where little after-effect is observed, this would imply the use of a positive re-weighting strategy and little remapping, i.e. a sub-optimal solution. This would indicate that the lack of an after-effect in the local rotation condition is the result of a less fully optimized adaptation to the perturbation.

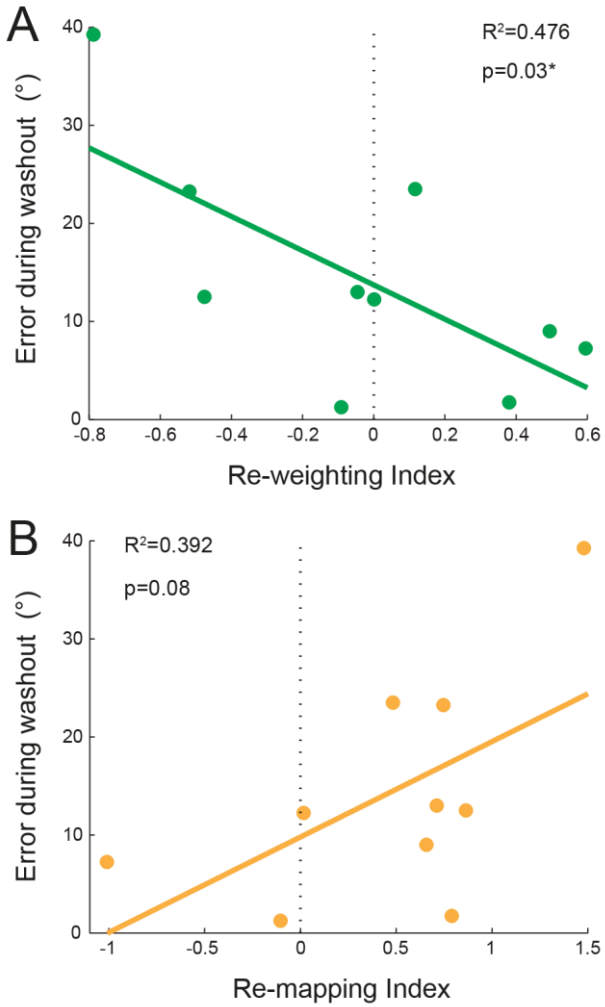


Figure 3.8 – After-effect v. Re-weighting Index and Remapping Index in the Local rotation condition

A – Mean RWI for the second half of the Adapt phase plotted against mean error for the first half of the Washout phase. The negative correlation implies that a greater RWI is associated with a lower error (i.e. a fuller adaptation results in a greater after-effect). R^2 value is 0.476 and p=0.03.

B – Mean RMI for the second half of the Adapt phase plotted against mean error for the first half of the Washout phase. The positive correlation supports the conclusion from 3.8A, that more optimal adaptation strategies are related to an increased after-effect. The R^2 value is 0.392 and p=0.08.

Plotting the average re-weighting index in the final two blocks of the Adapt phase against the average error in the first two blocks of the Washout phase results in an inverse correlation between the two, linking a high re-weighting value with a lessened after-effect (Figure 3.8A). If error is plotted against re-mapping index over the same period a positive correlation is observed (Figure 3.8B). The fit for re-weighting is significant (F-test on the regression model, $F=7.25$, $p=0.03$), and the fit for re-mapping in the local condition is close to significance level ($F=3.92$, $p=0.08$).

However, the data point at ~40° appears to be an outlier, potentially resulting in a correlation where one doesn't truly exist. Repeating the analysis with this point removed gives values of $R^2=0.22$, $F=1.97$ and $p=0.21$ for the re-weighting relationship, and $R^2=0.1$, $F=0.78$ and $p=0.41$ for the re-mapping relationship. Therefore the correlation between error and both adaptation strategies is not strong enough to be considered as contributing to the lack of an after-effect under a local rotation. It is also important to note that even if increased re-weighting did show a significant correlation with reduced error, the PD of the rotated muscles does correctly shift to the new DoA during the local perturbation, then returns quickly during the Washout phase. A heavy reliance on re-weighting would result in reduced error, but not the correct remapping of the rotated muscles. Therefore even if there was strong evidence for this interpretation, it would not fully explain the results.

PD changes in non-rotated synergistic muscles

The absence of overall PD changes in non-rotated muscles (Figure 3.7B) shows that subjects did not use a global re-aiming strategy to compensate for the directional errors induced by local perturbations. However, averaging across all muscles might obscure evidence for non-local adaptation amongst specific muscle groups such as natural synergists. Previously it was found that correlations among proximal muscle groups persist even when these hinder task performance (Radhakrishnan et al., 2008), and it was suggested that they reflect muscle synergies appropriate for natural arm movements. To identify putative hand muscle synergies, average muscle cross-correlation matrices were calculated for the Learn phase across all subjects (Figure 3.9A). For an individual subject, such correlations may reflect patterns of muscle co-ordination appropriate for a particular arrangement of DoAs, but since this arrangement is different for each subject,

any structure that persists in the group average reveals tendencies for subjects to co-activate particular pairs of muscles irrespective of their actions on the cursor.

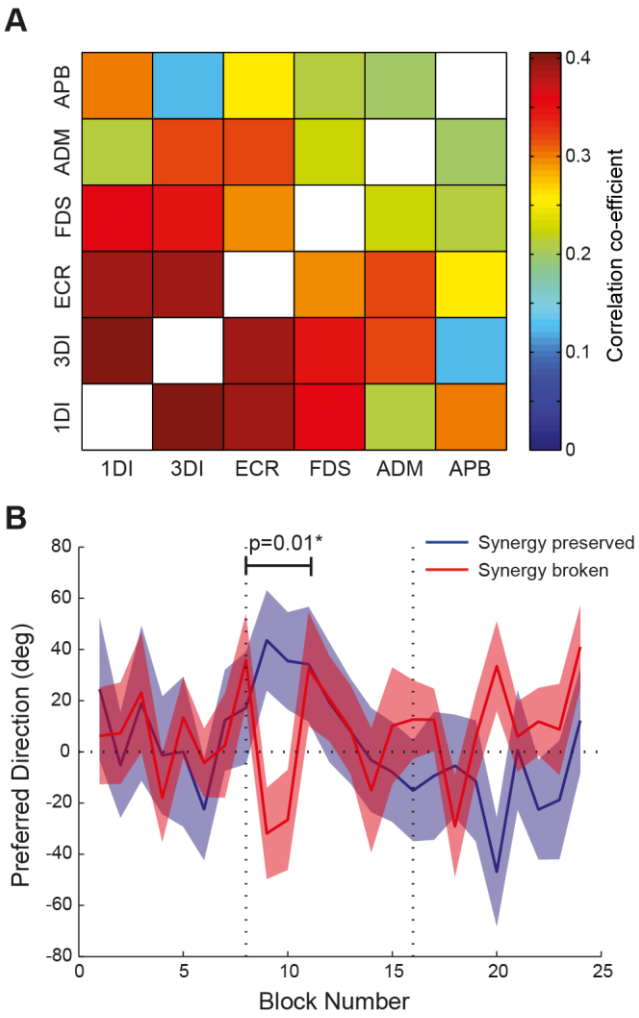


Figure 3.9 – Effect of correlated muscle activity on PD

A – Correlation matrix derived from Experiment 3.1. The values represent the correlation co-efficient between each pair of muscle EMGs over the full time of both conditions averaged over all subjects.

B – PD of non-rotated muscles grouped by Cases 1 and 2 as described in Figure 3.4. Immediately after the perturbation there is an increase in the PD of the non-rotated muscles where the synergy is preserved and the opposite when the synergy is broken. This lasts for approximately 2 blocks before both PDs return to 0. This indicates that the PD of non-rotated muscles initially shifts based on the previous mapping, but that this bias is quickly overcome. (P value shown is calculated over blocks 9 and 10). There appears to be a divergence between the two sets of muscles in block 20, but this difference is not significant (n=24, p=0.23, t_{24}=1.24).

In the local rotation condition, each non-rotated muscle was paired with two muscles with adjacent DoAs which were rotated. Of these adjacent non-rotated/rotated muscle pairs, one was preserved after the perturbation (i.e. the DoAs were still adjacent) and one was broken (i.e. the DoAs were no longer adjacent). The pair with the stronger correlation (determined from the matrix in Figure 3.9A) was defined as the synergist pair, and the non-rotated muscles were then divided according to whether the synergy was preserved or broken. When separated in this way, a clear pattern of PD changes was revealed (Figure 3.9B). When a synergy was preserved, the PD of the non-rotated muscle initially shifted in the direction of the rotation. In other words, a similar direction of adaptation was observed initially in both rotated and non-rotated members of preserved synergies. By contrast, if the synergy was broken, the PD of the non-rotated muscle shifted in the opposite direction. This opposing shift explains why no overall PD change was seen when all non-rotated muscles were averaged.

In both cases, the change in PD of non-rotated muscles was greatest in the first block following the perturbation after which the PD returned to the true DoA. This implies that non-local, sub-optimal adaptation occurs early after the perturbation, but with training an optimal local remapping of muscles patterns emerges.

3.3.2 Experiment 3.2: Adaptation to locally varying perturbations across limbs

Motivation

Based on the results of 3.1, there were two main aims of this experiment. The first was to attempt to observe the re-aiming strategy by creating a more ‘difficult’ task: increasing the number of muscles involved, and distributing them over two hands. The second was to look at the localisation of perturbations, in order to observe any differences in adaptation strategy selection between a perturbation confined to a single limb, and one where the perturbed muscles cross limbs. It is important to note that due to the redundancy of the task, all of the previously described adaptation strategies can be used to solve either perturbation.

Behavioural data

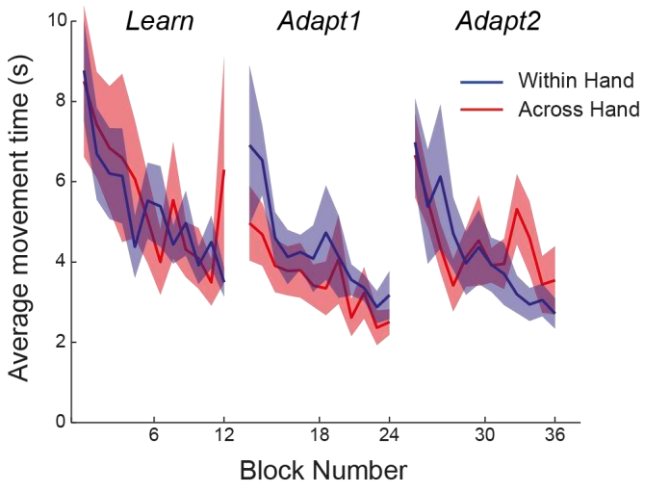


Figure 3.10 – Experiment 3.2: Movement times

Movement times for Experiment 3.2. Both conditions show similar reductions in movement time over the course of each phase.

Trial times again showed a progressive reduction after perturbation induced increases between phases, but there was no difference between the two sets of perturbations throughout the task (Figure 3.10).

Varying strategy use between locally varying perturbations

Both tasks demonstrated evidence of local re-mapping and re-weighting when quantified in terms of the relevant indices. However, there were significant differences between the two, indicative of differing speeds of adaptation.

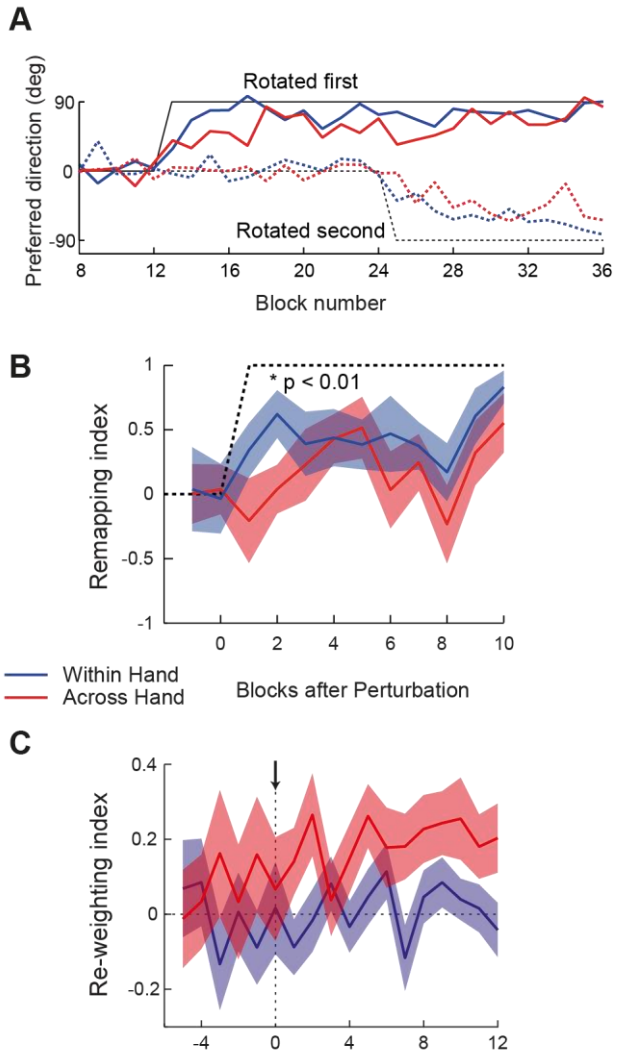


Figure 3.11 – Experiment 3.2: PD, RMI and RWI

A – PD for Experiment 3.2. The solid lines represent the PD of the muscles rotated first in each condition, while the dotted lines are those rotated second. In the Adapt1 phase, the rotated muscles in the Within Hand condition (solid blue line) reach the appropriate DoA more quickly.

B – RMI for Experiment 3.2 (as calculated in Equation 2.9), collapsed over both adaptation phases. The RMI for the Within Hand condition moves towards the optimal value more quickly than in the Across Hand condition ($n=12$, $p=0.003$, $t_{11}=3.85$). (P value is calculated over blocks 1-2 after the perturbation.)

C – RWI for Experiment 3.2 (as calculated in Equation 2.10), collapsed over both adaptation phases. The RWI for the Across Hand condition is higher than that for the Within Hand condition, but this trend is not significant.

Looking at the PD change during Adapt 1, the PD for the rotated muscles under the Within Hand condition was closer to the DoA than under the Across Hand condition,

indicating more local remapping (Figure 3.11A). This was also the case (to a slightly lesser extent) in Adapt 2. By collapsing the two phases together and using the re-mapping index (Equation 2.9), it can be seen that local re-mapping occurred significantly earlier (during the two blocks immediately following a perturbation: RMI = 0.46 ± 0.1 for Within Hand, -0.16 ± 0.13 for Across Hand, ($p=0.003$, $t(11)=3.85$) when the perturbation was consistent within limbs vs. varying across limbs (Figure 3.11B).

The re-weighting index (Equation 2.10) showed a divergence between the Within and Across Hand conditions when both Adapt phases were collapsed together (Figure 3.11C). The value of the index for the Within Hand condition stayed close to zero (0.01 ± 0.02), while there was an increase for the Across Hand condition (0.19 ± 0.02), indicating that use of the less optimal re-weighting strategy was only present in the Across Hand condition. However, this was not a significant trend ($n=12$, $p=0.1$, $t=1.7$).

Once again, there was little evidence of the sub-optimal global re-aiming strategy.

Correlations structure initially effects remapping

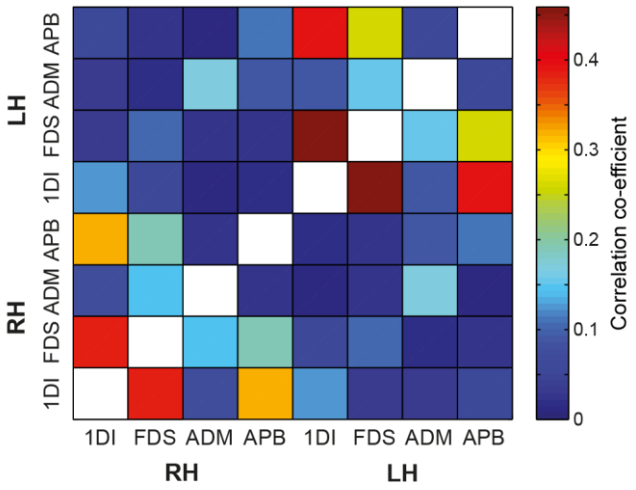


Figure 3.12 – Correlation matrix for Experiment 3.2

Correlation matrix derived from Experiment 3.2. The values represent the correlation co-efficient between each pair of muscle EMGs over the full time of both conditions and averaged over all subjects. RH and LH refer to right hand and left hand.

As expected, the correlation structure for the bimanual task showed strong correlations within hands and weaker ones across (Figure 3.12). The structure within each hand was similar to the structure observed in experiment 3.1. Taken with the less optimal remapping described in the Across Hand condition, this supports the interpretation that changes in relative use between muscles that are more highly correlated (occurring to a greater extent in the Across Hand condition than the Within Hand condition), results in sub-optimal adaptation until the synergistic bias can be overcome.

There was also a small correlative effect observed between the same muscles on opposite hands. Symmetrical use of muscles is natural in humans (Beaule et al., 2012), requiring less cortical activation than unilateral movements (Cincotta et al., 2004, Grefkes et al., 2008). As such, this effect is another representation of the bias towards naturalistic use of muscles.

3.3.3 Experiment 3.3: Adaptation to perturbations with no overall rotation

Motivation

In the previous section, the presence of an after-effect that was related to the extent of use of a re-weighting strategy was discussed. In order to look at whether re-weighting was the sole reason for the lack of this effect, I wished to look at a local perturbation in which a re-weighting strategy was not available. To achieve this, I used a local symmetric rotation in which two groups of muscles were simultaneously rotated in opposing directions.

The task was constructed as a 6-muscle, bimanual task with the three muscles in each hand selected randomly from a group of four. The phases followed the *Learn, Adapt Washout* structure as in Experiment 3.1.

Behavioural data

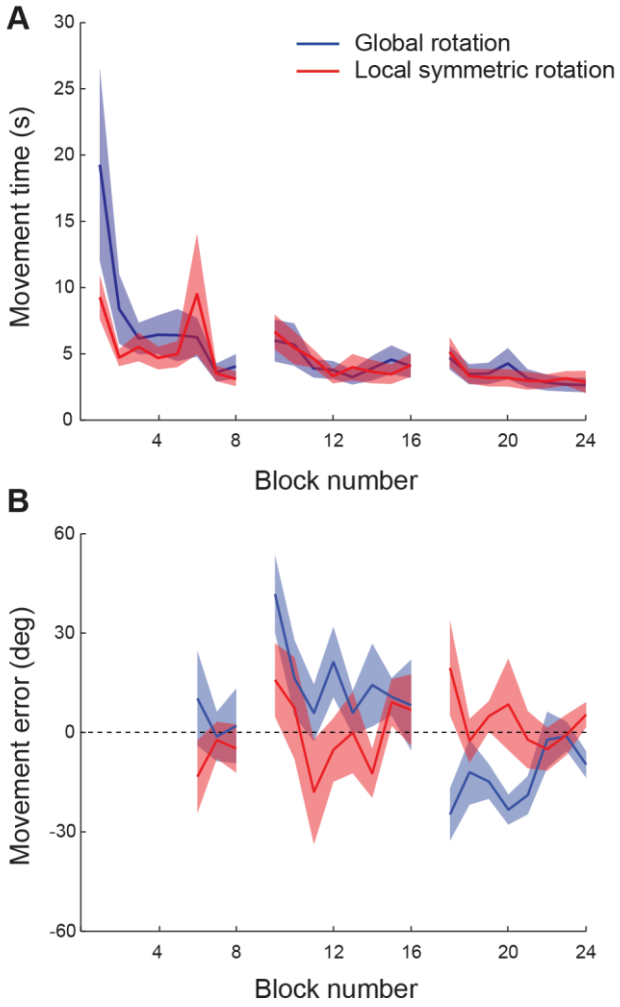


Figure 3.13 – Experiment 3.3: Movement times and Errors

A – Movement times for Experiment 3.3. The two conditions show similar movement times for each phase except for the beginning of the Learn phase where the times for the global condition are much higher. However, during this part of the task any differences are un-meaningful.

B – Errors for Experiment 3.3. Errors for the global rotation show the same pattern as the global rotation in Experiment 3.1 (Figure 3.5B). Errors for the local symmetric rotation do not diverge significantly from 0 throughout the task, due to the opposing directional rotations resulting in the lack of a clear error signal.

There were no differences in the movement times between the two conditions other than a larger initial starting time in the global rotation (19.3 ± 7.3s and 9.3 ± 1.7s for the first block) (Figure 3.13A). It is not clear why this difference exists, as the two conditions are effectively identical at this point. It is relevant though, that the task data is relatively

non-meaningful for the first few blocks, as subjects are still figuring out the nature of the task itself, making any conclusions about wider behaviour largely unfounded. Regardless, the difference here for the first two blocks was insignificant (n=12, p=0.15, t=1.56), and as such is likely to be due to the presence of a small number of anomalously long trials (timescale of minutes, as opposed to seconds). This is borne out by the median trial times for the first block (global: 5.5s, local: 4.79s). By block three, the two conditions had similar movement times and remained at a similar level to each other for the remaining duration of the task.

Errors

Little can be taken from the errors here due to the nature of the local symmetric rotation. Due to the opposite direction of the rotations the effective impact on cursor position is null when averaged across all trials. As a result, the errors for the local symmetric rotation remained close to 0 throughout the task (Figure 3.13B). The errors for the global rotation showed a shift to 49.9 ± 13.9° after the perturbation, gradually decreasing back towards zero through the phase. There was then a shift in the opposite direction at the beginning of the Washout phase (-29.7 ± 9.4°), which again returned to zero by the end of the phase. This matches the pattern seen in the errors for the global rotation in experiment 3.1.

PD and vectors

In the Adapt phase the PD in both conditions moved towards the DoA, reaching an average level of 44.1 ± 9.2° and 45.9 ± 6.5° for the global and local symmetric conditions respectively (Figure 3.14A). In the Washout phase, the PDs for the two conditions diverged, with the PD under the local symmetric condition moving towards the DoA quickly, remaining at an average level of 6.6 ±7.8°, and the PD for the global condition averaging 24.9 ± 5.5° for the first half of the phase before reaching 8.3 ± 6.2° by the end of the phase. This difference was not significant (n=12, p=0.08, t=1.96).

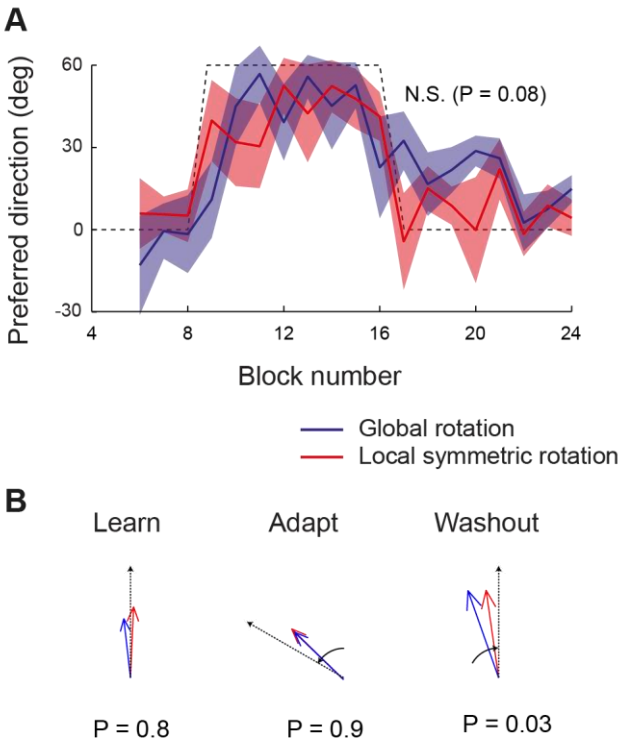


Figure 3.14 – Experiment 3.3: PD and Vectors

A – PD for both conditions progresses similarly in the Adapt phase. In the Washout phase, the PD for the global condition moves back towards 0 more quickly, but this trend is not significant.

B – Vector analysis for Experiment 3.3. In this case, during the Washout phase there is a significant separation between the global and local conditions, with the population vector for the local symmetric condition closer to the null value, indicative of a greater after-effect present in the global condition.

However, when looking at population vectors calculated from the average over the full Washout phase (Figure 3.14B), the two conditions showed a clear, significant ($p=0.03$, $t(95)=2.19$) divergence during the Washout phase.

Therefore there is a correct remapping of the rotated muscles followed by a lack of an after-effect present under a local symmetric perturbation, a similar outcome to that observed in the standard local perturbation indicating that the two conditions are adapted to via similar processes, even though directional error is available to a lesser extent in the local symmetric condition.

3.3.4 Experiment 3.4: Score-based task

Motivation

In the three preceding experiments the exposure time to perturbations was not controlled since each trial had a different length. In particular, trials immediately after perturbations are significantly longer than towards the end of a phase, meaning that during this time it was likely that there was a lot of learning going on that was not being captured. In order to deal with this problem, the score-based version of the task described in Chapter 2.2.1 was introduced.

To briefly recap, subjects were given a two second movement phase, followed by a one second hold phase in which the cursor was to be held in target. A score was then received based on the proportion of the hold phase spent in target and the coverage of the target by the cursor. The form of the task used was the 8-muscle, bimanual setup comparing Within Hand and Across Hand perturbations, with a three phase task structure consisting of Learn, Adapt and Washout phases.

Behavioural data

A major change in this version of the task was the switch from using movement times to trial score as a measure of performance (the definition of score is given in Chapter 2.2.1, Equation 2.1). Score was given in the range 0-100, with 0 equating to the cursor being completely separated from the target for the duration of the hold period, and 100 representing perfect coverage of the target during the same time (due to noise, a perfect score was effectively impossible to achieve).

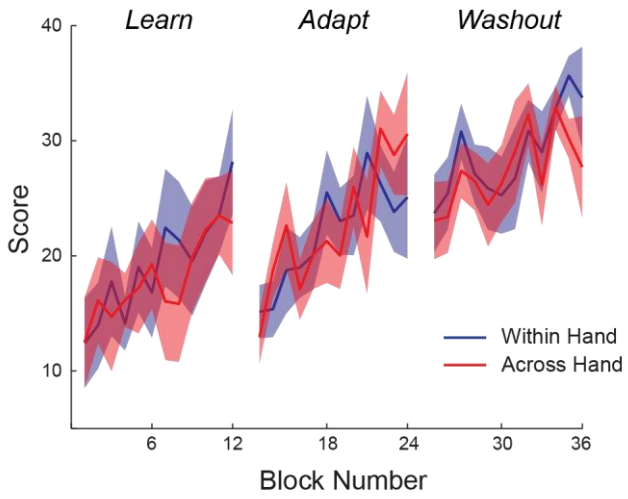


Figure 3.15 – Experiment 3.4: Score

Average scores for Experiment 3.4. Score is presented to subjects after each trial and is between 0 and 100. A perfect score represents complete coverage of the target by the cursor for the full duration of the hold period. Scores increases progressively during each phase, with drops occurring after perturbations. The two conditions show similar scores throughout the task.

Average score over the full task was 21.4 ± 2.3, with subjects reaching an average maximum score of 85.3 ± 0.7. Subjects showed a gradual increase over the Learn phase, a drop followed by further gradual improvement in the Adapt phase, and a further drop (but not back to baseline) in the Washout Phase (Figure 3.15).

Between the Across and Within limb conditions there was little difference in performance over time, and the average scores for the task were also similar (20.1 ± 2.3 for the within condition and 22.7 ± 3.2 for the across condition).

PD

In the learn phase, PD for both conditions remained close to 0, as would be expected. This indicates that subjects were performing the task correctly, and that no differences were arising due to the slightly differing initial mappings necessary for the Across and Within Hand conditions (Figure 3.16).

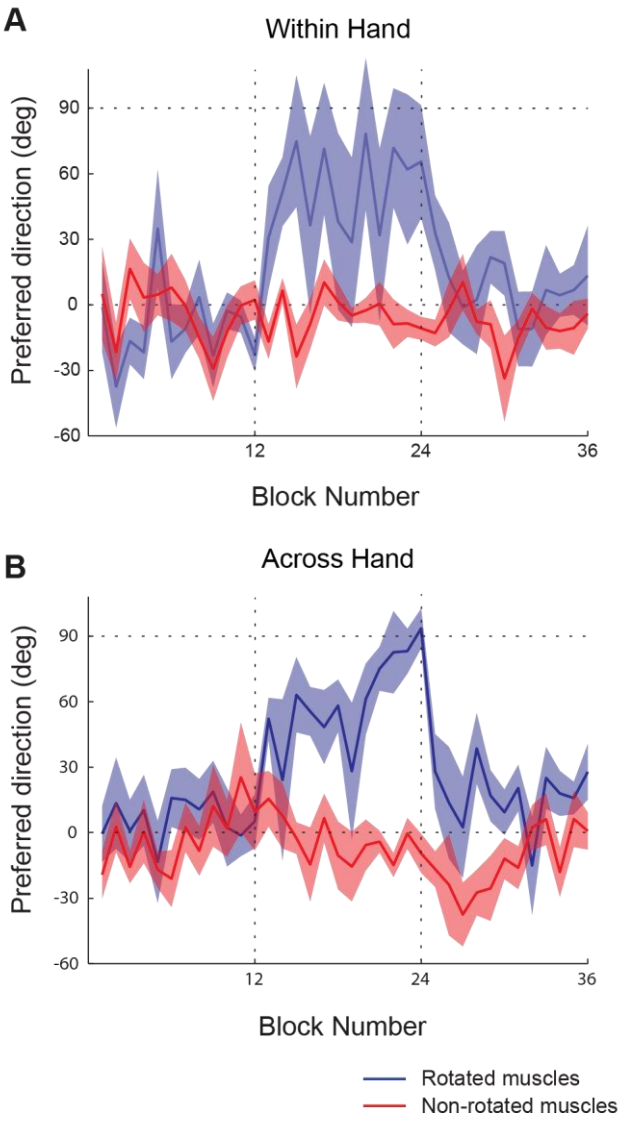


Figure 3.16 – Experiment 3.4: PD

A – PD for the Within hand condition for Experiment 3.4. PD is very noisy, but still shows a separation of the rotated and non-rotated muscles during the Adapt phase, albeit one where the rotated muscles do not reach their correct DoA.

B – PD for the Across hand condition for Experiment 3.4. PD is again noisy, but shows the separation of the muscle groups during the Adapt phase, with the rotated muscles reaching the correct DoA by the end of the phase. In the Washout phase there is some evidence of re-aiming, with the rotated muscles not reaching 0 and the non-rotated muscles compensating with a negative PD.

In the Adapt phase, the rotated muscles in the Within Hand condition quickly reached an average level of 53.5 ± 17.1° (although this was quite noisy). The non-rotated muscles stayed constant at -5.5 ± 4.0°, with no evidence of re-aiming. Under the Across

Hand condition, there was a gradual increase in PD in the rotated muscles from an average level of 50.1 ± 11.3° during the first half of the phase, to 88.2 ± 11.4° during the final two blocks. Interestingly, there appeared to be some evidence of re-aiming, with the non-rotated muscles starting at value of 15.4 ± 12.7 in the first block following the perturbation and descending to -9.6 ± 10.0 in the final block of the Adapt phase.

In the Washout phase, although the data was still somewhat noisy, there again appeared to be some evidence of re-aiming in the Across Hand condition. Under both conditions the rotated muscles did not immediately return to 0, with average values for the first half of the phase of 14.6 ± 15.0° and 18.1 ± 10.7° for the Within and Across conditions respectively. However, under the across condition, the non-rotated muscles shifted in the opposite direction (average value of -23.9 ± 8.6° for the first half of the phase), an effect that was not present in the within condition (-9.2 ± 7.4°).

It is of particular note that in the Across Hand task, there appeared to be progression from a sub-optimal solution to a more optimal one within a single condition. Subjects here were thus finding a successful solution and yet still moving towards a more optimal one.

3.4 Discussion

I have shown that when presented with an abstract, novel motor adaptation task, subjects reach the most optimal solution to solve the perturbation, even when successful sub-optimal solutions are easier to identify. Further to this, I have shown that although the optimal solutions are eventually reached, the exploration of the potential solution space can be biased by the structure of the perturbations, and constraints introduced by naturalistic movement.

3.4.1 Muscles quickly remap when a perturbation is applied

The redundancy of the task creates a choice for subjects in terms of how they complete the task and adapt to perturbations. In the case of the global rotation, subjects quickly reach the optimal solution. The local perturbation structure provides a more interesting response, as the nature of the perturbation results in the most easily found adaptive

strategy (global re-aiming) not being the optimum. However, little evidence of the sub-optimal re-aiming and re-weighting strategies was observed, with subjects quickly able to dissociate the two sets of muscles and arrive at the optimal local remapping solution.

When looking at the correlation between the muscles used for this task, it was shown that a higher level of correlation between two muscles has an effect on how they are used after a perturbation, but that this effect ultimately does not stop the remapping of those muscles to a more efficient orientation. This indicates that the initial response to a perturbation has a basis in synergistic relationships, i.e. muscles that would naturally work together are less likely to lose that association after a perturbation which removes their relationship. However, this initial response can be overcome, and the motor system can reach the optimal solution, regardless of whether that solution is natural. This supports the idea of motor primitives as priors that bias the structure of adaptation, as opposed to hardwiring that cannot be overcome.

(Nazarpour et al., 2012) showed that hand muscles could easily adapt to new relative functions, even when the muscles chosen were forced to act in a way that directly opposed their natural utilisation. In contrast, (de Rugy et al., 2012) showed that forearm muscles, when faced with similar kinds of adaptation tasks, could not adapt in the same way and remained constrained by their natural function. The conclusion in that paper was that muscle co-ordination was based on 'good enough' solutions, and did not reflect what would be predicted by an optimal controller. A similar task using the elbow joint (de Rugy et al., 2009) showed lower adaptation when natural muscle usage was perturbed, indicating synergy based limitations. My results show the opposite, that even when presented with a simple solution that will successfully complete the task (re-aiming), the system still reaches the more complex, but optimal solution (local re-mapping). However, there were two key differences between these studies. The first is that the initial mappings here were non-intuitive, as opposed to reflecting natural movement. In the case of the latter, subjects are likely to be heavily biased towards 'normal' muscle use, which would affect the level of adaptation observed. The second (and more interesting) difference is the active muscles, a factor that was previously remarked upon in (Radhakrishnan et al., 2008), where the relative ability of hand muscles and arm muscles to perform abstract tasks in an MCI paradigm was shown to be vastly differing. This indicates that in muscles where a greater level of dexterity is required, the constraints for adaptation tend towards the high level, whereas in muscles

where less adaptation potential is needed, solutions tend towards the low level, biomechanical constraints.

3.4.2 Motor hierarchy

This data supports the idea of a motor hierarchy governing exploration, with more highly correlated muscles having a greater initial bias to being remapped with respect to each other. In order to further explore this, I looked at a local perturbation where the perturbed units were either confined to a single hand, or distributed across two hands. This allowed comparison between conditions where the highly correlated muscles retained consistent relationships and ones where the optimal solution required remapping of relationships between correlated muscles.

It was found that in both conditions, subjects reached the optimal solution, although there were slight differences in how that solution was achieved. In the Across Hand task (the task with the more local perturbation structure) subjects took slightly longer to reach the full remapping solution and showed some evidence of reweighting (not present in the Within Hand task). This, although not fully conclusive, again supports a hierarchy of adaptation (Figure 3.17). Prior assumptions of what a perturbation has entailed descend from a global to local level, and thus take longer to adapt to.

Hierarchical re-mapping may reflect subjects' prior expectations about the perturbation structure within the task. An environmental change in most everyday situations would be expected to act on the body as a whole; therefore subjects would begin by exploring global re-mapping solutions (i.e. the optimal solution for a global rotation, the simplest form of perturbation). However, over time, the optimal solution (i.e. one that requires disassociation at the level of individual limbs, muscles or neurons, resulting in more noise, and hence more effort) is eventually learned.

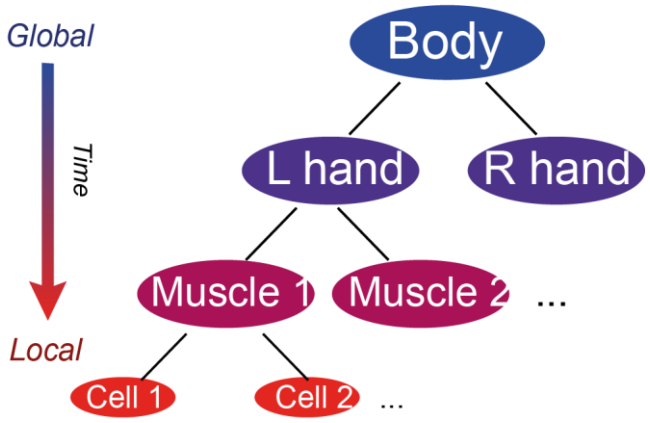


Figure 3.17 – The motor hierarchy

I propose that adaptation progress in a hierarchical fashion, with optimal performance achieved more efficiently when perturbations can be localized to an area that has a higher position in the hierarchy.

It should be noted that the concept of hierarchical motor control has been used with varying meanings throughout the literature. Here we define our version of a motor hierarchy as the required complexity of effector disassociation, ranging from simple global actions to those such as use of a BMI, where neuronal disassociation is required. It provides a context for navigating the vast solution space present as a result of the redundancy of the motor system, while still maintaining an ability to learn complex, novel patterns of usage. I hypothesise that exploration of this hierarchy is governed (to a certain extent) by motor primitives, but the key point is that they can be broken, and (certainly in the hand) quite easily.

3.4.3 MCIs and BCIs

This work has implications for the relationship between MCIs and BCIs. Under a motor hierarchy, visuomotor rotation is quickly adapted to; MCI re-mapping takes more time and BCI re-mapping takes the longest. This theory is supported by evidence from similar BCI tasks which show a greater tendency towards re-aiming as opposed to re-mapping. Since neurons are clearly more local (and thus more difficult to disassociate) under this hierarchy than muscles, the prediction of less optimal strategies over a similar timeframe is fulfilled. If the neuronal data from (Jarosiewicz et al., 2008) is then taken

into account, the prediction from an adaptation hierarchy is that the adaptation would reach the optimal strategies if left for long enough. This is backed up by (Ganguly and Carmena, 2009), in which neurons left to adapt over a few days show a more optimized adaptation than seen in the Jarosiewicz study.

3.4.4 After-effects

Interestingly, there was a significant difference in the after-effects in the washout phase of experiment 3.1 between the global and local rotations. It was suggested there that the use of a re-weighting strategy could account for the difference, and experiment 3.3 was designed partly to test this idea. It was shown there that under conditions in which a re-weighting solution was not available, remapping took place at a similar rate and again resulted in the lack of an after-effect in the washout phase. Therefore use of a re-weighting strategy cannot entirely account for the differences in the after-effect between global and local rotation conditions. This could be related to the structure of the perturbation determining the nature of the adaptation and hence how the internal model is updated. Following a rotation, if the global task structure is preserved then subjects only need to alter the mapping from the visual space to a set of (preserved) muscle combinations. For local perturbations, subjects need to learn new combinations of muscles. I hypothesize that these types of learning may be governed by distinct brain processes, which will be explored further in Chapter 5.

3.4.5 Information available from the error signal – Global v. local symmetric perturbation

The nature of the error signal differs between the global and local symmetric rotation conditions. In the case of the global rotation, there was a clear, consistent directional error between phases providing information regarding the nature of the rotation. In the case of the local symmetric rotation, this visual error was available to a lesser extent, due to the opposing directional rotations of the two groups of muscles. However, if the lack of clear directional error information were affecting the ability of subjects to successfully complete the task, then there should be behavioural evidence available.

With regards to the movement times, a significant difference between the two tasks would be expected in the Adapt phase. In the real data, this was not observed.

The other measure of adaptation to the perturbation is the PD. A slower move towards optimality in the Adapt phase would be expected, and again was not observed (the only difference being in the Washout phase).

If muscles were following perfect cosine tuning, then the directional error would be non-existent in the local symmetric condition, and subjects would be unable to dissociate rotated and unrotated sets of muscles in either the local or local symmetric conditions and only a re-aiming solution would be present. Therefore, since dissociation does occur, the trial-to-trial variability in muscle use is critical to how subjects learn the task.

Therefore the conclusion is again (as discussed with regards to after-effects) that there is more going on than use of the directional error to adapt to perturbations in which subjects are required to learn new combinations of muscles (i.e. local perturbations).

3.4.6 Comparison between success-based and score-based task designs

One of the main results of the first three experiments presented in this chapter was the lack of evidence of the sub-optimal global remapping strategy. However, it is useful for further study that conditions can be found under which re-aiming is observed.

It is possible that the structure of the task was part of the reason why re-aiming was not seen in experiment 3.1-3. Since data was quantified only at the beginning and end of each trial, there was time for learning to occur in the time between the movement point and the hold period (even though subjects were discouraged from ignoring targets in favour of exploration). Also, trials immediately following perturbations were likely to take much longer than average, with some trials taking minutes to complete as opposed to seconds. Therefore, there was a lot of learning data that was not being captured.

The score-based task (Experiment 3.4) was proposed as a solution to this problem, and was carried out with a focus on two specific aims. The first was to determine whether a consistent level of performance could be achieved from subjects such that it could be ascertained that they were able to perform to the task to a degree from which

conclusions could be made regarding their learning and adaptation. The second was to see if any evidence of the re-aiming strategy could be observed under these conditions.

Score is potentially a better measure than movement time, due to the floor effect that exists for the latter. Subjects in the hold task managed to reach movement times of around three seconds, which then become extremely difficult to improve on. In the case of score, subjects were performing well enough to be considered to have 'learnt' the task, but there was still space for improved performance if given more time.

The observed score demonstrated a similar progression of performance to what was observed with movement times. However, subjects did not reach a ceiling, indicating that improvement in performance was continuous throughout the duration of the task. This is potentially useful, as it allows for the possibility of effects that can be revealed via differences in performance, something that is difficult in the success based task due to the quick progression to minimum times.

In terms of PD, the score-based task showed a similar learning curve to the success-based task, although noisier in nature. The task was clearly difficult for subjects to perform optimally, again a potentially useful feature, allowing for effects that are only revealed when there is space available for improvement. In particular, there was some evidence of a re-aiming strategy being used in both the Adapt and Washout phases in the Across Hand condition, with progression towards an optimal separation of muscle groups towards the end of the Adapt phase.

Based on this dataset, the task may require fine tuning, as performance is variable, which could potentially obscure any effects (it is necessary to maintain a balance between a performance that is too good to reveal subtle differences, as in the success-based task, and one that is not close enough to 'correct' performance to draw any conclusions).

Potential ways of resolving this issue while keeping the timed task structure include:

1) Extending the task time: This would allow for greater performance progression, but would require concentration and commitment from the subject for a longer time. In the timed task there was no penalty to the subject for not trying, other than a low score. Therefore task times must be balanced between 'long enough to learn the task' and 'short enough to retain focus and minimise muscle tiredness'.

2) Beginning with an intuitive arrangement: An initial arrangement that is easy to learn gives subjects an immediate handle on the task, and will potentially allow for greater revelation of adaptation effects due to the inherent bias. Notably, an intuitive arrangement will still remain an abstract task, as it will not reflect natural muscle use, but will simply be easier to relate to due to the relationship between the movement of the muscles and the movement of the cursor in the task space.

3.5 Conclusion

In conclusion, I have shown that subjects can find the optimal solutions in novel, abstract motor tasks even when those solutions are difficult to find and not necessary for task completion. The exploration to find those solutions is biased by naturalistic muscle relationships, but they ultimately do not constrain the ability to find the optimal solutions. This indicates that motor primitives act as priors, but are not hardwired constraints on the motor system.

Optimal remapping was facilitated when high-level structure was preserved and, after locally-varying perturbations, progressed hierarchically from global to local levels. I conclude that adaptation even in abstract contexts is biased by prior expectations of perturbation structures that correspond to a naturalistic organisation of behaviour. Nevertheless, with training the motor system can optimise the control of individual muscles as appropriate for abstract task goals.

CHAPTER 4 - THE EFFECT OF tDCS ON STRATEGY IN A BIMANUAL MCI ADAPTATION TASK

In which I look at the effect of tDCS on the extent to which subjects use either a global re-aiming solution or a local remapping solution in a bimanual adaptation task.

4.1 Introduction

Having shown in Chapter 3 that a range of strategies are utilised by subjects in order to adapt to a local rotation, the next step was to investigate whether the use of those strategies could be altered via brain stimulation.

M1 and the cerebellum are both known to be involved in motor adaptation (Li et al., 2001, Maschke et al., 2004, Morton and Bastian, 2004), but the exact nature of their individual contributions is not fully established. (Galea et al., 2011) looked at the effect of tDCS on a visuomotor adaptation task (pointing to a target) and found that stimulation of the motor cortex affected the retentive aspects of the task, whilst stimulation of the cerebellum affected the adaptation to error. Here, I wished to investigate these individual contributions using a task with two particular features.

Firstly, the task used here is a complex one in which the simplest solution to solve the problem created by the perturbation is not the optimal solution. This allows examination of the effect of excitability changes in in M1 and the cerebellum on a task that approximates 'real' motor performance to a greater extent than previous work. Secondly, the measure of performance used is the extent of the use of global and local adaptation strategies. Generally, experiments studying motor adaptation have used error reduction as the metric of performance (Kagerer et al., 1997, Krakauer, 2009, Turnham et al., 2012). This is true also of those studies examining the effect of tDCS on adaptation (Jayaram et al., 2012, Block and Celnik, 2013). The intention here is that, instead of looking at whether the task is completed successfully, I can investigate how that success is achieved and determine how excitability changes in M1 and the cerebellum could affect the ability to achieve a 'good' performance.

Therefore, in this chapter I wish to look at how the processes that drive varying strategies depend on different brain areas, with the aim being to dissociate M1 and cerebellum in terms of their contributions to the process that drives remapping in a local perturbation task.

4.2 Methods

Forty subjects (22 male, aged 20-57), all right handed were recruited for this experiment. Subjects were divided into groups of eight, each group completing the same task under differing conditions. The task consisted of a bimanual, local rotation where the perturbed muscles were distributed across both hands (described as an Across Hand rotation in the previous chapter. See Figure 3.2A). The differing conditions were as follows:

i) Task performed with no tDCS.

ii) Task performed with anodal M1 stimulation.

iii) Task performed with cathodal M1 stimulation.

iv) Task performed with anodal cerebellar stimulation.

v) Task performed with cathodal cerebellar stimulation.

Ultimately, datasets from two subjects could not be included in the analysis due to technical issues while recording, one from condition 3 and one from condition 5.

4.2.1 Task Structure

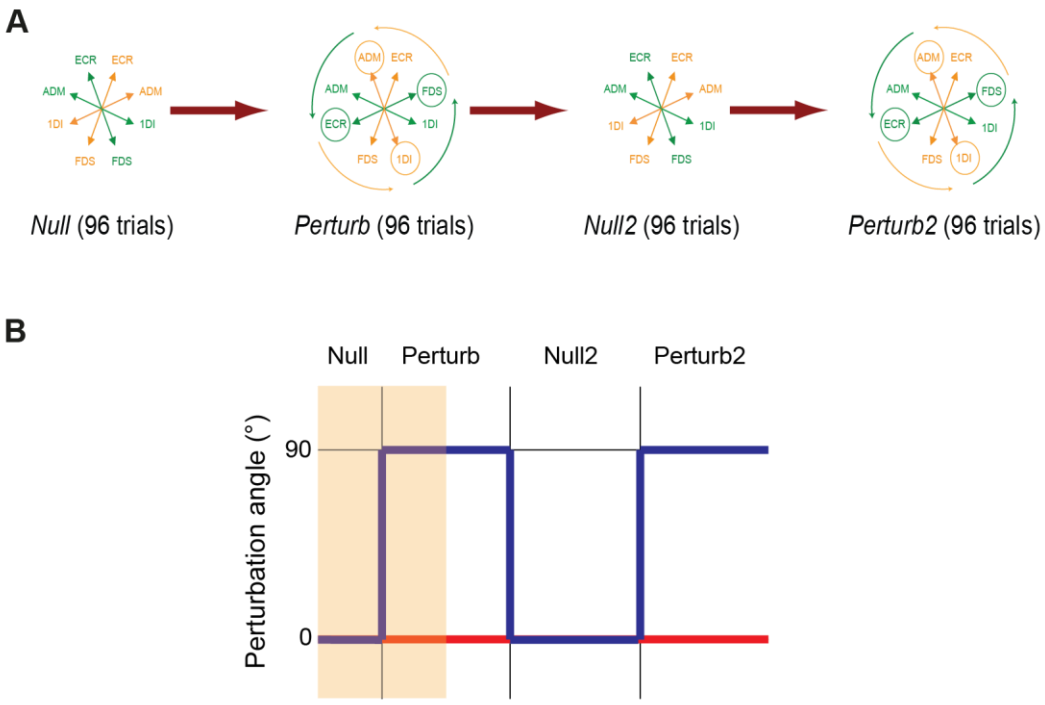


Figure 4.1 – Task structure

A – The task consists of four phases alternating between two different mappings. The Null mapping has the same general structure as the Across Hand mapping (Figure 3.2A), except here the initial muscle DoAs are the same for all subjects. The perturbation is a 90° rotation affecting half of the muscles in each hand, the figure shows an example.

B – Generalized task structure. Half of the muscles in each hand follow the blue line, the other half the red. tDCS time is represented by the shaded area.

Subjects completed a single condition consisting of four phases, alternating between an initial and an adapted DoA-muscle mapping (Figure 4.1).

All subjects began with the same initial mapping. The muscles used in the task were the same in each hand and consisted of a distal pair acting in opposing directions, 1DI and ADM, and a flexor/extensor pair, FDS and ECR. The initial mapping was set up so that pairs acted in opposing directions (Figure 4.1A), and that the directional effect on the cursor of each muscle was the same (or close to) its movement in real space when

correctly positioned for the experiment (hand placed palm down pointing towards the screen).

The perturbations of the DoA-muscle mapping were then counterbalanced for the set of rotated muscles (the flexor/extensor pair from one hand and the distal pair from the other) and the direction of the rotation. This allowed the creation of a scenario where the remapping would take longer (due to the move from an intuitive mapping to a non-intuitive one), but would not reflect the specific idiosyncrasies of one particular muscle arrangement.

The initial mapping was designed as intuitive in order to highlight any strategy progression in the perturbation phase. The experiments in the preceding chapter failed to show any evidence of the global re-aiming strategy, meaning it would be advantageous to weight towards this being the initial solution, in order to show more clearly the differences in improvement between stimulation protocols

4.2.2 tDCS

Each subject in conditions 2-5 completed the task while receiving DC stimulation over either M1 or the cerebellum, with this stimulation being either anodal or cathodal. Subjects were counter-balanced for whether the left or right hand was the target of stimulation. Electrode placement and basic stimulation protocol is described in Chapter 2.4.1.

Here M1 stimulation lasted for 10 minutes and cerebellar stimulation lasted for 15 minutes, with the starting point being after 48 ‘training’ trials, or halfway through the Null phase. Even though the stimulation period was based on a set time (as opposed to trials completed) there was little variability in the endpoint, with all subjects finishing within the same block (15 for M1 stimulation, 21 for cerebellar stimulation). The persistence of the effect of M1 has been well studied, and 10 minutes of stimulation is sufficient for 30 minutes required for the induced effect to persist throughout the task (Nitsche et al., 2005). However, cerebellar tDCS is less well studied, and most likely the exact effects of tDCS differ from those of M1. Therefore it was decided to increase the stimulation time to 15 minutes in order to ensure that the effect lasted throughout the

task (this stimulation time has been shown to produce after-effects lasting up to 30 minutes (Galea et al., 2009)).

The strength of stimulation was 1mA (0.029 mA/cm^2 current density) for M1 and 2mA for the cerebellum (0.057 mA/cm^2). Again, the effect of the strength of stimulation on excitability modulation in the cerebellum is less well studied and this level has been shown to reliably produce clear changes in excitability (Galea et al., 2009). Since the results from M1 and the cerebellum are only being compared in a qualitative manner, the difference in the nature of stimulation is justified. (It should be noted that even identical stimulation protocols for the two cortical regions could not be compared quantitatively (at least in terms of effect on remapping), due to the lack of ability to exactly quantify the amount of stimulation the targeted region has effectively received).

Within a single subject the active muscles can be divided into four categories based on whether they were rotated or un-rotated, and stimulated or un-stimulated.

4.2.3 Data Analysis – RMI differences between phases

In order to simply show the effect of tDCS under multiple conditions, I defined an index to quantify how local the adaptation was by use of a single number applying to each hand in each condition.

In terms of PD, matching the DoA is indicative of optimal performance. In the case of the non-rotated muscles, the DoA remains constant, so there is no difference between phases. In the case of the rotated muscles, however, the DoA modulates between phases. In the previous chapter, I used a Remapping Index (RMI) in order to quantify the difference between the rotated and non-rotated muscles.

$$Re-mapping\ index = \frac{\Delta PD_{rotated} - \Delta PD_{non-rotated}}{\Delta DoA_{rotated}}$$

Eq. 2.9

Given its definition it follows that there is an optimal value of RMI for each phase which varies depending on whether the mapping has been perturbed or is in its null state,

and the difference between this value and the observed value is a measure of optimality for each phase.

Because of this variation, the difference between the RMI for the Perturb phases and the Null phases can be used as a measure of optimality. The higher the value of that difference, the closer the adaptation is to the optimum, as it demonstrates that the RMI is modulating optimally between phases. RMI difference is defined as the difference in PD between the same set of muscles between phases, or the difference in RMI between phases (Equation 4.1).

$$RMI\ difference = \left(\frac{\widehat{PD_{rot}} - PD_{rot}}{90^{\circ}}\right) - \left(\frac{\widehat{PD_{non-rot}} - PD_{non-rot}}{90^{\circ}}\right)$$

$$= \left(RMI_{perturb}\right) - \left(RMI_{null}\right)$$

Eq. 4.1

Where $\hat{x}$ represents the value of x in the Perturb phases, and x represents the value of x in the Null phases. This value is calculated for each hand individually, in order to compare the effect of stimulation across limbs.

4.2.4 Prediction

Given the facilitative effect of anodal stimulation in previous studies, I predict that anodal stimulation will result in an enhancement of the use of the local remapping strategy and cathodal stimulation will cause the reverse, pushing the system towards the sub-optimal, global re-aiming solution. By stimulating M1 and the cerebellum, I wish to dissociate the two areas in terms of how they contribute to the process that drives remapping.

4.3 Results

4.3.1 Behavioural data

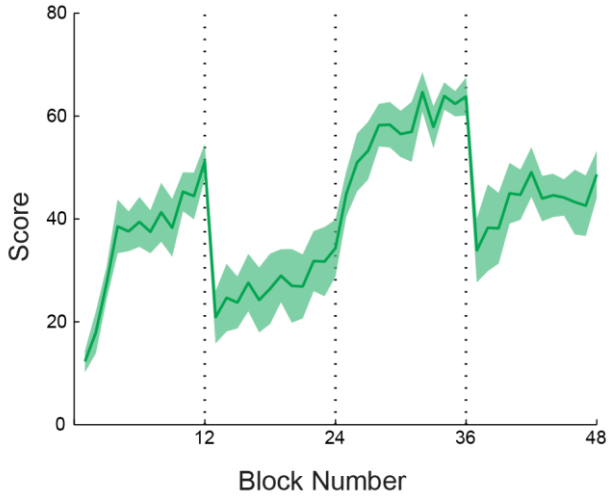


Figure 4.2 – No stimulation task: Score

Score shows a progressive increase during each phase, with drops occurring immediately following perturbations. Subjects perform better during the Null phases (where the intuitive mapping is in place).

Score in the no stimulation task had an average value of 41.0 ± 3.5 with maximum scores of 87.9 ± 0.4. Gradients of lines fitted to each of the four phases were 2.79 (r^2=0.79, p<0.001), 0.96 (r^2=0.81, p<0.001), 1.41 (r^2=0.75, p<0.001), and 0.79 (r^2=0.43, p=0.02). Subjects showed clear improvement of performance in each phase, with drops to indicate the presence of a perturbation (Figure 4.2). Performance was better in both Null phases, most likely due to the intuitive mapping. Therefore subjects were performing the task at a consistent level that was high enough to progress to the use of DC stimulation.

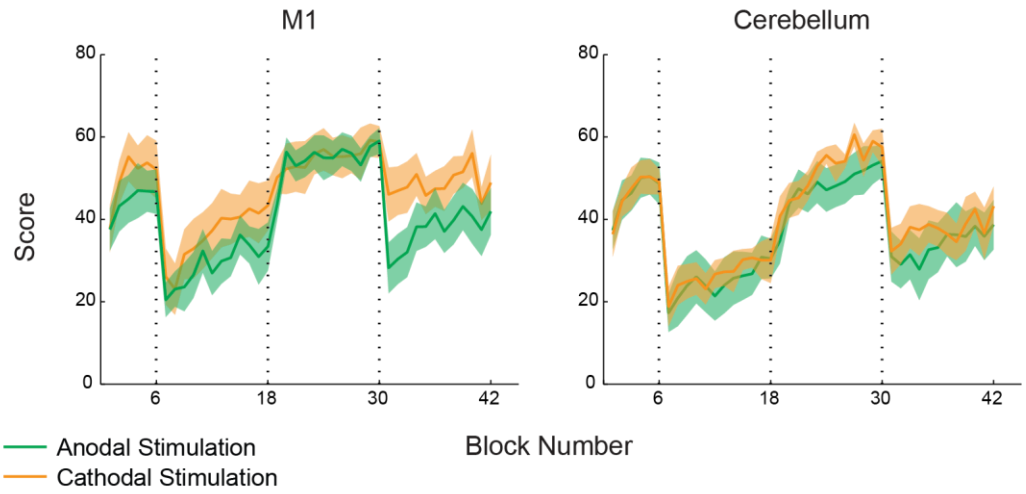


Figure 4.3 – Scores for all tDCS conditions

Scores follow a similar progression to those in the no stimulation condition (Figure 4.2). The scores for the M1 cathodal condition appear to be slightly higher that the M1 anodal condition during the Perturb phases, but this trend is not significant.

Average scores for all tasks were as follows: Anodal M1 stimulation - 40.9 ± 4.2, cathodal M1 stimulation - 47.1 ± 4.8, anodal cerebellar stimulation - 37.1 ± 4.3, and cathodal cerebellar stimulation - 39.9 ± 3.2.

In the cerebellar stimulation task, the scores matched each other closely throughout the task, but looking more closely at scores during individual phases in the M1 stimulation task, there appeared to be better performance in the Perturb phases in the cathodal stimulation condition (Figure 4.3). Scores averaged across both Perturb phases gave 33.2 ± 5.0 (anodal) and 42.4 ± 5.1 (cathodal) (unpaired t-test, $p=0.22$, $t(13)=1.29$). This difference was clearest at the beginning of the Perturb2 phase (blocks 31-32), but was also not significant (unpaired t-test, $p=0.07$, $t(13)=1.98$).

4.3.2 Experiment 4.1 - No stimulation

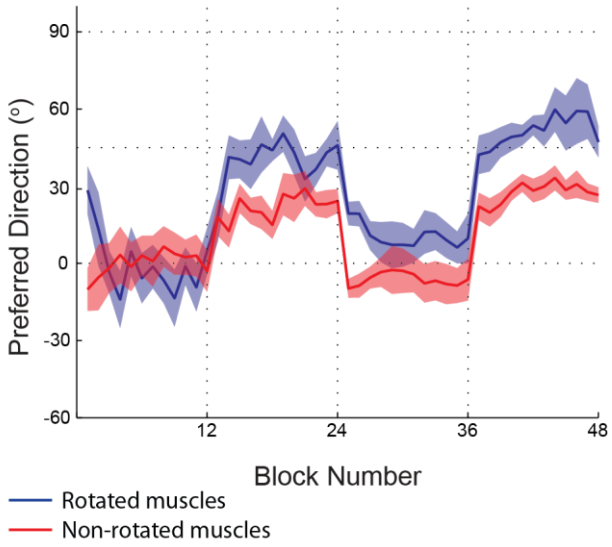


Figure 4.4 – No stimulation task: PD

For the first time there is evidence of a re-aiming strategy. During the Perturb phases, shifts in PD occur in both the rotated and the non-rotated muscles.

Both sets of muscles had an average PD close to 0 in the Null phase, with no differences between the two sets (-0.4 ± 3° for the (yet to be) rotated muscles and 1 ± 3° for the non-rotated muscles).

The most obvious effect from the PD (Figure 4.4) was the appearance of a re-aiming strategy. In the Perturb phases, there was a positive shift away from the DoA in the non-rotated muscles, suggesting that subjects were using a more global strategy. This was consistent across both phases, with the average PD in the Perturb phase being 40.0 ± 2.4° and 21.8 ± 2.4° and the average PD in the Perturb2 phase being 51.4 ± 2.3° and 27.4 ± 2.3° (rotated and non-rotated muscles).

The re-aiming effect extended to the Null2 phase, with average PDs of 10.7 ± 2.1° and -6.2 ± 2.2° (rotated and non-rotated muscles).

This effect can also be observed by looking at the RMI (Figure 4.5). For the Null phase the RMI remained constant at -0.08 ± 0.2 (calculated for the last half of the Null phase), shifting to 0.19 ± 0.06 during the Perturb phase. However, having reached this level, the

RMI changed very little during the final two phases, indicative of a global re-aiming strategy that was used throughout the task.

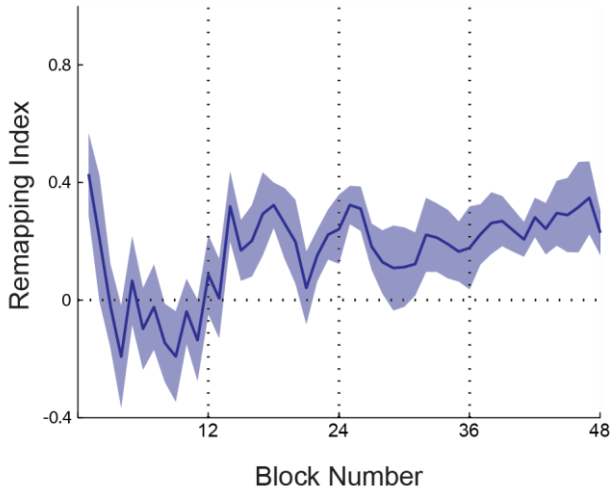


Figure 4.5 – No stimulation: RMI

RMI stays constant at an average value of 0.19 ± 0.06 from the first block of the Perturb phase to the end of the task.

The appearance of this effect in this experiment (as opposed those described in Chapter 3) was likely due to the use of an intuitive DoA mapping as the initial mapping for all subjects.

4.3.3 Experiment 4.2 - M1 stimulation

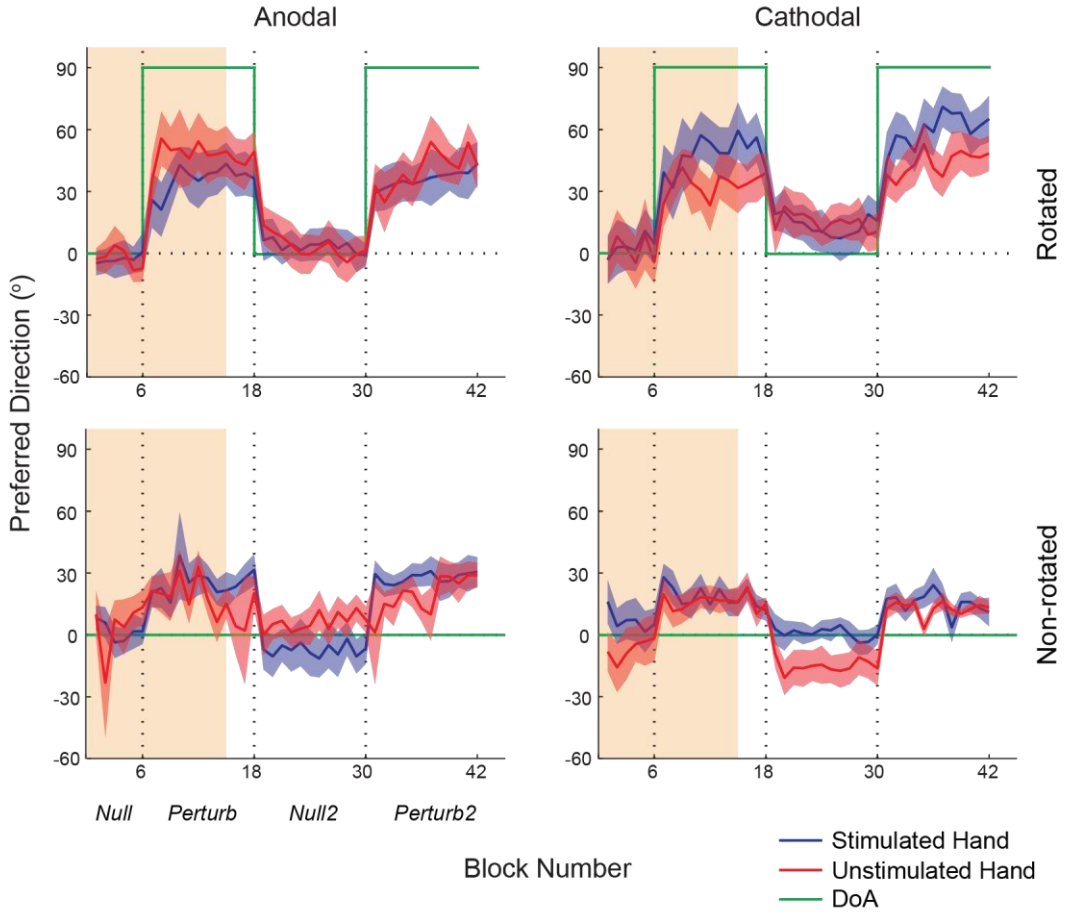


Figure 4.6 – M1 PD

Preferred direction of all subsets of muscles in the M1 stimulation task. The top line shows the rotated muscles, the bottom line the non-rotated while muscles in the anodal stimulation task are shown in the left hand column, and muscles in the cathodal stimulation task, the right hand column. DoA is represented by the green line and the match between the PD and DoA is a measure of the nature of the adaptation strategy, with a closer match being indicative of a strategy that is more local.

Under anodal stimulation, the PD of the unstimulated muscles (red line) matches to the DoA better than the PD of the stimulated muscles (blue line), while the reverse is true for cathodal stimulation.

The green line in Figure 4.6 shows the DoA of the rotated muscles during the task. The distance between the lines of PD and the line of DoA gives a measure of how local the adaptation strategy is. Starting with anodal stimulation, in the Perturb phase the PD of the rotated, stimulated muscles reached an average level of 42.5 ± 3.2°, while the rotated, unstimulated muscles reached an average value of 49.6 ± 3.2°. For the non-

rotated muscles, the stimulated and unstimulated values were 24.8 ± 3.3° and 11.0 ± 3.3°, respectively. Therefore, under anodal stimulation, the PDs of muscles in the unstimulated hand were closer to the actual DoA than in the stimulated hand. This implies that the adaptation strategy in the unstimulated hand better reflects the local structure of the perturbation.

The reverse was true for the cathodal stimulation, with average PD values of 48.5 ± 3.8° and 33.5 ± 3.9° for the rotated, stimulated and unstimulated muscles respectively and 18.4 ± 3.9° and 16.1 ± 3.8° for the non-rotated stimulated and unstimulated muscles. Under cathodal stimulation, the adaptation strategy in the stimulated hand better reflects the local structure of the perturbation.

Further insight can be obtained by looking at the RMI. Looking solely at the PD does not fully reflect the nature of the adaptation strategy, as the critical determinant of how well the system has adapted is not the absolute values of the PD, but how well the rotated and non-rotated muscles have separated, i.e. the extent to which remapping has occurred.

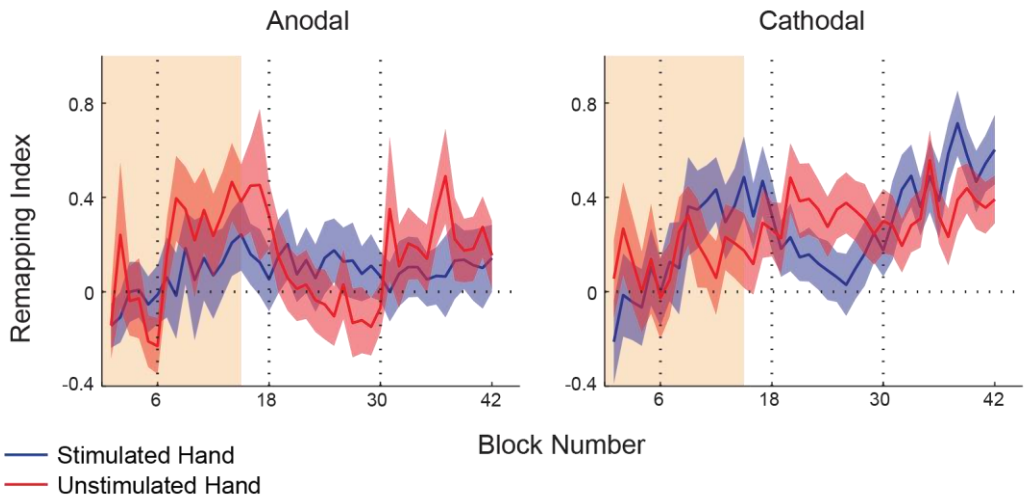


Figure 4.7 – M1 RMI

RMI for the anodal (left) and cathodal (right) stimulation of M1. RMI is given in Equation 2.9. A local remapping solution would be represented by an RMI of 0 in the Null phases, and a value of 1 in the Perturb phases. As such, under anodal stimulation the unstimulated hand shows a performance that is more local and the reverse is true for cathodal stimulation.

RMI for anodal and cathodal stimulation is shown in Figure 4.7. A value closer to 1 in the Perturb phases and closer to 0 during the Null phases indicates a more local adaptation strategy. In the Perturb phase under anodal stimulation, the stimulated hand had an average RMI of 0.18 ± 0.05, while the unstimulated hand had an RMI of 0.43 ± 0.06. In the same phase under cathodal stimulation, the stimulated hand had an average RMI of 0.33 ± 0.05 and the unstimulated hand a value of 0.19 ± 0.04. For the Null2 phase, the stimulated RMI value under anodal stimulation was 0.21 ± 0.04, and the unstimulated value was 0.05 ± 0.04, while for cathodal stimulation the stimulated value was 0.14 ± 0.04 and the unstimulated value was 0.35 ± 0.04.

Finally, in order to provide a single value for each hand, the PD values in the Null and Perturb phases were averaged and then used to calculate an RMI value for each set of phases. The difference between the two numbers is then a single measure of how local the adaptation strategy is for each hand. For anodal stimulation the stimulated value was -0.04 ± 0.08 and the unstimulated value was 0.31 ± 0.09. For cathodal stimulation the stimulated value was 0.27 ± 0.08 and the unstimulated value was -0.07 ± 0.09. These numbers are compared with the same values for no stimulation and cerebellar stimulation in Figure 4.10.

4.3.4 Experiment 4.3 – Cerebellar stimulation

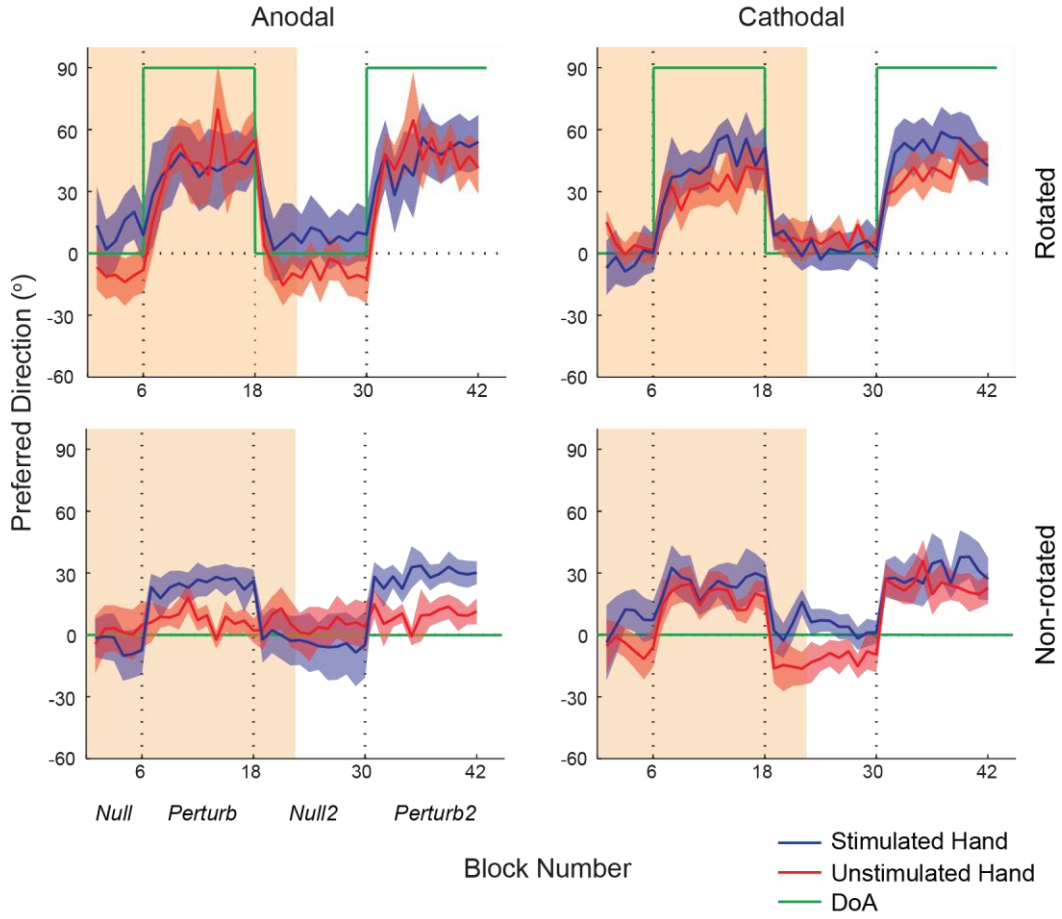


Figure 4.8 – Cerebellum PD

Preferred direction of all subsets of muscles in the cerebellar stimulation task. The top line shows the rotated muscles, the bottom line the non-rotated while muscles in the anodal stimulation task are shown in the left hand column, and muscles in the cathodal stimulation task, the right hand column. DoA is represented by the green line and the match between the PD and DoA is a measure of the nature of the adaptation strategy, with a closer match being indicative of a strategy that is more local.

Under anodal stimulation, the PD of the unstimulated muscles (red line) matches to the DoA better than the PD of the stimulated muscles (blue line), while the reverse is true for cathodal stimulation.

Again beginning with anodal stimulation, in the Perturb phase the PD of the rotated, stimulated muscles had an average value of 41.9 ± 4.9°, while the rotated, unstimulated muscles had an average value of 44.7 ± 4.9°. For the non-rotated muscles, the stimulated and unstimulated values were 24.5 ± 5.1° and 7.4 ± 4.9°, respectively.

Cathodal stimulation produced average PD values of 43.6 ± 3.5° and 33.0 ± 3.6° for the rotated, stimulated and unstimulated muscles respectively and 25.2 ± 3.6° and 19.0 ± 3.6° for the non-rotated stimulated and unstimulated muscles (Figure 4.8).

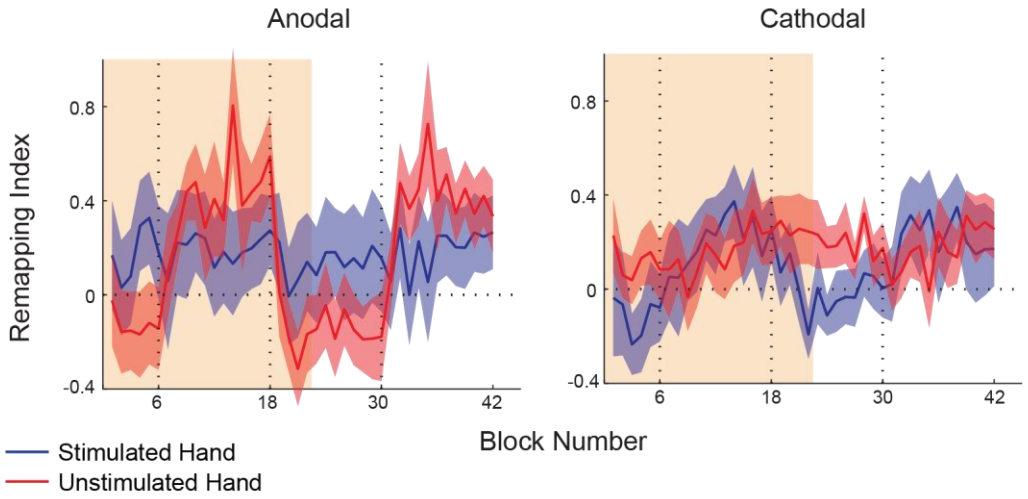


Figure 4.9 – Cerebellum RMI

RMI for the anodal (left) and cathodal (right) stimulation of M1. RMI is given in Equation 2.9. A local remapping solution would be represented by an RMI of 0 in the Null phases, and a value of 1 in the Perturb phases. As such, under anodal stimulation the unstimulated hand shows a performance that is more local and the reverse is true for cathodal stimulation.

RMI for anodal and cathodal stimulation is shown in Figure 4.9. In the Perturb phase under anodal stimulation, the stimulated hand had an average RMI of 0.19 ± 0.06, while the unstimulated hand had an RMI of 0.41 ± 0.06. In the same phase under cathodal stimulation, the stimulated hand had an average RMI of 0.2 ± 0.05 and the unstimulated hand a value of 0.16 ± 0.04. In the Null2 phase, the anodally stimulated value was 0.14 ± 0.06, and the unstimulated value was -0.15 ± 0.05, while for cathodal stimulation the stimulated value was -0.01 ± 0.04 and the unstimulated value was 0.22 ± 0.03.

For the RMI difference analysis, under anodal stimulation the stimulated value was 0.06 ± 0.12 and the unstimulated value was 0.56 ± 0.17. For cathodal stimulation the stimulated value was 0.22 ± 0.06 and the unstimulated value was -0.05 ± 0.09.

Cerebellar ipsilateral stimulation therefore has an effect that is similar to M1 contralateral stimulation, with the muscles in the unstimulated hand showing adaptation that reflects a strategy that is closer to the optimum under anodal stimulation, and the opposite effect under cathodal stimulation.

4.3.5 Analysis of RMI modulation over all conditions

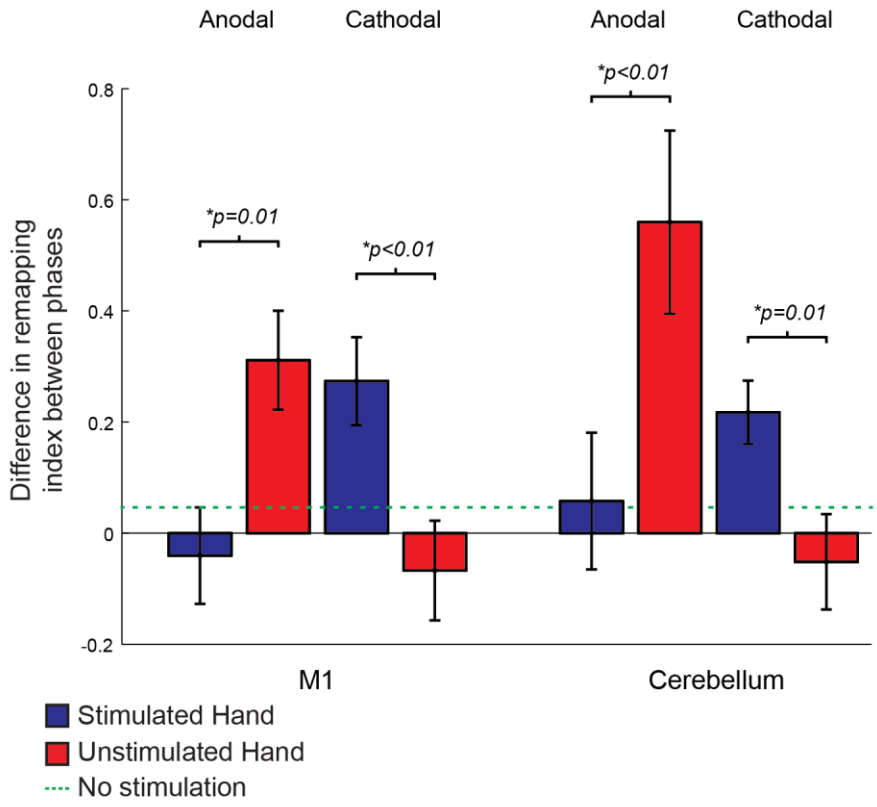


Figure 4.10 – Difference in RMI between Null and Perturb phases

Difference in RMI between phases gives a simple measure of whether the adaptation strategy is more global or local in nature; a higher value indicates a performance that is more local. The green line shows average RMI difference for the no stimulation task. In all the cases, the higher performing hand has a value greater than the no stimulation level, and all low performing hands have a value approximately equal the same. Error bars represent S.E.M, significances are paired t-tests.

In each condition, stimulation increased RMI modulation for one hand in a way that depended on the stimulus polarity. Under anodal stimulation, the RMI modulation in the unstimulated hand increased, while under cathodal stimulation the RMI modulation in

the stimulated hand increased. In all conditions, the hand with the greater RMI modulation also had a greater value than that for the no stimulation condition, with the other hand retaining a low value in a similar range to no stimulation (Figure 4.10).

Within each condition, RMI modulation in the stimulated and unstimulated hands was significantly separated. (M1: Anodal: $p=0.01$, $t(7)=3.29$, Cathodal: $p=0.008$, $t(6)=3.86$, Cerebellum: Anodal: $p=0.006$ $t(7)=3.88$, Cathodal: $p=0.01$, $t(6)=3.47$). ANOVA comparing mean RMI difference across stimulation target (M1, cerebellum) and stimulation polarity (anodal, cathodal) showed no significant difference for target ($f=2.27$, $p=0.14$) or target x polarity interaction ($f=3.39$, $p=0.08$), but a significant difference for polarity ($f=41.69$, $p<0.0001$).

4.4 Discussion

I predicted that anodal stimulation would have a facilitative effect on local remapping and cathodal stimulation would result in a sub-optimal solution being used. In fact the reverse was true, with the strategy in the stimulated hand being more global under anodal stimulation and more local under cathodal stimulation.

I was unable to dissociate M1 and the cerebellum in terms of their contributions to this process, with contralateral stimulation of M1 and ipsilateral stimulation of cerebellum under both polarities leading to the same effect on strategy use between the two hands.

4.4.1 Re-aiming is observed in a bimanual task with an intuitive initial mapping

One of the points raised in the previous chapter was that there was a lack of the global re-aiming strategy (as described in Chapter 2.3.2) observed in any of the experiments shown there. In experiment 3.4, I attempted to observe this strategy by using a timed version of the task, with some success. It was suggested there that use of an intuitive mapping as the initial muscle-DoA mapping in the task would be more likely to result in use of a clear re-aiming strategy, firstly as subjects are likely to have a preference to use muscles in a naturalistic way and secondly as during the initial mapping there is no opportunity to learn any non-naturalistic use of the muscles involved. Therefore when

the perturbation occurs, subjects are more likely to utilise the simplest available adaptation strategy.

Here I used an intuitive mapping consisting of wrist extension and flexion for the *y* axis, and 1DI and ADM for movement along the *x* axis. Subjects performed as expected, with a clear re-aiming solution observed in the Perturb phases.

I suggest that this is due to the lack of disassociation required in the initial phase. Since subjects are initially using the muscles in a relatively natural way, the change to a non-intuitive mapping presents a greater challenge and therefore subjects tend toward the simpler solutions, ones that do not require changing the current relationship between individual muscle uses.

Notably, subjects retained a re-aiming strategy during the Null2 phase, even though they were returning to an intuitive mapping. One possible explanation is that the structure of the necessary adaptation has overcome the naturalistic biases present in the mapping, and since the system has 'solved' the problem, there is no need to alter a successful solution. (Izawa et al., 2008) noted that adaptation to a perturbation is not necessarily a return to baseline, but a process of re-optimization, meaning that the system may have satisfied its conditions for optimal performance without requiring a return to the initial solution. However this is merely a suggestion and the exact reason for this is beyond the scope of this PhD (although it could potentially be investigated further by using a Within Hand rotation for the same task structure).

4.4.2 Anodal stimulation results in sub-optimal task performance in the stimulated hand

Anodal tDCS of both M1 and cerebellum resulted in an adaptation strategy for the stimulated hand that is more global, while cathodal stimulation causes more local remapping. In each condition, one hand showed an increased RMI modulation significantly above that in the control condition. In the other hand, RMI modulation levels stayed low or became negative. (A negative RMI difference is interesting in that it represents a higher level of remapping present in the Null2 phase than in the Perturb phases, exactly the opposite of what should be occurring – however, the negative levels

found here were all >-0.1, and therefore simply represent very little difference between phases).

Previous work and effort minimisation

In previous studies, anodal stimulation of M1 has been shown to have beneficial effects on motor tasks, having been used to improve performance in sequential finger movement tasks (Vines et al., 2006), visuomotor co-ordination tasks (Antal et al., 2004), and in the SRTT (Serial Reaction Time Task), a measure of implicit motor learning (Nitsche et al., 2003b). With regards to the cerebellum, multiple studies have shown anodal tDCS to have a facilitative effect on motor adaptation (Galea et al., 2011, Jayaram et al., 2012, Block and Celnik, 2013) . However in this case, anodal tDCS of both M1 and the cerebellum resulted in adaptation that was less beneficial for minimising effort.

Throughout this chapter I have looked at the extent to which subjects have used adaptation strategies along a spectrum ranging from fully global (no disassociation of muscle sets) to fully local (complete disassociation of muscle sets). If it is assumed that the cost function for this task is effort, and the focus of the system is to minimise this cost in order to reduce variability and improve task performance or minimise energy consumption, then the local remapping strategy is the optimal solution to the adaptation problem. Further to this, even if these assumptions are not true, then the local remapping solution can still be thought of as 'better' as the PDs match the DoAs. Under a global re-aiming strategy this is not the case.

The assumption of effort as the cost function is supported by the broad tuning functions exhibited by the active muscles in an MCI task (see Chapter 3 – Figure 3.6A). As detailed in Chapter 1.2.1 – Optimal Control and Cost Functions, there is evidence to support this interpretation of the task, but it should be stated that this assumption of the local solution as the optimum and the global solution as sub-optimal cannot be said to be definitive.

The effect on the error signal

The error signal drives adaptation. As discussed in Chapter 3, I hypothesized that a sub-optimal solution will compensate for that error, reducing the signal available to drive finding of the optimal solution and the ability to further explore the solution space. I suggest that in redundant tasks, increased cortical and cerebellar excitability induced by anodal tDCS may produce a sub-optimal adaptation strategy if errors generated by locally-varying perturbations are compensated for by global corrections. In other words, anodal stimulation may facilitate inappropriate learning by muscles that have not actually been perturbed. This explanation then fits with the studies mentioned previously, as in a task where there is no locally varying structure, anodal stimulation will result in improved learning/adaptation due to the lack of simple alternate strategies being available.

4.4.3 A symmetric effect exists between the stimulated and unstimulated hands

Stimulation increased the level of local remapping in one hand relative to the control condition (no stimulation). Small decreases in the level of local remapping were also observed in the other hand, although these decreases were not significant relative to control. However, this could be due to the use of an intuitive initial mapping as the basis for the task. This was useful in providing evidence of the re-aiming strategy, but it created an issue where the control condition showed an example of remapping modulation that was very low, meaning there was no room for a lower performance induced by stimulation. An interesting follow up to this work would be to run the same experiment with a non-intuitive initial mapping, hopefully giving a result for the control condition which showed a slightly greater level of remapping modulation (one that could be both improved on and reduced). However, based on the results of Experiment 3.4, this task structure might be difficult for subjects to perform to a useful standard.

This symmetry also explains the lack of a difference between scores for the anodal and cathodal conditions (Figure 4.3). If one hand is pushed towards a local remapping solution (and hence improves in performance due to the lessened signal-dependent noise), then the other hand will reflect a more global solution and provide a less positive contribution to overall performance. Since score represents the contribution of both

hands to performance, and there is no way of disassociating score to reflect stimulation locality, there would be no observed difference between scores for the two conditions.

Interhemispheric interaction

With previous work it has been difficult to ascertain a generalizable effect of anodal and cathodal tDCS on motor tasks. (Sohn et al., 2012) found a facilitative effect for the Jebsen-Taylor Hand Function Test of the non-dominant hand under anodal stimulation of M1, but no corresponding decrease in performance under cathodal stimulation. During the task presented here, stimulation of one hand resulted in the opposite effect on strategy modulation in the other, with this symmetric effect being present under all stimulation conditions. Further to this, the overall effect of remapping modulation (as shown in Figure 4.9) in the improved hand is an increase from the baseline defined in the no stimulation condition.

Modulating the excitability of one hemisphere can produce indirect excitability changes in the other via interhemispheric inhibition (Ferbert et al., 1992, Bloom and Hynd, 2005). There has been some work done on the effect on excitability changes in M1 on ipsilateral motor control, as it has potential applications for stroke rehabilitation. (McCambridge et al., 2011) found that cathodal stimulation improved selective muscle activation in the ipsilateral upper limb and (Kobayashi et al., 2004) demonstrated that reduction of the excitability of the ipsilateral M1 via 1Hz rTMS improved performance of sequential figure movements. Again, both studies reached conclusions that are in opposition to the effect described here, but do support the existence of motor effects arising from ipsilateral M1 stimulation.

Another possibility is that improvement in one hand reduces the error signal that drives learning in the other hand. Since the two hands are coupled in terms of task performance (i.e. using the same error signal to drive adaptation), then anodal stimulation resulting in lowered performance in the stimulated hand would induce adaptation driven by the error signal in the unstimulated hand and cathodal stimulation would result in the reverse. By this mechanism the symmetric effect would be achieved without the need for learning effects via interhemispheric interaction.

In terms of effects on both ipsilateral and contralateral control within the same task, as far as I am aware there have been no studies on the effect of single hemisphere tDCS on the performance of bimanual motor tasks in normal subjects. The same is true for studies of the effect of tDCS of the cerebellum on contralateral control.

4.4.4 Simple and Complex Tasks

In previous studies of the effect of tDCS on motor learning and adaptation, simpler task have been used, ones in which the simplest solution to acquire is the optimal solution. For example, hand movement coupled with an onscreen cursor the relationship between which is then perturbed (Mazzoni and Krakauer, 2006, Galea et al., 2011) or force field paradigms in which the movement of the arm along a straight line is perturbed using a manipulandum (Hunter et al., 2009). Both of these fall under what I have defined as global perturbations, i.e. the perturbation affects all of the relevant effectors in the same way. In terms of the hierarchy discussed in Chapter 3, tasks that require adaptation of more global parameters (e.g. how groups of muscles, such as a limb, relate to each other) are easier to adapt to than tasks that require adaptation of more local parameters (e.g. how individual muscles relate to each other). In the task used here, multiple solutions exist, with the more global solution being sub-optimal. The fact that anodal stimulation did not have a facilitative effect suggests that increased excitability in the motor cortex is not necessarily universally beneficial.

Further to this, (Ganesh and Burdet, 2013) suggested that the simple tasks that have been the basis of the majority of motor learning and adaptation research have potentially created biases towards theories and models that may not necessarily explain more complex behaviour, i.e. motor tasks with multiple solutions. The results here appear to support this, with a task with multiple solutions responding to tDCS in a way that does not fit with other work.

It should be noted that although the task used in this chapter is ‘more complex’ in the sense that it provides multiple successful solutions, it nonetheless does have a clear optimal solution, whereas tasks approximating true complex motor behaviour would have multiple optimal solutions (Ganesh et al., 2010). Tasks such as ball-catching (Cesqui et al., 2012) and skittles (Muller and Sternad, 2004) have been studied with this

in mind, but the analysis is difficult due to the high task complexity. The task used here has the benefit of direct control over each of the effectors involved (in terms of both defining how they are supposed to act and recording how they actually act), eliminating the need for sophisticated biomechanical modelling.

4.4.5 A consistent effect between M1 and the Cerebellum

As discussed in the introduction, M1 and the cerebellum are thought to be involved in different aspects of the adaptation process. The consistent response between them here suggests that increased excitability causes suboptimal performance at different levels of the adaptive process. However, is difficult to disassociate the processes of adaptation and retention when the measure of performance is strategy use. The different contributions of M1 and the cerebellum to motor tasks involving local structure are investigated further in Chapter 5.

4.4.6 Experimental Design

There is a particular strength to this experimental design in that with this task, there exists the ability to look at the effect of stimulation within single subjects by utilising a bimanual setup. This makes the task particularly powerful, as there can be a significant amount of variation between individuals as to how tDCS affects them (Datta et al., 2012). By having a measure that compares within subjects, during the same task, this issue is partly avoided

Critically, the metric studied is not the error reduction itself, but the way in which that error reduction occurs. That is, remapping is not a measure of the success of adaptation, but the form that that adaptation has taken. Therefore, the use of error reduction and retention as means of analysis in this experiment is not useful, as both are reflective of adaptation taking place, not the nature of the adaptation itself. In fact, the structure of the experiment makes looking directly at error reduction difficult, as both score and error show the cumulative contribution of both hands (stimulated and un-stimulated). Subjects' success at performing the task is therefore not affected by stimulation, and as

the point of the experiment is to show strategic differences between limbs in a single subject, the relevant metric is optimality of each involved hand.

Although this appears to be a disadvantage, part of the strength of the experiment lies in the fact that the comparison takes place in a single subject during a single task. The experiment could have been designed to be done twice, once with anodal stimulation, and once with either cathodal or no stimulation, but in this scenario the second task would be identical to the first, losing the naivety that is inherent in the structure presented here. It is also not necessarily true that performance would provide a more useful measure. Performance is a reflection of optimality, and it is possible that the effect is too subtle to be picked up properly by score/error.

Finally, the null condition here (the no stimulation task) was simply the task without tDCS, as opposed to the more traditional sham tDCS that is generally used as a null condition in DC(Nitsche et al., 2008). The lack of a sham stimulation condition could be perceived as an issue, but the focus of the study means that this is not true. Since the comparison between no stimulation and anodal or cathodal is not used as part of the statistical assessment in this study, the question of the null condition being no stimulation or sham becomes essentially moot. The choice to compare anodal vs cathodal directly as the main body of the experiment stemmed from not knowing whether DCS would have any effect at all, and therefore looking at the comparison most likely to reveal an effect. As a result, the question asked by this study is 'Does stimulation of M1/the cerebellum result in a behavioural effect?' as opposed to 'Is this effect attributable to anodal or cathodal stimulation specifically?'. Based on the result shown by no stimulation, it is likely that the answer to the second question is no, but this could be definitively answered in a further study utilising a sham stimulation condition. (This argument also applies to some of the experiments described in Chapter 5).

It is an assumption inherent in this experiment that anodal and cathodal tDCS will have directly opposing effects, an assumption that remains to be verified in this task. (Stagg et al., 2009) showed that the neurochemical response to cathodal and anodal tDCS in M1 is not a simple case of exact opposition, indicating that the effects of each may not be so simple. However, it is demonstrably true that the two polarities of current do increase/decrease excitability (Nitsche and Paulus, 2000), and how this translates into

effects on adaptation may depend on the subtlety of the effect being studied. The assumption here is borne out by the results in that anodal and cathodal tDCS do result in opposing effects, with the no stimulation condition effectively sitting in the middle.

4.5 Conclusions

- Anodal tDCS of both M1 and the cerebellum has been previously suggested to have a facilitative effect on motor tasks. Here, I found that anodal stimulation of one hand in a bimanual task pushed that hand towards a sub-optimal solution, with the reverse observed under cathodal stimulation.

- I suggest that previously described facilitation was a result of reinforcement of appropriate learning and will not necessarily arise in more complex tasks where the optimal solution has not been located, the example here being an adaptive task where the optimal solution is not the simplest solution to find.

- I was unable to disassociate the contributions of M1 and the cerebellum to strategy use in this task, with stimulation resulting in the same qualitative effects on performance. This suggests that both areas contribute to the process of strategy selection.

CHAPTER 5 - THE EFFECT OF PERTURBATION STRUCTURE ON THE NATURE OF ADAPTATION

In which I look at a series of experiments designed to investigate the effect of perturbation structure on current and future adaptation. Differing forms of adaptation depending on structure would indicate that current structure determines the nature of the adaptation used, while previous perturbation structure biasing future adaptation would indicate that structural learning effects are present.

5.1 Introduction

5.1.1 Modular learning

Adaptation to perturbations is often explained by alteration of a single internal model over multiple time-scales in response to movement errors (Kawato, 1999, Tin and Poon, 2005). These changes are revealed by after-effects once the perturbation is removed, as well as spontaneous recovery if feedback is subsequently withheld (Rescorla, 2004, Smith et al., 2006). However, under many circumstances learning occurs without interference with previously learned behaviour, suggesting multiple internal models can be acquired and updated in a modular fashion according to the context in which errors occur. The factors that determine how novel tasks are dealt with in terms of internal models are currently unknown (Miall, 2002). In order to understand how different individual models can be recalled it is important to investigate the contexts in which alteration and formation occur (Gandolfo et al., 1996, Cothros et al., 2009, Shadmehr et al., 2010).

In this chapter I aim to look at the effect of perturbation structure on the nature of the learning taking place, and if there is any difference arising from global and local rotations in terms of how the perturbation is adapted to.

5.1.2 Structural learning

The concept of structural learning was discussed in Chapter 1.2.1. To recap, it is the idea that the underlying structure of prior learning can be generalized and used to facilitate future learning that shares that common structure. (Braun et al., 2009) discussed several key features of structural learning; facilitation of learning of tasks with a shared structure, biased learning towards previously learned structural features and reduced interference when switching between tasks requiring opposing motor strategies. These features can be used to determine whether structural learning has taken place.

In this chapter I explore this concept in terms of an abstract MCI task, with the common structure being local and global perturbations. The aim was firstly to investigate whether these kinds of tasks were able to be generalized by subjects and if that proved successful to see whether it was possible to determine limits on task features that could be utilized in order to facilitate later learning.

5.2 Experiment 5.1: Structural and Modular Learning

5.2.1 Methods

The basic setup of the experiment was the single hand MCI task described in Chapter 2.2.1 - Rotation task.

The task was divided into six phases of 96 trials consisting of the original mapping (A), the first rotated mapping (B) and the second rotated mapping (C) with the ordering ABABAC. This meant that there were three phase transition types occurring within a single condition, from phase A to phase B (A→B), phase B to phase A (B→A) and from phase A to phase C (A→C).

Twelve subjects (7 male, ages 20-22) performed two conditions. In the first, the initial perturbation (A→B) had a global structure whilst in the second that perturbation had a local structure. The final perturbation, A→C, was always a global rotation, rotated in the opposite direction to A→B. Experimental structure for both conditions is shown in Figure 5.1.

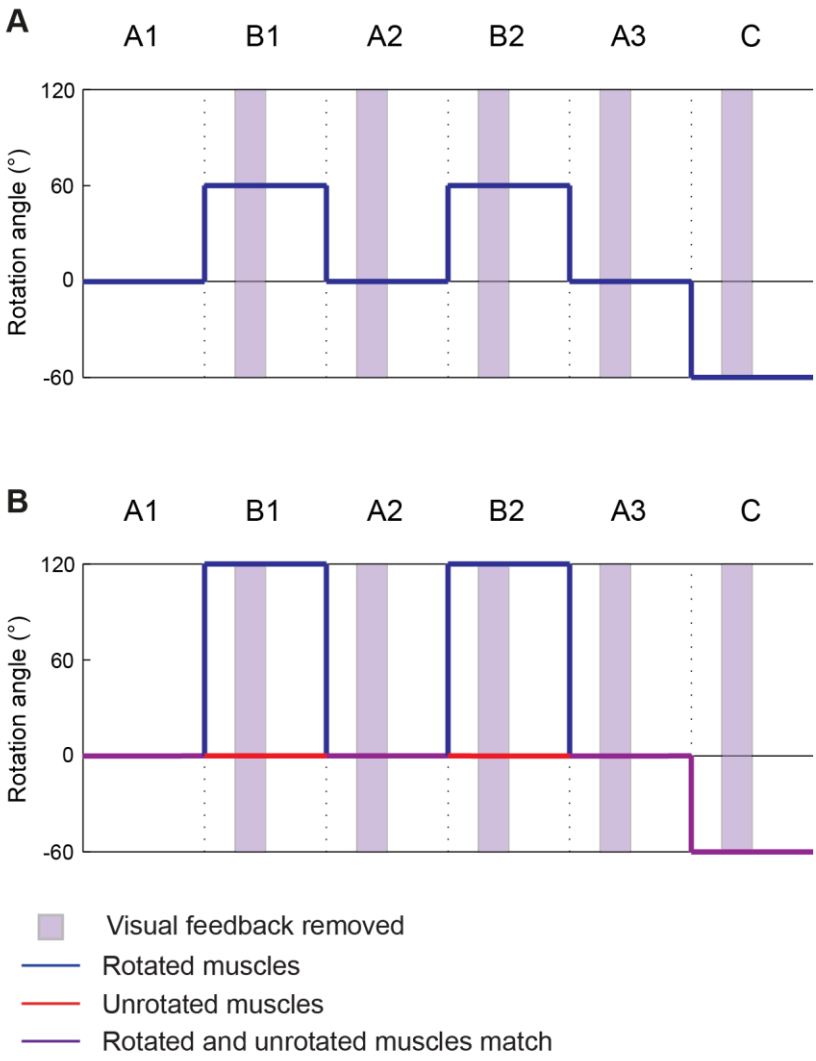


Figure 5.1 – Experimental structure for 5.1

A: The perturbation A→B is a global rotation and the perturbation A→C is a further global rotation, but in the opposite direction.

B: The perturbation A→B is a local rotation, and the perturbation A→C is a global rotation in the opposite direction.

Subjects were counterbalanced for the condition completed first and the direction of rotations. All initial muscle-DoA mappings were randomised.

In this chapter I also introduce the use of error clamp trials (Criscimagna-Hemminger and Shadmehr, 2008, Huang et al., 2011), in order to probe the state of the feed-forward component of the internal model. Error clamping involves removing the visual feedback of a task, thus removing the ability to update the internal model based on visual

feedback. For the experiments in 5.1, during blocks 3 and 4 of each phase (excepting the initial learning phase) the visual feedback of the cursor was removed as soon as subjects left the trial starting zone. The target position was the only available visual information. These blocks are referred to in the text as no-visual-feedback (NVF) blocks. Scores were recorded for these trials, but subjects did not receive score feedback. All other trial specifications (timing, pseudorandom target positioning etc.) remained the same.

Predictions

Spontaneous recovery of an adapted state when visual feedback is removed is indicative of an adapted internal model as it is a result of continuous learning processes that retain information throughout the perturbation and the return to the initial state. Our prediction is that modular learning would result in the formation of a new internal model following adaptation, meaning that the original can be recalled if necessary. Evidence for modular learning would therefore be revealed by the absence of spontaneous recovery of the adapted PD structure during the NVF blocks.

In terms of structural learning, learning a given structure for a perturbation would lead to generalisation of that structure. Therefore, when presented with a new perturbation, the initial response should be to attempt to solve the perturbation using the generalised structure. In phase C, I predict that in the global condition subjects will tend towards a global solution and that in the local condition a local solution will be used. Evidence for this outcome would then be improved performance in phase C in the global condition, both in terms of score and PD, and a separation of PDs during phase C in the local condition, with the unrotated muscles staying closer to zero.

5.2.2 Results

Behavioural data

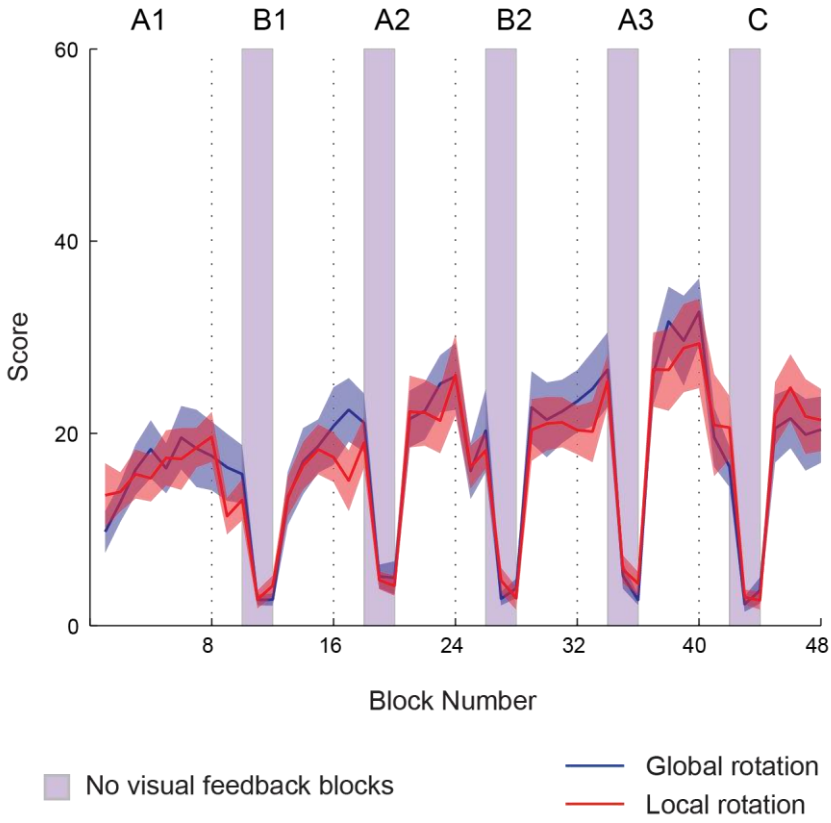


Figure 5.2 – Scores for Experiment 5.1A

Subjects show gradual improvement over time. The scores for the global and local conditions show little difference throughout the task.

The scores for the two conditions showed comparable patterns, with gradual improvements in performance over time while adapting to the A and B phases (with slight drops when changing phases), and a drop in performance in phase C (Figure 5.2). During the NVF trials the score almost dropped to zero, although this was expected due to the lack of the error signal.

Score is not a useful measure for gauging spontaneous recovery as we cannot differentiate between a low score due to lack of feedback vs. recovery of an inappropriate adapted state. Since score only provides a value greater than zero when

the cursor is in target, it cannot be used to look at a graduated effect. Therefore little can be said regarding modular learning based on the score alone.

Trial scores also failed to demonstrate an effect produced by structural learning. If the global rotation is being generalised in phase C, then the expectation is a higher score for the condition in which all perturbations are global, as opposed to the local rotation conditions. However, no significant difference was seen between the two. (Average score over first two blocks of phase C: 18.1 ± 2.1 (global), 20.8 ± 4.0 (local), p=0.6, t(11)=0.54).

There are two possibilities that explain the lack of effect observed in the trial score. Either no effect is present, or trial score is not a sensitive enough measure to pick up any differences. A more likely measure in which to see an effect is the PD.

PD

Global rotation condition

In phase B1 for the global rotation (Figure 5.3), the expected shift towards 60° was observed, although the PD didn't quite reach the DoA in the two blocks before the NVF period, peaking at 55.3 ± 5.8°. In the NVF period the PD sharply moved towards 0° (average value of 18.2 ± 15.7° for the NVF blocks) before rising towards the DoA once the visual feedback was returned (56.3 ± 5.1°). A similar pattern was seen in phase B2, with the PD not quite reaching the DoA initially (57.1 ± 6.3°), returning towards 0 (16.8 ±14.8°), then rising again to 50.7 ± 3.2 (again not matching the DoA).

Due to the lack of visual feedback, the standard error in the NVF blocks is large.

In phases A2 and A3, the PD quickly returned to zero after the perturbation, and did not shift during the NVF period. A small spike of 9.5 ± 17.2° was observed in the first NVF block in phase A2, but was not significantly separated from 0 (p=0.59, t(11)=0.55).

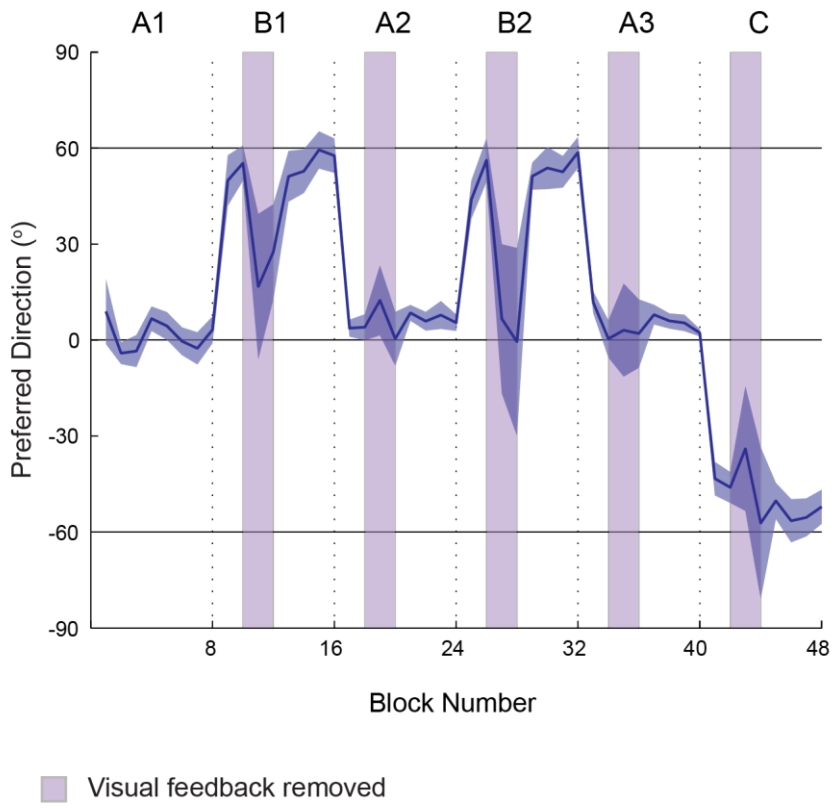


Figure 5.3 – PD in global condition

In the A and B phases PD shifts to the correct DoA within the first two blocks of the phase. During the NVF blocks in the B phases, the PD shifts towards the A state. During block C the PD takes longer to reach the correct DoA and shifts slightly towards the A state during the NVF blocks.

In the first two blocks of phase C, the PD moved towards the DoA without reaching it (-44.6 ± 2.0°), similar to the B phases. In the NVF period, the PD spiked towards 0 (-17.8 ± 18.3°), before finally reaching an average value of -52.9 ± 2.4° when the visual feedback was returned.

Local rotation condition

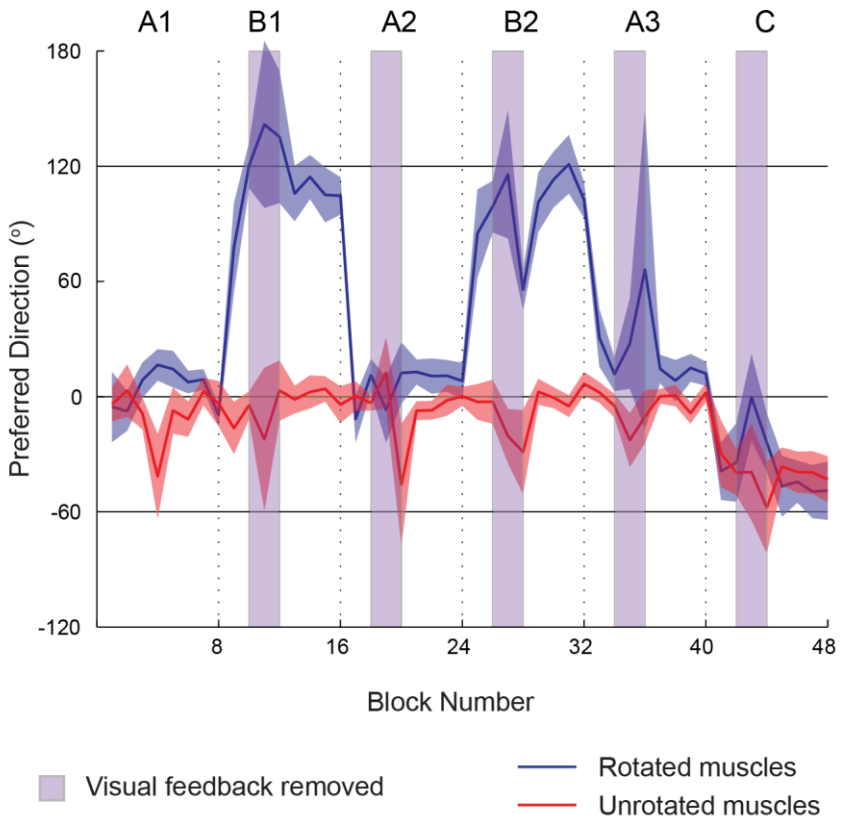


Figure 5.4 - PD in Local condition

PD of the rotated muscles quickly shifts to match the DoA after the perturbations. There is no evidence of spontaneous recovery during the NVF blocks. In phase C, both muscles sets move to match the DoA, and there is no separation between the two.

The rotated muscles showed a shift in PD towards 120° during phases B1 and B2, while the non-rotated muscles remained close to 0° degrees (Figure 5.4). During the NVF periods in all A and B phases, there was no significant deviation from the DoA in either the rotated or the non-rotated muscles. (One notable point is block 36, where the rotated muscles appeared to shift towards the previous state DoA. The mean value for this block was 66 ± 82°, and it was not significantly separated from 0 ($p=0.91$, $t(11)=0.12$)).

In phase C, both groups of muscles underwent a full rotation (here they will continue to be referred to as rotated and non-rotated muscles with respect to their previous perturbation). The rotated muscles reached -36.6 ± 13.9 in the two blocks following the

perturbation, whilst the non-rotated muscles reached -34.7 ± 12.1. In the NVF period, the rotated muscles spiked back towards 0° before reaching a consistent level of -47.4 ± 12.1 for the last blocks of the phase. The non-rotated muscles spiked slightly in the opposite direction during the NVF period, reaching an average PD of -48.5 ± 14.3 before settling at -39.6 ± 11.8 during the final blocks.

Comparison of global and local conditions in phase C

Directly comparing the average PD reached during the first two blocks of phase C, the PD reached in the global condition was higher than that in the local condition, but this difference was not significant (global: -44.6 ± 2.0°, local: -35.8 ± 9.0, $p=0.27$, $t(11)=1.16$). This relationship continued into the final four blocks of the phase (global: -53.6 ± 2.4, local: -43.0 ± 9.7, $p=0.18$, $t(11)=1.42$).

5.2.3 Discussion

Summary of key features

- During the phase B NVF blocks under the global rotation, the PD moved towards the previous state. Under the local rotation this did not occur.
- Under the global rotation in phase C, muscles that had previously experienced the same structure reached a greater PD than those that had previously experienced a local structure, but this difference was not significant. In both conditions the rotated muscles spiked towards their previous state when visual feedback was removed.
- There was no difference between previously rotated and unrotated muscles in the local condition when both underwent a global rotation.

Evidence for modular learning of local perturbations

Looking solely at the NVF blocks in the B phases, the differing nature of the PD shifts between the global and local perturbations is interesting in that shifts towards the original mapping (A) were present under global conditions, but not local conditions.

This indicates that there is a difference in how the two structures are adapted to, spontaneous recovery of the adapted state being a hallmark of adaptation. This is further investigated in the following experiment; 5.2.

No evidence of structural learning

There was no evidence of structural learning of the global rotation, with similar performances observed in phase C in both conditions. There are two possible reasons for this. The first being that no structural learning took place and the second that structural learning did take place, but the effect was not strong enough to be significantly separated from subjects experiencing a global rotation following a local rotation. This could be because it is easier to use two previously disassociated groups of muscles together than it is to separate out a single group. Therefore it would be beneficial to repeat this experiment with a local structure in phase C and determine whether previously experiencing a local rotation is beneficial for repetition of the same structure.

Further to this, it is possible that the structure of this task was overly complex. By attempting to look at two effects within a single task, evidence that would have supported either hypothesis could have been obscured. In terms of structural learning, the addition of the NVF blocks, and hence the disruption of feedback mediated learning of the nature of the perturbation structure may have affected the observation of a score/PD progression in phase C that would differ between conditions. Any repetition of this experiment should consider structural and modular learning separately.

A further consideration is that the time spent on the initial structure was not long enough for its structural features to be learned. For example, participants in a prism adaptation experiment received training over multiple weeks in order to produce structural learning effects (Roller et al., 2001), and subjects performing simple visuomotor perturbations during a reaching task had a training period of 800 trials after which structural learning effects were observed (Braun et al., 2009). In addition to this, in previous structural learning work, it has been shown that learning along the structure is necessary for structural learning to be achieved. For example, the structural feature of

a rotation can be learned via exposure to rotations of varying angles i.e. the invariance between different contexts is the key feature of learning (Braun et al., 2009).

5.2.4 Conclusion

To summarise this section, there was evidence present for modular adaptation occurring under local conditions and classic adaptation occurring under global conditions, but neither of these effects were conclusive in their existence, most likely due to issues with the experimental design. Therefore, the aim in the next section was to design a simpler experiment in order to investigate the nature of global and local adaptation further, and their relationship to brain areas involved in those processes.

5.3 Experiment 5.2: Classic Adaptation vs. Modular Adaptation

Motivation

As discussed at the beginning of this chapter, the factors that determine whether learning proceeds via adaptation of an existing model or the creation of a new one remain unclear. Given the inconclusive results of the preceding work, the experiments in this section were designed to look specifically at this question. Further to this, I used tDCS in order to investigate the brain areas responsible for these processes.

As such, the experiments described here combine brain stimulation and error clamping. This is of particular interest as it was highlighted in (Galea et al., 2011) that a task fully centred on error-dependent learning could mask adaptation effects arising from brain stimulation. In this task, by introducing trials where the visual feedback is removed, those effects can be potentially be revealed.

5.3.1 Methods

Two experiments were completed.

5.2A. The difference between local and global perturbations – does perturbation structure effect the nature of the adaptation?

5.2B. tDCS of the motor cortex or cerebellum during adaptation to local and global perturbations

All experiments followed the same basic task structure – similar to that described in Chapter 2.2. (unimanual rotation task)

The task consisted of three phases. In the first (Learn), subjects were presented with a randomised mapping of six muscles for 96 trials. In the second (Adapt), this mapping was perturbed, again for 96 trials. In the final phase (Probe), subjects alternated between 24 trial (2 blocks) groups of either normal trials or removed visual feedback of cursor position once it had left the central position. Experimental structure is shown in Figure 5.5.

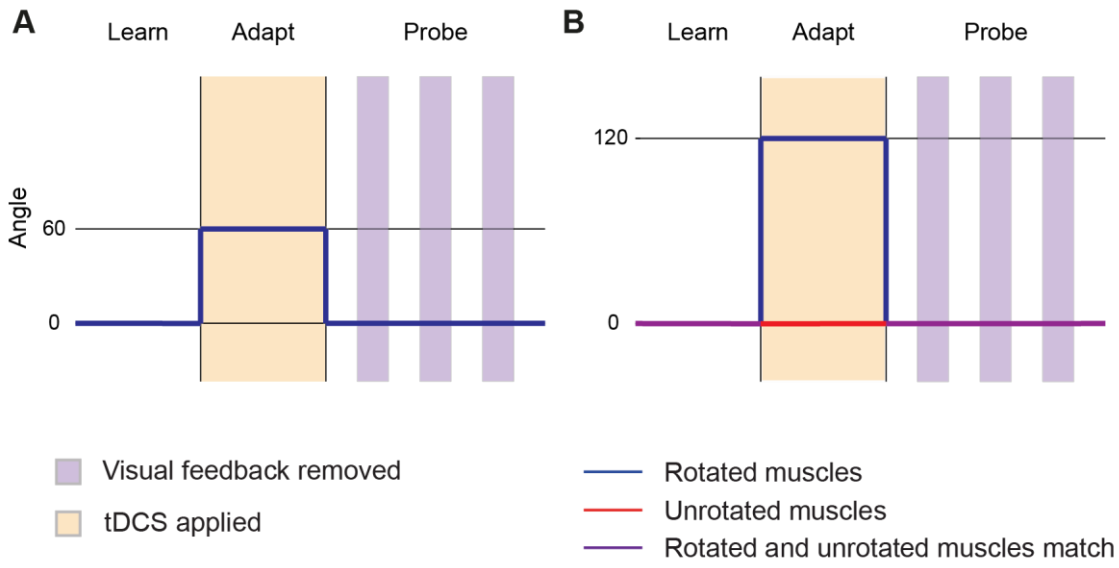


Figure 5.5 – Experimental structure for 5.2

A: A global rotation in the Adapt phase was followed by a return to the initial mapping.

B: A local rotation during the Adapt phase was followed by a return to the initial mapping

In both conditions the Probe phase consisted of alternating 2-block groups of visual feedback being given or withheld.

In order to make reasonable conclusions regarding the adaptation effects, subjects were required to reach a minimum average score to be included in the analysis. This was set

as an average score of 10 for each condition. Subjects excluded due to poor performance are noted in the relevant sections for each experiment.

5.3.2 Experiment 5.2A: Motivation and Methods

Prediction

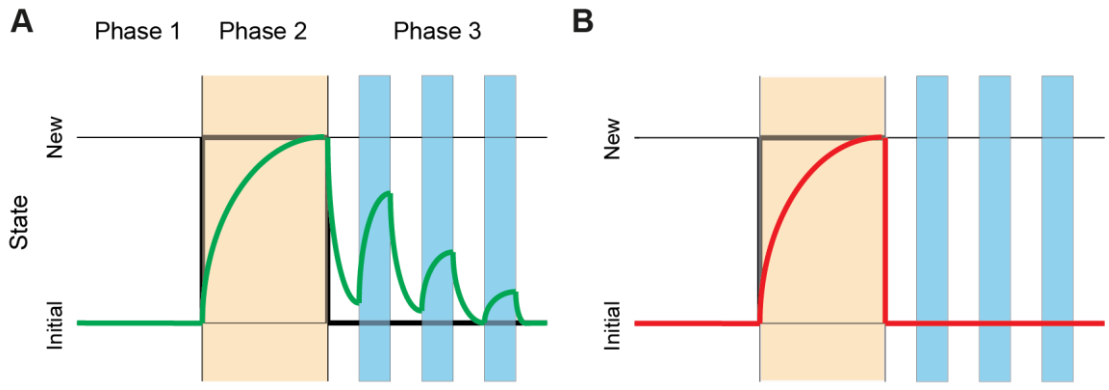


Figure 5.6 – Classic and Modular adaptation

A: Upon a return to the original mapping after classic adaptation (alteration of a single internal model), a persistent after-effect will be present that is gradually reduced over time. When visual feedback is removed, the system will return towards the perturbed state, due to the interaction of multiple adaptive processes acting on different timescales.

B: Under modular adaptation (creation of a new internal model), no after-effect will be present and spontaneous recovery of an adapted state will not be observed.

There are two possible outcomes I expect to observe in this experiment. The first is an example of classic adaptation, determined by the presence of an after-effect upon the return to the initial mapping in the Probe phase, and spontaneous recovery of the adapted state in the NVF groups within the Probe phase. (Figure 5.6A)

The second is what I will refer to as modular adaptation, indicated by the absence of the two effects present in classical adaptation to this particular task (Figure 5.6B). This arises due to switching between internal models.

Methods

Seven naïve, right handed subjects (4 male, ages 20-38) completed a global rotation and a local rotation in a single session. Subjects were counterbalanced for the rotation completed first, the direction of rotation and the placing of the DoAs.

1 subject was excluded from both conditions due to poor performance.

5.3.3 Experiment 5.2A: Results

Behavioural data

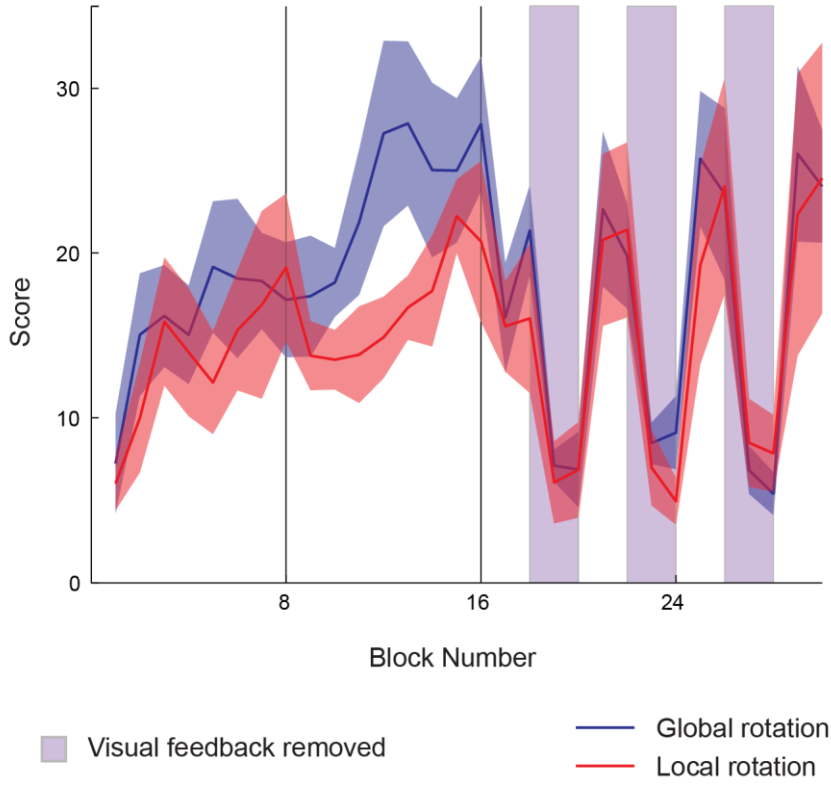


Figure 5.7 – Scores for the global and local rotation conditions

During the Adapt phase there was improved performance in the global condition over the local condition, although this difference was not significant. There was no separation of performance during the Probe phase.

Figure 5.7 shows the score progression for the global and local conditions. Average scores were 18.0 ± 2.6 and 14.9 ± 2.9 for the global and local conditions respectively. The two scores remained at a similar level to each other during the Learn phase, but during the Adapt phase the score for the global condition increased at a greater rate over the first half of the phase, although this difference was not significant (global: 2.6 ± 0.9, local: 0.73 ± 0.56, $p=0.07$, $t(5)=2.27$). A greater drop in score between the Adapt and Probe phases under the global condition was also observed (-11.8 ± 3.1 and -5.2 ± 6.7 for the global and local conditions respectively). This difference was not significant ($p=0.38$, $t(5)=0.97$). No further differences were observed during the Probe phase.

PD

With regards to the PD (Figure 5.8A), in block 17 of the global rotation (the beginning of the Probe phase, in which the original mapping is restored) there was an average PD of 14.1 ± 7.5°. In the same block of the local rotation (Figure 5.8B), the average PD of the rotated muscles was -6.3 ± 8.7°, with the overall average PD being -3.6 ± 7.6°. This indicates the presence of an after-effect in the global rotation that is not present in the local rotation ($p=0.01$, $t(5)=3.89$).

The average PD for the global rotation for block 19 (the first block of trials with removed visual feedback) was 32.4 ± 12.1°, significantly greater than zero ($p=0.04$, $t(5)=2.81$). For the local rotation this value was -21.3 ± 28.7° for the rotated muscles and -6.7 ± 10.8° for the non-rotated muscles, neither of which were significantly separated from zero ($p=0.68$, $t(5)=0.43$ and $p=0.35$, $t(5)=1.02$ respectively). In the subsequent periods of removed visual feedback, the average PD for the global rotation gradually decreased, in line with the prediction of classic adaptation (Figure 5.6A). During the NVF blocks of the local rotation there was no such recovery of the adapted state in the rotated muscles, with negative spikes in PD in the first two NVF groups. The unrotated muscles showed positive PD shifts in the final blocks of each NVF group. None of these shifts were significantly separated from 0. Even though these shifts were present, they are not representative of spontaneous recovery of the adapted state – if they are real effects, then there are other processes at work. As a result, there is evidence of spontaneous recovery when the rotation is global, while this is not present for the local rotation.

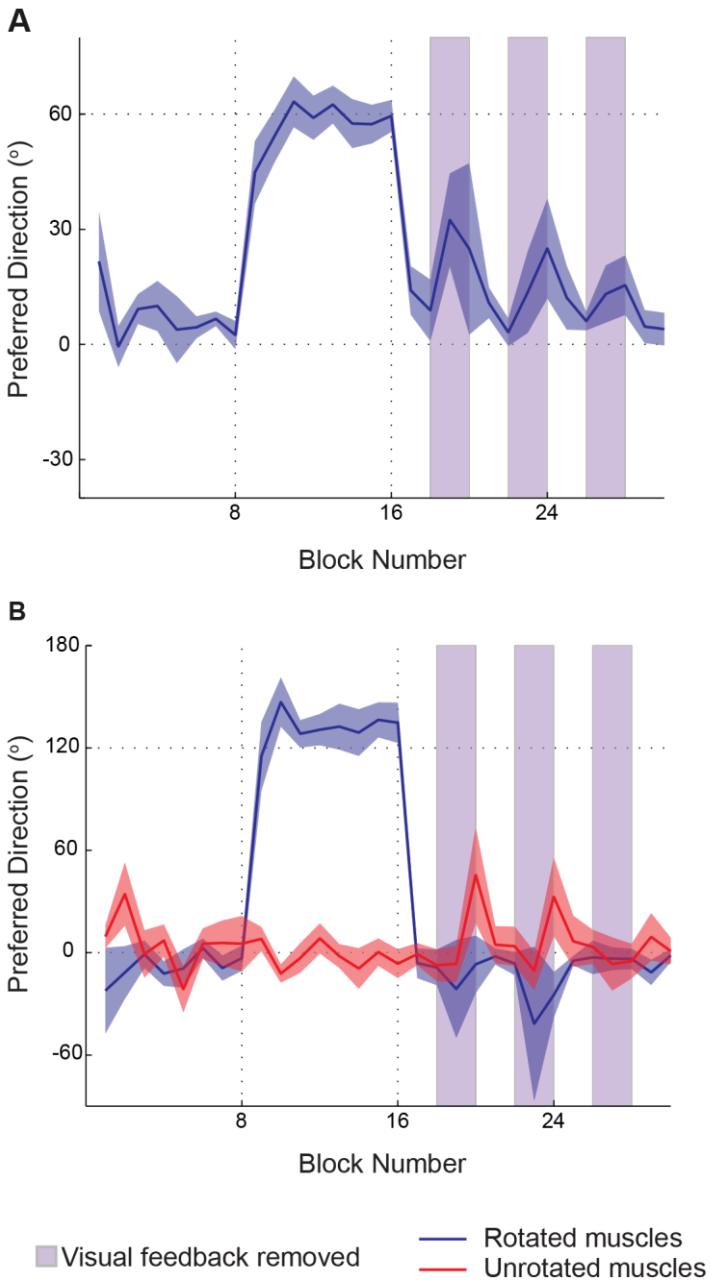


Figure 5.8 – PD under global and local perturbations

A: Global perturbation. The PD moves to match the DoA during the Adapt phase and there is evidence of an after-effect and spontaneous recovery during the NVF blocks in the Probe phase.

B: Local perturbation. PD quickly matches the DoA during the Adapt phase. No after-effect is present, and there is no evidence of spontaneous recovery of the adapted state.

5.3.4 Experiment 5.2B: Motivation and Methods

Motivation

Given that in experiment 5.2A I described two tasks that result in different forms of adaptation, the continuation of the work was to investigate the brain areas that may be involved in these processes. It was discussed in Chapter 1.2.1 – tDCS and the Motor Cortex, how M1 stimulation has resulted in enhanced after-effects in tasks that would be considered classic adaptation (Galea et al., 2011), and in Chapter 1.2.2 – The Cerebellum and Motor Adaptation, that the cerebellum has been theorised to be heavily involved both in the creation of internal models (Ito, 2008) and error reduction during adaptation tasks (Diedrichsen et al., 2005, Tseng et al., 2007). (Imamizu et al., 2004) also linked cerebellar activation to both the creation and modular switching of internal models.

In terms of the effect on PD, if the two learning mechanisms rely on different brain areas, we would expect to observe different effects arising from tDCS depending on whether M1 or the cerebellum has been stimulated.

Methods

Thirty-three naïve, right handed subjects (17 male, ages 20-45) completed two sessions in which they either completed global or local rotations (the second session being the same form of rotation as the first, with a different initial muscle-DoA mapping). All initial mappings used the same muscles as given in Table 2.1 for a unimanual experiment, and were randomised.

Subjects received DC stimulation of either contralateral M1 or the ipsilateral cerebellum (again, consistent between the two sessions) during the task, however the polarity of stimulation differed, with each subject completing one session with anodal stimulation and the other with cathodal stimulation. Subjects were counter balanced for whether they completed the cathodal or anodal session first and for the directions of rotation.

Therefore, subjects performed one of four tasks:

i) M1 stimulation, global rotation – (8 subjects, 1 excluded due to poor performance)

ii) M1 stimulation, local rotation – (8 subjects, none excluded)

iii) Cerebellar stimulation, global rotation – (8 subjects, 1 excluded due to poor performance, 1 excluded due to technical issues)

iv) Cerebellar stimulation, local rotation – (9 subjects, 1 excluded due to poor performance, 1 excluded due to technical issues)

Electrode placement and basic stimulation protocol are described in Chapter 2.4.1. Stimulation was given for eight minutes, starting at the first trial of the Adapt phase and lasting for the full duration of that phase. Sessions were separated by a minimum of 24 hours in order to avoid retained effects of the tDCS.

5.3.5 Experiment 5.2B: Results

Global rotation

M1 Stimulation

Task performance

Average scores for the two conditions were 16.7 ± 2.8 and 17.2 ± 2.9 under anodal and cathodal stimulation respectively. Subjects showed similar levels of performance throughout the Learn and Adapt phases up until the final two blocks of the latter, during which performance under anodal stimulation reached a higher level (Figure 5.9). Also of note is the change from the last block of the Adapt phase to the first block of the Probe phase. There was a change of -10.4 ± 5.7 under anodal stimulation that was not observed under cathodal stimulation (a change of 1.3 ± 6.1 between the two blocks). This difference was again not significant ($p=0.17$, $t(6)=1.53$), but could be indicative of stronger retention of the adapted state under anodal stimulation if reflected in the PD.

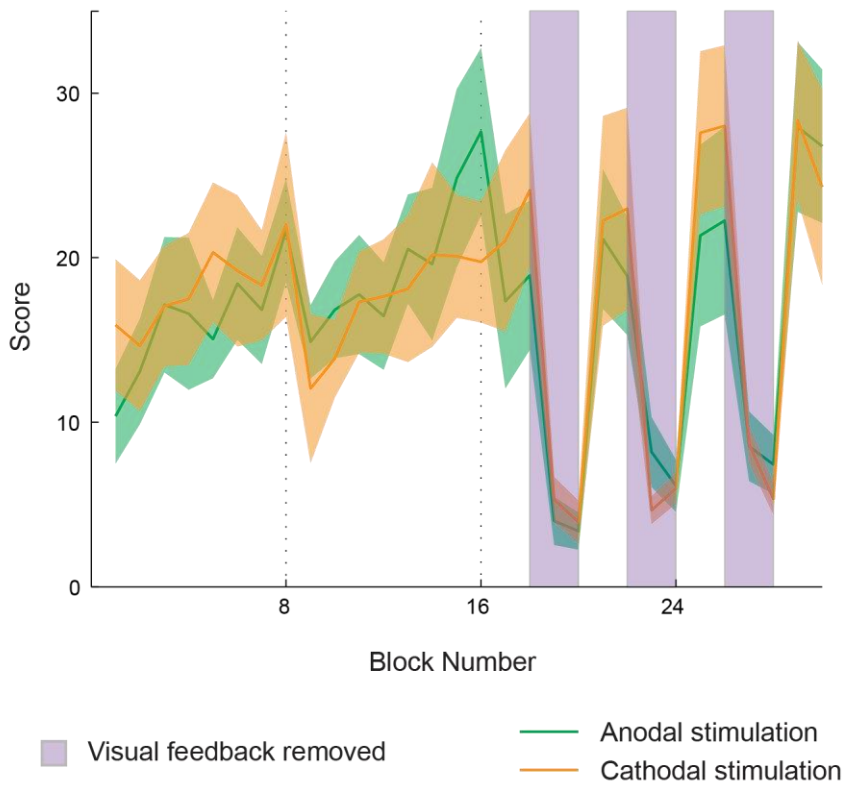


Figure 5.9 – Scores for global perturbation under stimulation of M1

Scores for both conditions remain similar to each other throughout the task.

PD

Under anodal stimulation, the PD quickly moved towards the DoA, with an average value of 58.5 ± 4.4° for the full Adapt phase (Figure 5.10). The PD under cathodal stimulation showed much weaker adaptation, with a PD of 33.7 ± 5.2° for the first two blocks of the phase, rising to 46.6 ± 4.3° by the final two blocks. For the full Adapt phase the separation was significant ($p=0.003$, $t(6)=5.00$).

Immediately following the return to the initial mapping, the PD under anodal stimulation demonstrated the presence of an after-effect, with a value of 23.4 ± 7.5° in block 17. The PD at the same point under cathodal stimulation was 7.2 ± 3.7°. These values were significantly separated with $p=0.05$, $t(6)=2.42$. The after-effect persisted strongly under anodal stimulation, and had vanished completely under cathodal stimulation.

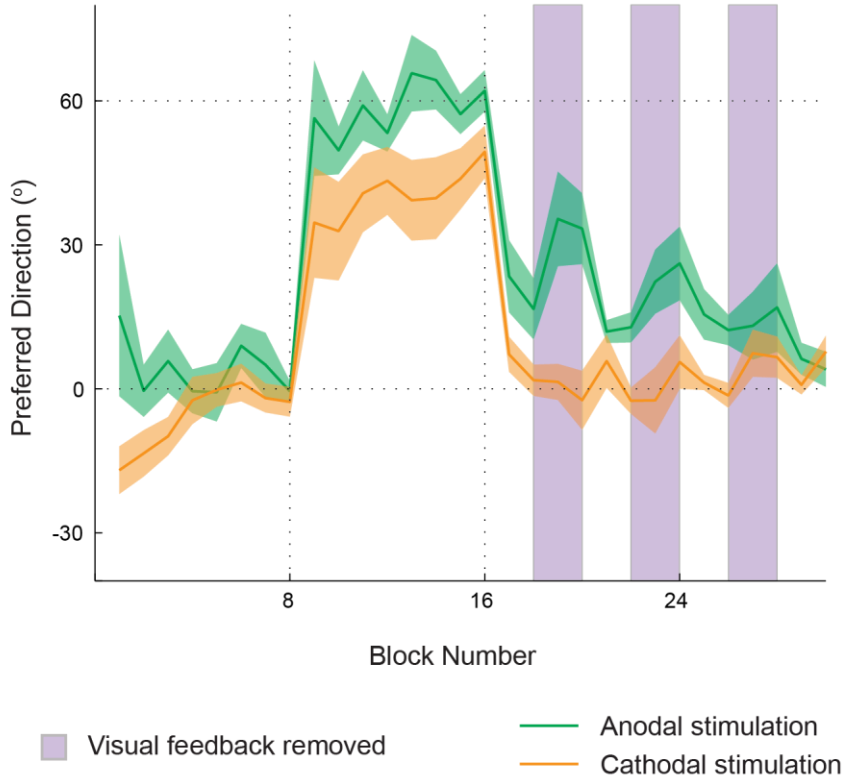


Figure 5.10 – PD for a global perturbation under M1 stimulation

Under anodal stimulation there is no effect on adaptation or spontaneous recovery, but there is a strongly persistent after-effect throughout the Probe phase. Under cathodal stimulation, adaptation is reduced and there is only a small after-effect and no spontaneous recovery.

During the first NVF blocks the PD under anodal stimulation shifted back towards its adapted state, as expected under classic adaptation (average value of 34.3 ± 6.9° over the two blocks). This effect was observed in all three NVF groups, decreasing over time as seen under no stimulation. For the same blocks the PD under cathodal stimulation was -0.48 ± 5.5° (comparing to anodal stimulation, $p<0.001$, $t(6)=6.36$), and no spontaneous recovery was observed in the following NVF blocks.

Cerebellar Stimulation

Task performance

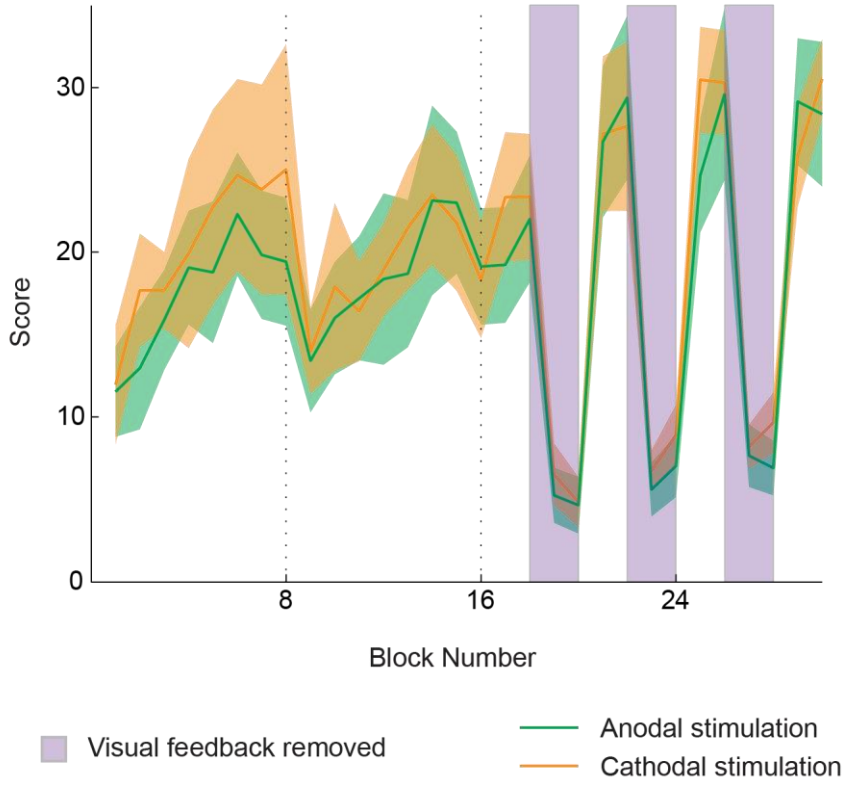


Figure 5.11 – Scores for a global perturbation under cerebellar stimulation

Scores remain similar to each other throughput the task

Average scores for each condition were 17.9 ± 2.6 and 19.3 ± 2.8 for the anodal and cathodal stimulation conditions respectively. There were no points during the task where the two scores diverged (Figure 5.11). Score progression was comparable to that observed under M1 stimulation.

PD

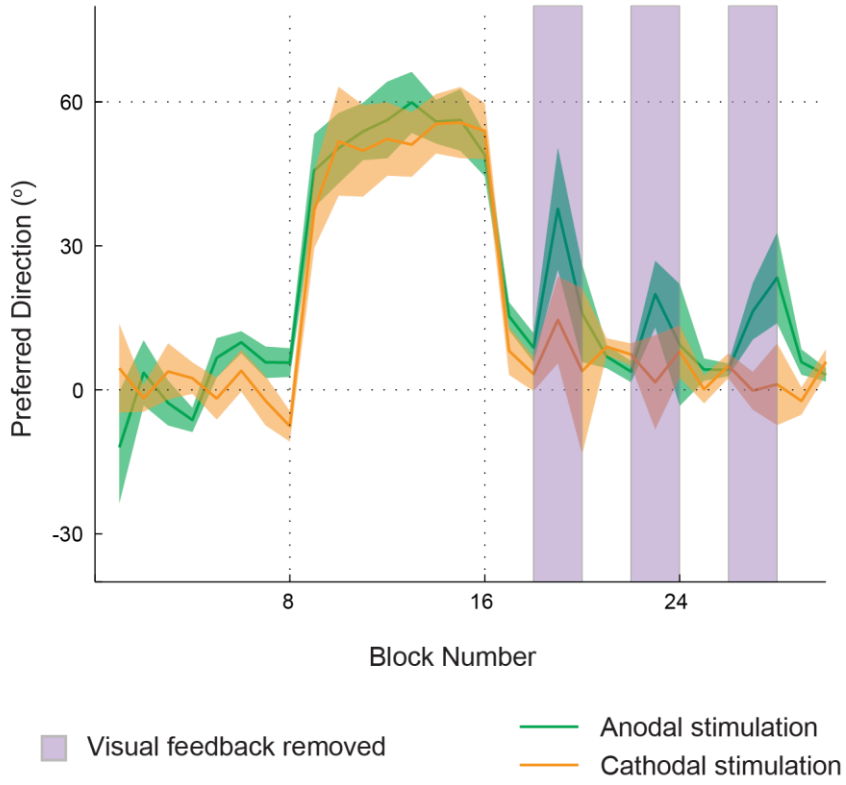


Figure 5.12 – PD for a global perturbation under cerebellar stimulation

There is no effect on adaptation under either polarity of stimulation. The presence of the after-effect and spontaneous recovery are both slightly reduced by cathodal stimulation, and not affected by anodal stimulation.

Figure 5.12 shows the PD for the global perturbation condition under cerebellar stimulation. During the Adapt phase there was no difference in the PD between anodal and cathodal stimulation and there was very little effect in comparison to no stimulation. The PDs under both conditions showed a similar progression, but did not quite reach the correct DoA. From the second block of the phase onwards, under no stimulation the PD had a value of 59.1 ± 4.2°, whereas under anodal stimulation that value was 54.5 ± 3.2° and under cathodal stimulation was 52.9 ± 4.1° ($p=0.83$, $t(5)=0.23$, for comparison of anodal and cathodal PDs).

The after-effect at the beginning of the Probe phase was present under anodal stimulation, and reduced to a similar level as under M1 cathodal stimulation in the cathodal condition (anodal: 15.3 ± 2.9°, cathodal: 8.1 ± 5.0).

Positive PD shifts representative of spontaneous recovery were present in all NVF blocks under anodal stimulation. Under cathodal stimulation, a positive shift (14.6 ± 9.0°) was present in the first NVF block, but the PD stayed constant afterwards, with no shifts in PD during the final two NVF blocks.

Summary

With respect to the adaptation to the global perturbation, stimulation of M1 resulted in a polarity specific, detrimental effect on adaptation. Stimulation of the cerebellum showed little effect under either polarity of stimulation.

During the Probe phase, M1 anodal stimulation strengthened the after-effect and retained the spontaneous recovery observed under no stimulation. Cathodal stimulation resulted in a loss of the after-effect and the spontaneous recovery. Anodal stimulation of the cerebellum had no effect on the PD compared to no stimulation. Cathodal stimulation again resulted in the reduction of the after-effect and a lessening of the spontaneous recovery (although not to the same extent as under M1 stimulation).

The effect could be argued as being DC stimulation resulting in the shifting of the time constants in the two phase model, with a greater retention of the slow process observed under anodal stimulation, and the reduction of the slow process under cathodal stimulation. This will be examined through modelling in Chapter 7.

Local rotations

M1 Stimulation

Task performance

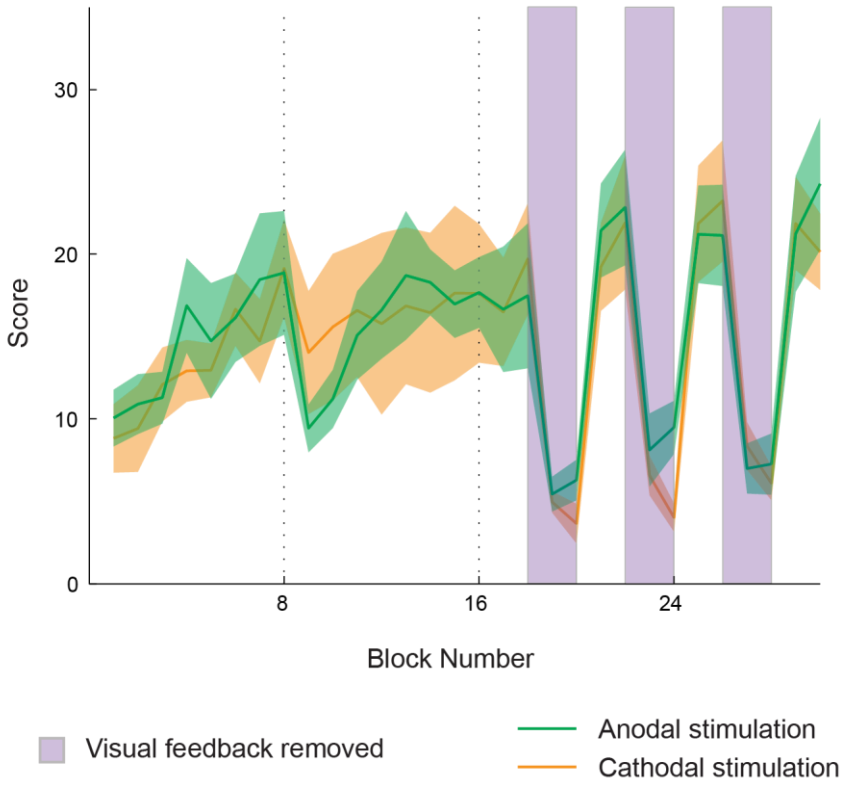


Figure 5.13 – Scores for a local perturbation under M1 stimulation

The drop in score at the beginning of the Adapt phase is greater under anodal stimulation, but this difference is not significant. There are no other points where the scores diverge during the task.

The scores for the two conditions generally did not diverge throughout the duration of the task (Figure 5.13). Average scores for each condition were 15.1 ± 2.0 and 14.5 ± 2.1 for the anodal and cathodal conditions respectively. The only point at which there was a difference between the two conditions was the 1st block of the Adapt phase, during which there was a greater drop from the previous phase in the anodal condition. However, this difference quickly vanished and was not significant ($p=0.32$, $t(7)=1.06$).

PD

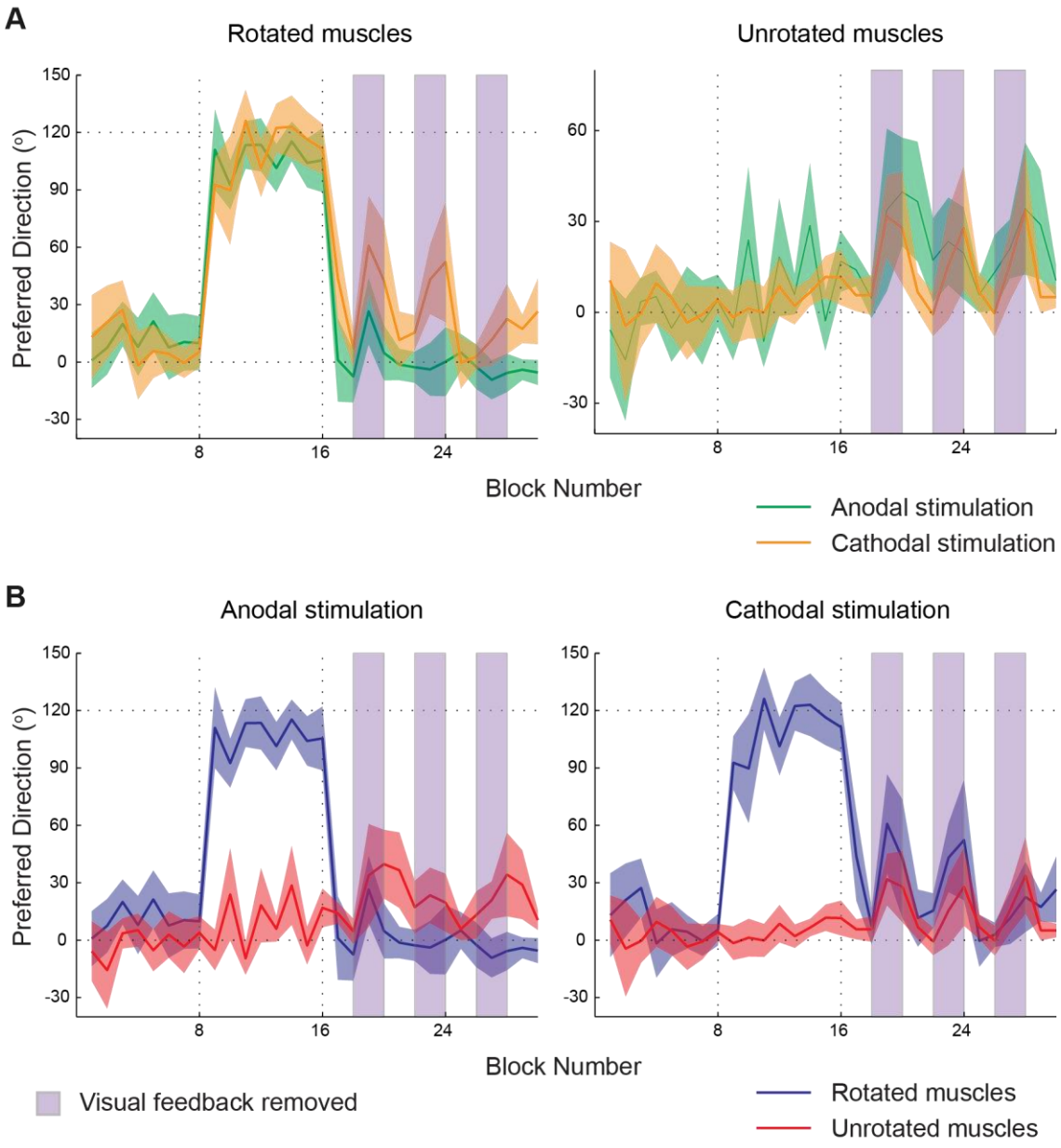


Figure 5.14 – PD for a local perturbation under M1 stimulation

A: PD divided by rotated and unrotated muscles.

B: PD divided by anodal and cathodal stimulation

Figure 5.14 shows the PD for the local perturbation condition under stimulation of M1, PDs are compared in terms of rotated vs. unrotated muscles and anodal vs. cathodal stimulation. During the Adapt phase, there was no difference between anodal and

cathodal stimulation, with both sets of rotated muscles moving quickly to match the DoA. Average values for the Adapt phase were 95.3 ± 16.1 and 106.2 ± 9.9 for anodal and cathodal stimulation respectively ($p=0.76$, $t(7)=0.31$).

There was the appearance of a greater after-effect in the rotated muscles under cathodal stimulation, but this was not significant (anodal: 1.1 ± 23.2°, cathodal: 43.9 ± 21.9°, $p=0.14$, $t(7)=1.66$).

Looking at the rest of the Probe phase, under anodal stimulation, after a small positive shift in PD in the first NVF group, the rotated muscles stayed stable at a value of -3.0 ± 11.8° for the rest of the phase, with no shifts in PD observed in the latter two NVF blocks. The unrotated muscles were noisier, but following the first NVF group consistently stayed at a greater PD than that of the rotated muscles for the remainder of the phase. However, the difference between the two sets was within the limits of variability and not significant.

Under cathodal stimulation there was evidence of classical adaptation effects in the NVF blocks that was not present in either the no stimulation or anodal stimulation conditions. Positive shifts in PD were observed in both the rotated and unrotated muscles, despite the latter not experiencing a rotation.

Cerebellar stimulation

Task performance

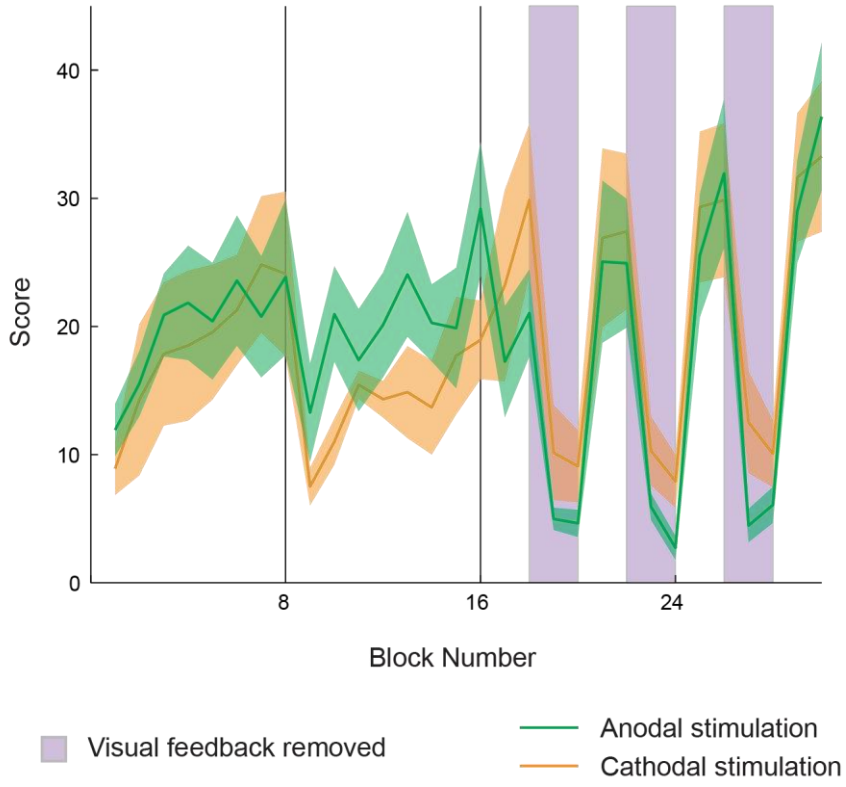


Figure 5.15 – Scores for the local perturbation under cerebellar stimulation

Performance is reduced under cathodal stimulation during the Adapt phase, and the change from the Adapt to the Probe phase differs between conditions. Scores remain similar throughout the rest of the task.

Figure 5.15 shows scores for the local perturbation condition under cerebellar stimulation. There was a difference between the two conditions in the Adapt phase, with a greater drop in score from the Learn phase observed in the cathodal condition (-10.6 ± 7.8 (anodal), -16.6 ± 7.5 (cathodal), p=0.58, t(6)=0.59), with this difference persisting through to the end of the phase (average score for the Adapt phase: 20.6 ± 3.9 (anodal), 14.2 ± 2.1 (cathodal), p=0.1, t(6)=1.96). Following this, the drop in score between the Adapt and Probe phases was greater under anodal stimulation compared to cathodal stimulation (-11.9 ± 8.6 (anodal), 4.3 ± 7.0 (cathodal), p=0.24, t(6)=1.30). None of these differences were significant, but again could reflect differences that are clearer in the PD.

PD

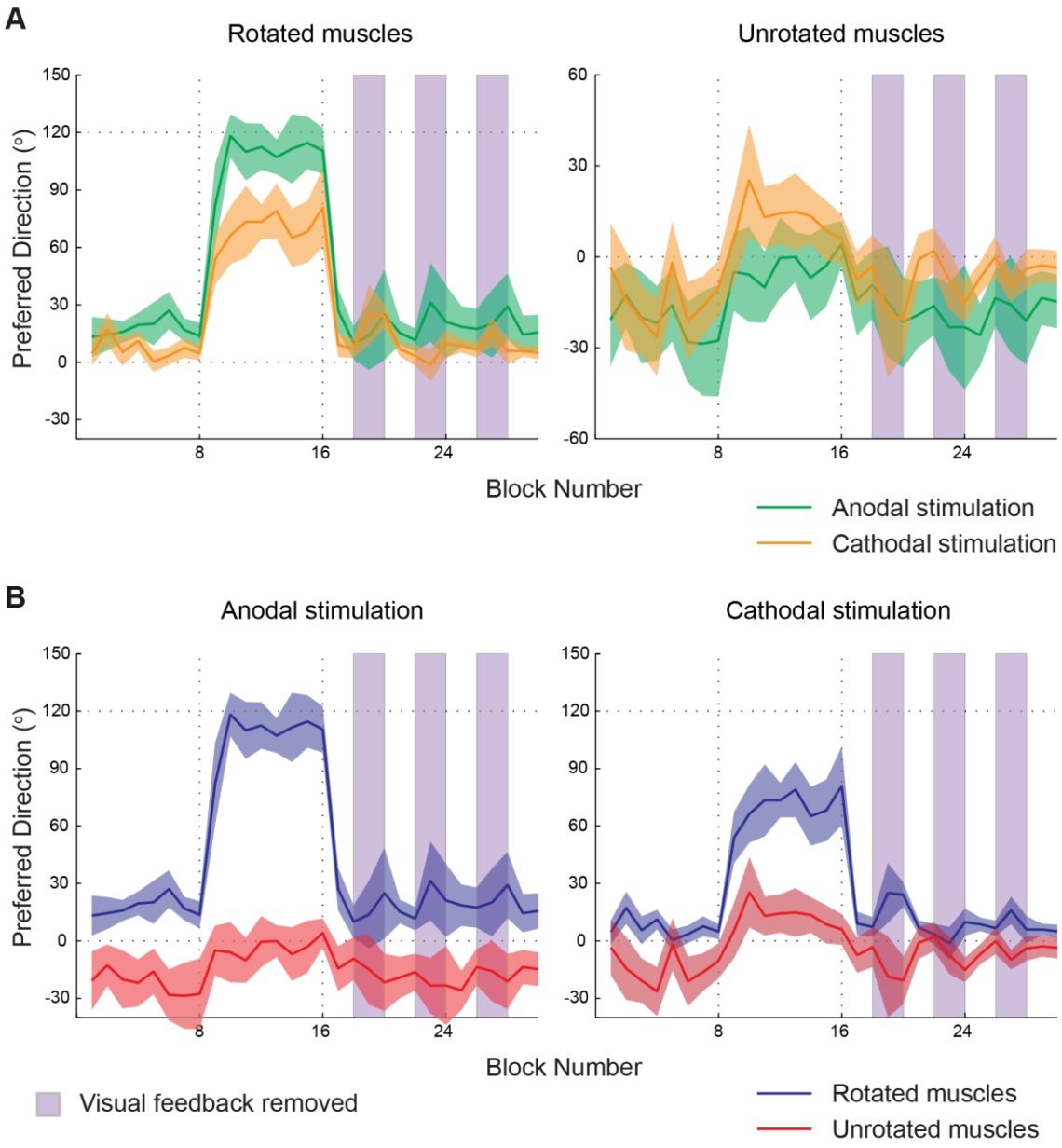


Figure 5.16 – PD for the local perturbation under cerebellar stimulation

A: PD divided by rotated and unrotated muscles

B: PD divided by anodal and cathodal stimulation

Figure 5.16 shows the PD for the local perturbation condition under stimulation of the cerebellum. PDs are compared in terms of rotated vs. unrotated muscles and anodal vs. cathodal stimulation. Looking first at anodal stimulation, the PD during the Adapt phase

was unaffected compared to no stimulation. However, during the Probe phase, there was a slight after-effect present in block 17 (27.1 ± 11.1°), and some evidence of spontaneous recovery in the rotated muscles during the NVF blocks. The unrotated muscles showed little variation throughout the condition, staying at a constant level during the Adapt phase and showing no clear shifts in PD during the NVF blocks. There was an average separation in PD of 39.6 ± 18.3° between the rotated and unrotated muscles present during the Learn phase that appeared to persist throughout the task. There was no obvious reason for this, since the difference precedes stimulation. Upon examination of individual subject PDs, it was found that this was due to a single subject, where a consistent deviation was present throughout the Learn and Probe phases (Mean PD values; Learn phase: 72.0 ± 10.8, Probe phase (calculated based only on the visual feedback groups): 86.9 ± 10.9). This was likely a result of the specific muscle arrangement used in those phases for that subject. No other outliers were observed via inspection of single subject PDs.

Under cathodal stimulation, there was evidence of re-aiming during the Adapt phase. The rotated muscles reached an average PD of 61.5 ± 8.4° for the first two blocks of the phase, with unrotated muscles shifting upwards to an average value of 21.2 ± 17.0° for the same range. By the final two blocks of the phase, the respective PD values were 67.0 ± 14.6° and 2.8 ± 7.0°. A small after-effect was present in the rotated muscles under cathodal stimulation, with a PD of 9.1 ± 6.2° in block 17. During the 1st NVF group there was a small positive shift in the rotated muscles (24.7 ± 9.5°) and a negative shift in the unrotated muscles (-17.5 ± 13.5°) ($p=0.02$, $t(6)=3.01$) . In the latter two NVF groups neither set of muscles shifted significantly away from 0.

Directly comparing anodal and cathodal stimulation, the PD reached by the rotated muscles during the Adapt phase clearly differed. Under anodal stimulation the PD reached an average value of 107.8 ± 11.0° over the Adapt phase. In the same range under cathodal stimulation, the PD only reached 68.6 ± 10.5° ($p=0.05$, $t(6)=2.42$). The after-effect in the rotated muscles between the two conditions also differed, but this was not significant ($p=0.14$, $t(6)=1.70$).

Summary

Beginning with the Adapt phase, there was a polarity specific effect on the adaptation to the rotated mapping that was present under cerebellar stimulation and not under M1 stimulation. In addition to the effect on the rotated muscles, under cathodal stimulation of the cerebellum, the unrotated muscles showed a positive shift at the beginning of the Adapt phase, followed by a decline towards 0. This demonstrates a movement from a re-aiming solution to a remapping solution.

The lack of presence of an after-effect upon the return to the initial mapping is a feature of the local perturbation when stimulation is not applied. An after-effect was seen in the rotated muscles under cathodal stimulation of M1 and anodal stimulation of the cerebellum, although neither of these effects were significant when compared to the alternate polarity, in which no after-effect was observed.

Finally, differences between stimulation polarities and targets were observed in the NVF blocks in the Probe Phase. Under anodal stimulation of M1, there was little change in the PDs during the NVF blocks, although from approximately block 20 through to the end of the phase, the average PD in the unrotated muscles was higher than that of the rotated muscles. Under cathodal stimulation there were positive shifts in PD in both the rotated and unrotated muscles during the NVF blocks. Under anodal stimulation of the cerebellum, some recovery of the adapted state was observed in the rotated muscles, with positive shifts in PD observed in all of the NVF groups. There was no corresponding effect during those blocks in the unrotated muscles. Under cathodal stimulation during the first NVF group, there was a separation of the rotated and unrotated muscles, with the two sets moving in positive and negative directions respectively.

5.3.6 Discussion

Adaptation to global and local perturbations is driven via different adaptive mechanisms

In this chapter I described two predictions of responses to a perturbation. The first, referred to as classic adaptation, is defined by the presence of an after-effect upon the

return to an initial state following a perturbation, and spontaneous recovery of the adapted state when visual feedback is removed. The second, modular adaptation is then defined by the lack of these effects upon return to the initial mapping. The difference between the two arises either due to the adaptation process consisting of alteration to a single internal model (classic) or creation of a new internal model (modular) in response to a perturbation. Experiment 5.1A then consisted of a task which was designed to look at the difference in response to perturbations with global and local structures. When presented with a global rotation, both an after-effect and spontaneous recovery were observed, meaning that global rotations are adapted to in a classical manner. In the case of local rotation, neither of these effects were present, indicating modular adaptation.

As such, the two tasks are adapted to in fundamentally different ways; even though the error signal for the two tasks is initially the same (the appearance of an overall 60° shift in cursor position). This implies that the structure of a perturbation at least partly determines how it is adapted to.

This also explains the after-effect observed in the global rotation washout in Chapter 3 (Figure 3.5B). If a global rotation involves an adjustment of the internal model (as in classic adaptation), then an after-effect would be expected after a perturbation. No such after-effect was seen in the local rotation, strengthening the idea that it involves the creation of a new internal model, as opposed to adapting the original.

It is particularly interesting that no after-effect at all was observed in the local rotation condition as one would be expected immediately following a perturbation regardless as to whether the internal model is being switched or altered. It is possible that an after-effect does exist on the level of single trials, but the variability introduced by the different target positions means that there is not enough data within a single trial to comment on the existence of any such after-effect. As a result, when the lack of an after-effect in relation to the local condition is discussed, it means that an after-effect that is observable on the level of blocks was not present, whereas in the global condition, it was.

As to exactly why this difference between the two conditions exists, I cannot currently definitively answer. However, one potential explanation is the differing nature of the effector relationship between phases. As previously noted, one of the key differences between the global and local rotations is that during the former all muscles retain their

relationships to each other throughout the task, whereas under the latter those relationships change between phases. As such, the nature of relative muscle usage could be a determinant of how the motor system chooses to adapt to task alterations. In terms of previous work looking at switching contexts, (Karniel and Mussa-Ivaldi, 2002) found that subjects were unable to switch between multiple internal models of force field perturbations even when trained on the individual tasks on separate days. This study used a task in which effector relationship remained consistent, perhaps explaining why disassociation of internal models proved difficult. This question requires further investigation.

Much of the previous work on switching internal models has focused on the ability of the motor system to learn to switch models based on contextual cues, and has described varying success for cues including colour (Hinder et al., 2008), target location (Woolley et al., 2007) and target shape (Baldeo and Henriques, 2013). As such, these experiments have used tasks that initially interfere with each other, meaning that the disassociation must be learned. The focus of this work is different in that I have described a task where, depending on the structure of the perturbation, the internal model is either altered or switched as soon as the novel context is introduced, even without cues to either alert the subject to the presence of a perturbation, or the nature of that perturbation.

The effect of stimulation on adaptation differs depending on the structure of the perturbation

The effect of DC stimulation on the rate of adaptation during the Adapt phase is particularly interesting as there is a double dissociation between M1 and cerebellar stimulation.

With a global perturbation structure, cerebellar stimulation had little effect, with both polarities of stimulation resulting in the PD shifting to match the DoA. However, M1 stimulation resulted in a different effect between anodal and cathodal stimulation, with the latter resulting in a reduced rate of adaptation and the PD at the end of the phase not matching the DoA (49.4 ± 5.5° compared to a PD of 62.1 ± 4.3° under anodal stimulation).

This effect is reversed when applied to a local perturbation structure. M1 stimulation had no effect on the rate of adaptation of the rotated muscles, but cathodal cerebellar stimulation resulted in the rotated muscles again having a slower rate of adaptation and failing to match the DoA. This effect is demonstrated in Figure 5.17.

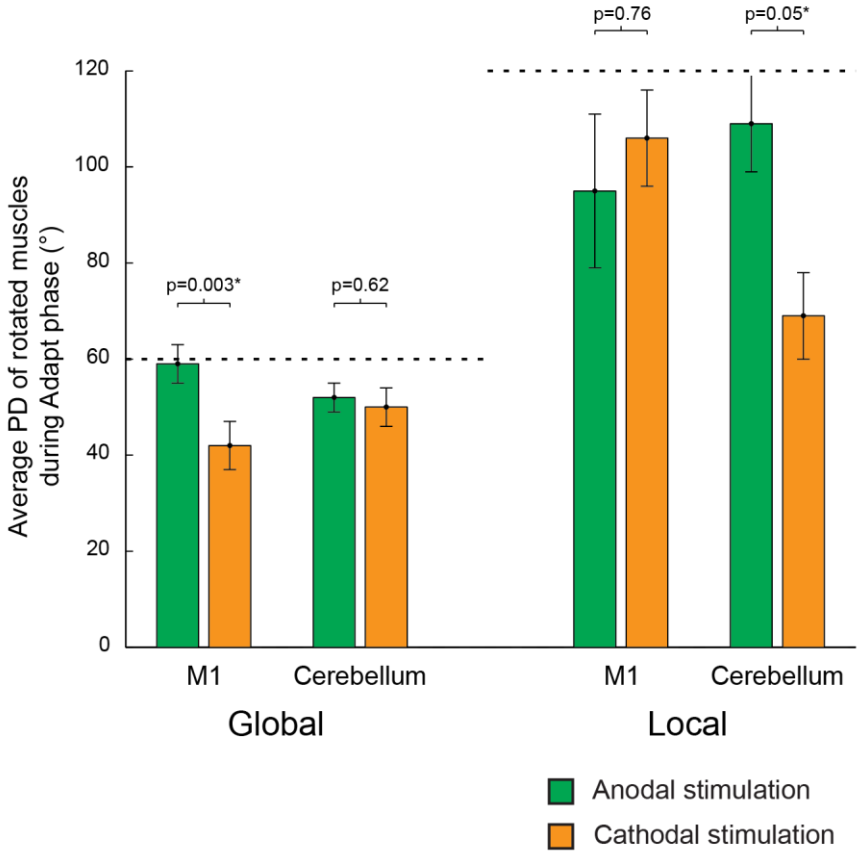


Figure 5.17 – Comparison of average PD during Adapt phase for anodal and cathodal stimulation of M1 and cerebellum under global and local perturbations.

The difference between anodal and cathodal stimulation is significant for stimulation of M1 during a global perturbation and for cerebellar stimulation during a local perturbation.

Therefore stimulation of M1 has a polarity specific effect on adaptation to a global rotation, while stimulation of the cerebellum has a polarity specific effect on adaptation to a local rotation. This difference indicates that global and local perturbations are not only adapted to via different processes, but that those processes are located in different areas of the brain.

Interestingly, the effect of cathodal M1 on adaptation is in contrast to various other studies, which have shown stimulation of M1 to affect only the retentive aspects of adaptation (Hadipour-Niktarash et al., 2007, Reis et al., 2009). The effect of M1 stimulation on a classic adaptation task is supported by (Hunter et al., 2009) where it was shown that anodal tDCS resulted in an increased after-effect in a force field adaptation task, and (Kaski et al., 2012) where an anodal tDCS induced after-effect was seen in response to the 'broken escalator' phenomenon.

Few studies have been done on the effect of tDCS of the cerebellum on adaptation, but previous work has suggested that adaptation to a perturbation can be enhanced via anodal stimulation of the cerebellum, an effect that was not observed here (Galea et al., 2011, Block and Celnik, 2013).

M1 and the cerebellum drive different adaptive processes

The use of removed visual feedback during the Probe phase was designed in order to look at the state of the underlying adaptive processes. The response differed between stimulation of M1 and cerebellum, and within those targets between stimulation polarities.

	M1 stimulation	**Cerebellar Stimulation**
Anodal Stimulation	Non-rotated muscles have a greater average value than rotated during Probe phase, however the difference is not significant.	Separation of rotated and non-rotated muscles throughout task, no clear features during Probe phase.
Cathodal Stimulation	Appearance of spontaneous recovery of a re-aiming solution, despite use of remapping during Adapt phase – peaks are not significantly separated from 0.	Divergence between rotated and unrotated muscles in 1st NVF group – indicative of the decay of a slow learning process.

Table 5.1 – Comparison of Probe phases under all stimulation types in the local rotation condition

Global perturbations:

In the global rotation condition, after-effects and spontaneous recovery of the adapted state were wiped out under cathodal stimulation of M1, while the retained after-effect was strengthened under anodal stimulation. Anodal stimulation of the cerebellum had little effect on the Probe phase, while cathodal stimulation slightly reduced the after-effect and spontaneous recovery. This again implies an M1 dependency on the process driving adaptation to a global perturbation.

Local perturbations:

Looking at the local rotation structure, regardless of the stimulation site or polarity, the PDs of the two sets of muscles are separated by the end of the Adapt phase. However, the progression of the PD during the Probe phase reveals different processes, and hence differing contributions of M1 and the cerebellum to the overall adaptation.

In the case of cathodal stimulation of the cerebellum during a local perturbation, the resulting effect was adaptation that can be described as the combination of two processes; a fast, global process that adapts quickly to the perturbation but cannot separate the two sets of muscles, and a slow, local process that separates out the two sets of muscles, but is slow both to take effect and decay. This explains the three key features of the PD observed during the condition:

1) The increase in PD in both the rotated and unrotated muscles immediately following the initial perturbation occurring as a result of the fast process adapting to the perturbation without separating the two sets.

2) The correct separation of the two sets of muscles towards the end of the Adapt phase, with the rotated muscle PD increasing and the unrotated muscle PD moving back to 0, resulting from the combination of the two processes.

3) The positive and negative shifts in PD in the rotated and unrotated muscles respectively during the first NVF group being due to the effect of the slow process having not fully decayed away and acting to separate the two sets, with the fast process having already fully decayed.

An important aspect to note here is that this was a local perturbation condition, but no evidence of modular switching was observed.

Comparing this with cathodal stimulation of M1 during a local perturbation, there was no effect on the adaptation, indicating that the modular context switching process was intact. However, during the NVF blocks in the Probe phase, there were positive shifts in both the rotated and unrotated muscles, indicating the presence of a slow, global process.

Stimulation of each area during local adaptation in some way disrupts the adaptive process, indicating that both areas are involved in this form of adaptation. However, the differing response between stimulation sites reveals the differing contribution to the overall process contributed by each area. The exact nature of these contributions is discussed in the following section.

Strength of comparisons within and between M1 and the cerebellum:

The exact nature of how tDCS affects M1 and the cerebellum is not fully understood. Further to this, the effect of stimulation of M1 and the cerebellum on performance of this task may not be entirely disassociated, due to connections between the two areas (Ito, 1984). As a result, it is difficult to say a priori exactly what the effect on performance from stimulation of a given area would be when compared to baseline. To avoid this issue, this experiment was designed to compare anodal and cathodal stimulation of the same area within subjects. This allows us to best comment on whether an area is involved in a given process, i.e. if there is a clear separation in performance between the two polarities then the area is most likely involved. Simply comparing a single polarity of stimulation with baseline could potentially miss effects, as proved here with anodal stimulation of M1 during a global perturbation. That condition resulted in little difference from baseline, but cathodal stimulation showed a clear detrimental effect. Regarding comparisons between two different areas, again, comparing differences between polarities has more meaning than directly comparing effects as it negates the need for absolute definitions of how an area has been affected by a single polarity with respect to baseline. The comparison of polarities with a single area is then potentially a better measure than measuring individual polarities in different areas and comparing them solely against baseline.

Potential differences in the effect of tDCS between phases

tDCS is known to produce persistent effects on excitability that last beyond the period of stimulation. It is possible, however, that behavioural effects arising from periods when the stimulation is active and periods following its completion could differ in nature. Investigation of any differences is prohibited to a certain extent by time limits placed on the length of stimulation via safety considerations, but it is worth noting here that since tDCS ends at the end of the Adapt phase, behavioural effects during the Probe phase may differ from what would be observed under continued stimulation.

A unified model to explain global and local effects

Based on the results discussed above, it is evident that a simple two-state, fast/slow process model cannot account fully for the effects observed here. In particular, some form of context dependent modularity must be introduced in order to explain the ability of the motor system to adapt to a local perturbation without the presence of after-effects upon the return to the original mapping.

A relatively simple, two-stream model can explain several of the effects observed here (although not all). The model (Figure 5.18) consists of a local stream and a global stream, with the path followed determined by the nature of the perturbation. These paths can be considered equivalent to modular and classic adaptation respectively. Under normal conditions, the global pathway consists of a fast, global process and a local, slow process that acts as a global process. The local pathway then provides a modular component, triggering creation of a new internal model and hence the lack of after-effects.

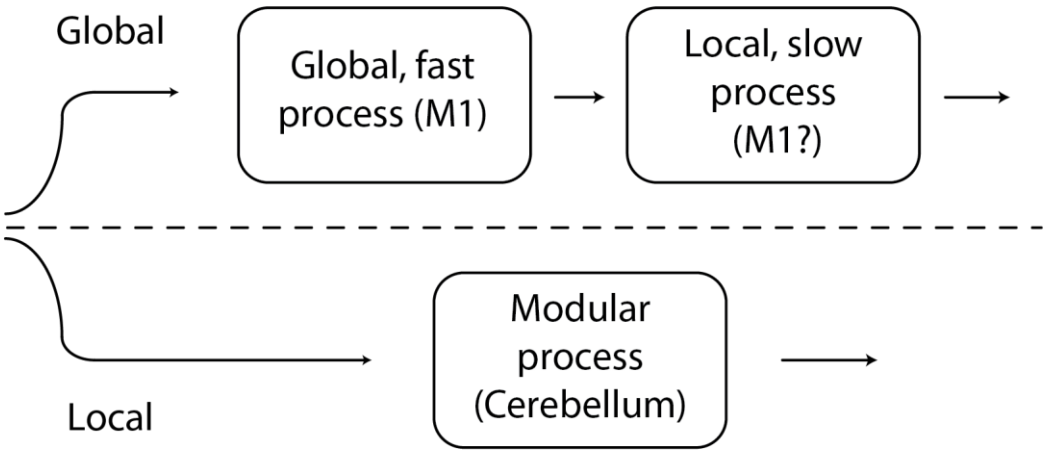


Figure 5.18 – A two-stream, context dependent model can account for multiple effects on global and local adaptation.

Based on the site specific effects of tDCS, the global, fast process and potentially the local, slow process were determined to be M1 dependent and the process by which the stream is selected and new internal models created was set to be cerebellum dependent.

Looking first at the global stream, adaptation to a global perturbation without stimulation is well described by a single fast and a single slow process. Under this setting, cathodal stimulation of M1 during the global adaptation then detrimentally affects the global pathway, resulting in the reduced adaptation and hence the lack of after-effects. Stimulation of the cerebellum then should have no effect on adaptation or the presence of an after-effect/spontaneous recovery. This is upheld to a certain extent, with anodal stimulation of the cerebellum having little effect, but cathodal stimulation reducing both the after-effect and the recovery (albeit to a lesser extent than M1 stimulation). The model then also accounts for the increased persistence of the after-effect under anodal M1 stimulation by having the slow process also be M1 dependent (although this is less supported by previous research). The effect of stimulation on adaptation to a global perturbation in terms of fast and slow processes is looked at further in Chapter 7.

Turning to the local condition, when stimulation is not applied the adaptation becomes the learning of a new internal model, with the model of the original mapping not being overwritten. When stimulation is applied, the strongest evidence for the local stream

selection being dependent on the cerebellum is the effect of cathodal stimulation on the cerebellum when the perturbation is local. In that case, the adaptation could be described by the combination of a fast, global process and a slow, local process, successfully explaining the initial adaption present in both sets of muscles, eventual separation of the two sets and retention of the separation when visual feedback was removed. Since the combination of these two processes can also be used to describe normal adaptation to a global perturbation, this implies that cathodal stimulation of the cerebellum has affected the stream selection process and caused the system to follow the global pathway when the local pathway would be more appropriate. However, the model cannot explain the presence of what appears to be a global, slow process, the presence of which is revealed under cathodal stimulation of M1.

In summary, the simple two-stream model can account for some of the effects observed here, but it is clear that as adaptation becomes more complex, adaptive processes driven at multiple sites are revealed. The concept of multiple adaptive contexts is not new, (Lee and Schweighofer, 2009) introduced a model of 1-fast, n-slow adaptive processes, where slow processes are switched on a contextual basis in order to explain the effect of dual adaptation, the ability to switch between similar tasks without interference (i.e. learned switching of internal models over time (Wada et al., 2003, Shadmehr et al., 2010). The formulation of this idea that I have presented here is one where switching also occurs at a higher level, i.e. the creation of a new internal model follows the local stream, but dual adaptation would take place within the global stream, leading to switching between slow processes. This could be tested by a study focusing on switching repeatedly between differing global or local rotations, in order to investigate how the system adapts when the two differing contexts are no longer completely novel.

5.3.7 Conclusions

- Adaptation to global and local perturbations is driven via different learning mechanisms, which I have described as classic and modular adaptation. It is possible that the key difference is the consistency of the relationship of the contributing effectors, but this requires further investigation.

- There is a double dissociation between M1 and the cerebellum with respect adaptation to global and local perturbations. This suggests that the different processes depend on different areas of the brain.

- The cerebellum is involved not only in the creation of new internal models, but the process by which the motor system determines whether the current model should be altered or switched.

CHAPTER 6 - OPTIMAL FEEDBACK CONTROL OF AN MCI

In which I describe an experiment designed to investigate a prediction of optimal control feedback theory, that optimal control is the result of feedback control using a state estimate that combines sensory and predictive components. I investigate this by creating artificial perturbations to cursor position using median nerve stimulation and TMS.

6.1 Introduction

As discussed in Chapter 1.2.1, optimal feedback control is based on the idea that an internal state estimate is used to control movements, and that it is updated via both predictive and feedback components. The predictive element is derived from the efference copy, a copy of the motor command generated by the motor system, which is used to update the internal state estimate in terms of the predicted effect on the body and the environment. Sensory feedback of that action is then used to further update the internal state estimate as it becomes available. A prediction of optimal control is that only task relevant errors will be corrected by the internal feedback policy. The following experiment used this feature in order to examine the origin of the efference copy used to update the state estimate.

In the first iteration of this experiment, subjects were presented with elliptical targets where the major axis of the ellipse was aligned with the axis of positive or negative covariation in muscle space, with muscle directions aligned such that targets were horizontally or vertically aligned with respect to the target space. Subjects were then asked to direct a cursor to the targets in order to achieve a high score (score being determined by time spent within the target). Cursor movement was controlled using two muscles in the dominant hand. It was shown that subjects could optimally control variability based on the constraints of the task (Nazarpour et al., 2012). Further to this, pairs of both synergistic and non-synergistic muscles could be used to perform the task successfully, overcoming biomechanical constraints arising from task requirements.

In a further experiment, once the cursor was in target its position was visually perturbed along the axis of a single muscle, requiring subjects to compensate for the error. The aim was to establish evidence for the existence of a ‘smart controller’ acting predominantly along the task relevant dimension, in this case the minor axes of the ellipses.

It was hypothesised that if corrections are aligned to the task-relevant axis, this will be apparent as a target-dependent response in the unperturbed muscle. (Figure 6.1)

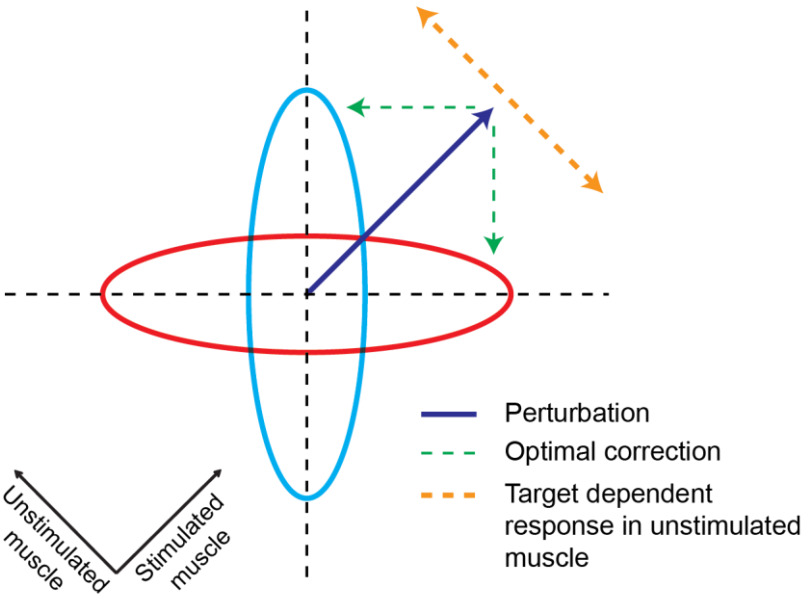


Figure 6.1 – Prediction of target specific response to perturbation

A perturbation along the axis of activation for the stimulated muscle (blue line) will result in the optimal correction (green lines) lying along the task-relevant axis, with this being dependent on the orientation of the target. The differing required corrections are themselves dependent on the response in the unstimulated muscle (orange line). Therefore if differing responses are observed in the unstimulated muscle, then this provides evidence of a ‘smart controller’ acting along the task-relevant dimensions.

The final aim of this experiment was using electrical perturbations, via use of peripheral nerve stimulation, in order to look at the effect of reflex actions. It was theorised that stimulating one muscle would create a mismatch between signal and feedback, resulting

in a proprioceptive induced corrective response in the non-perturbed muscle. However, this was not observed, with the lack of proprioceptive feedback contributing to the forward model proposed to be the reason (if full visual feedback is available, subjects tend to ignore proprioceptive feedback, as found by (Radhakrishnan et al., 2008)).

While being able to comment on the existence of optimal control present in the use of sensory feedback, this experiment did not look at the predictive aspect of OFCT. Therefore the motivation of the work described in this chapter was to test whether the predictions of OFCT could be demonstrated through an effect on the predictive updating of the internal state estimate.

To achieve this, I used TMS in order to disrupt the predictive input to the state estimate by creating the illusion of movement i.e. the creation of an efference copy that results in a mismatch between the target and the predicted cursor position. If a target orientation modulated response appears in the non-stimulated muscle to correct for the perceived perturbation, the existence of a 'smart controller' operating on a cortical efference copy can be confirmed, as it demonstrates that the system is using a state estimate to drive movement on the basis of high level constraints (target orientation). In conjunction with this, median nerve stimulation was again used in order to provide a control for sensory feedback, and confirm the previous results.

M1 was chosen for the target for stimulation as it has previously been suggested as a location for the creation of the efference copy. In particular, (Haggard et al., 2002) reported creation of mismatches between action and effect through motor cortical stimulation.

6.2 Methods

The work in this chapter follows on from a different MCI based experimental design (described in Chapter 2.2.2 – Displacement task). In this task only two muscles were used. Figure 6.2 is provided as a reference.

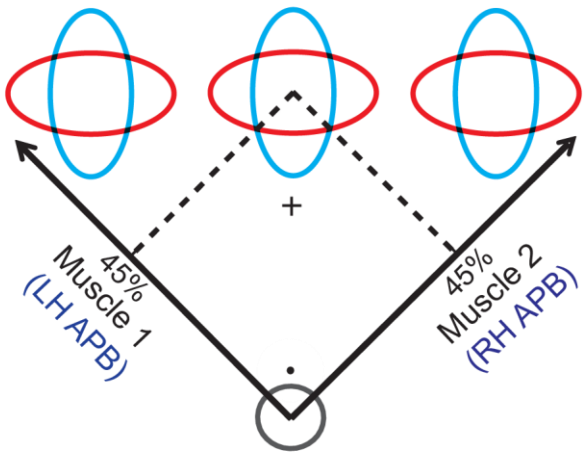


Figure 6.2 – Trial Structure (Displacement task)

Two muscles (APB in left and right hands) act along orthogonal axes oriented diagonally to the screen co-ordinates. Elliptical targets appear in one of three potential locations, and are either horizontally or vertically oriented. Approximately 45% of maximal voluntary contraction simultaneously in both muscles will take the cursor to the centre of the screen.

8 subjects (5 male, ages 22-35) controlled the movement of an onscreen cursor using the APB muscle in each hand.

6.2.1 Stimulation

Two forms of stimulation were used, transcranial magnetic stimulation (TMS) and median nerve stimulation (MNS). The protocols are described in Chapter 2.4.2 and 2.4.3 respectively. TMS level for the M1 experiment was set at 110% of the resting motor threshold for APB (the stimulus required to produce an m-wave in APB when the muscle is at rest). MNS level was set at 120% of resting motor threshold.

6.2.2 Trial structure

There were two phases to the experiment, involving different types of trials.

Phase 1: Learning

The learning phase consisted of four groups of ninety six trials each. This was to allow subjects to explore the space and learn the optimal route to task success (defined by the score given at the conclusion of each trial). Trials were split equally between the two target shapes (horizontal and vertical ellipses), and then by the three target locations (left, right and centre). This resulted in six distinct trial types which were distributed equally and randomly through each group of ninety-six trials.

Phase 2: Stimulation

Trials were split between two types; stimulation and no stimulation. In the first set, stimulation was given 300ms after trial commencement. The second set was further subdivided into trials with and without visual feedback. In the no visual feedback trials, feedback was removed after 300ms. An equal distribution of vertical and horizontal targets was used for each subset. Stimulation trials were then further divided between median nerve stimulation (MNS) and TMS.

Target location was confined to the centre as the purpose of targets in other locations was to provide subjects the opportunity to learn optimal muscle usage.

Scores were given after each trial. In the no stimulation trials, scores were calculated over the entire hold period. In the stimulation trials, the score was calculated from the first 300ms and the last 200ms, in order to avoid giving feedback to subjects based on random information i.e. the target position based on the stimulation. The stimulation phase consisted of eight groups of ninety six trials.

As a result of the different trial sub-types, there were eight distinct trial types in the stimulation phase. These types were distributed equally and randomly within each group. (Each group had the same arrangement of trial types, but given that the

experiment consisted of a maximum of eight groups, and subjects were not aware of the divisions, it would be impossible for any underlying structure to be identified).

As it was not known upfront how the artificial perturbation was conceptualised, it was difficult to make a prediction about exactly how the unstimulated muscle would respond. The disruption of the efference copy should perturb the current state estimate. If this perceived perturbation is responded to in an optimal feedback manner then a target specific feedback correction should be observed. Therefore, although it is difficult to make an exact prediction about the nature of the response, the strong prediction arising from optimal control feedback theory is that the response will be target specific.

6.3 Results

All muscle responses are expressed as fractions of maximum voluntary contraction, where 0 is the muscle at rest and 100% is the recorded MVC. As detailed in Chapter 2.2, successfully holding the cursor in target required approximately 45% MVC in each muscle.

6.3.1 Median Nerve stimulation

(One subject was excluded due to the median nerve stimulation not working correctly during two of the blocks)

Figure 6.3 shows the responses in both hands. In the range 90-140ms after perturbation, there was a response present in the un-stimulated muscle. At the peak of the response (100-115ms), the horizontal target gained a value of 53.4 ± 4% and the vertical a value of 50.9 ± 5% ($p=0.29$, $t(5)=1.19$) The lack of an observed difference between the responses for the horizontal and vertical targets demonstrates that the response was not target specific.

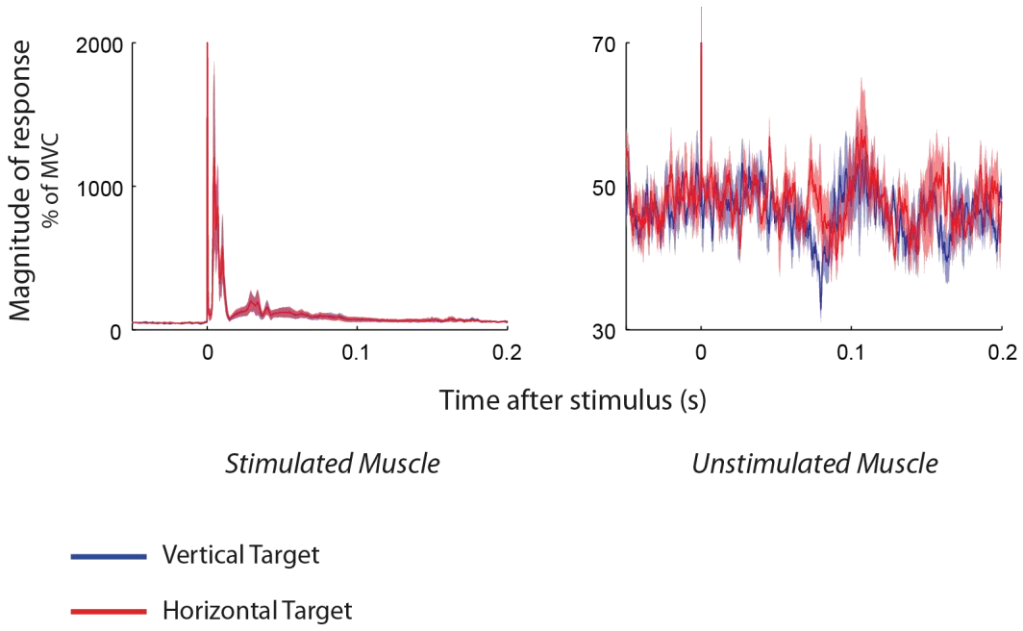


Figure 6.3 – Response to Median Nerve stimulation

The figure shows the response to median nerve stimulaiton in both the stimulated and unstimulated muscles for the first 200ms after stimulation. The MEP in the stimulated muscle results in an electrically induced perturbation of cursor position from the perspective of the subject. In the unstimulated muscle there is an increase in muscle activity occurring 90ms after stimulation, but this increase is not target specific.

6.3.2 M1 Stimulation

(Two subjects were discarded due the presence of MEPs in the unstimulated hand.)

Figure 6.4 shows the averaged data from the other five subjects. In the un-stimulated hand there was a response occurring in the interval 60-100ms after stimulation. The average contraction level for the horizontal targets in this range was 50.5 ± 3% and the value for the vertical targets was 48.6 ± 2%. They were not significantly separated ($p=0.13$, $t(5)=1.82$), and the response was not dissimilar enough to be considered target specific.

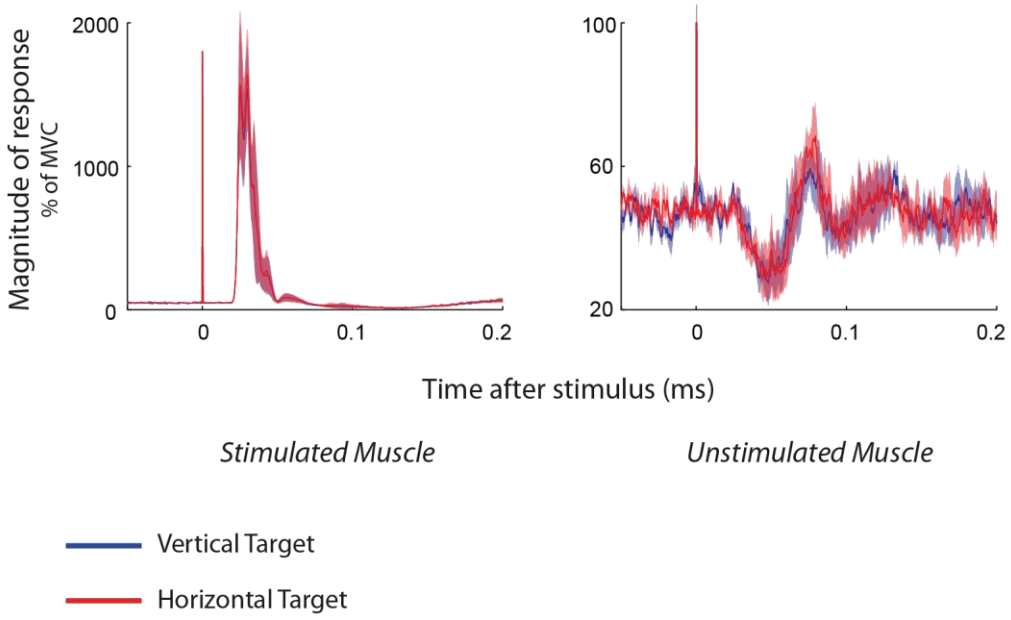


Figure 6.4 – Response to Transcranial Magnetic Stimulation

The figure shows the response to TMS in both the stimulated and unstimulated muscles for the 200ms following the stimulation.

6.4 Discussion

6.4.1 Median nerve stimulation

In the previous experiment, a response was observed in the unstimulated muscle, but that result was inconclusive, due to the difficultly of stimulating a single muscle in the hand itself. Therefore here the muscles were separated across hands, in order to remove the confounding factor of stimulation resolution, and a non-target specific response was observed in the unstimulated muscle. Since the response is non-target specific, it is difficult to say whether it is cortically modulated, however it does provide a basis for further experiments based on bimanual co-ordination.

6.4.2 M1 stimulation

A response was observed in the unstimulated hand, but again this response was not target specific. The nature of the response is an increase in activity in the unstimulated

muscle for both targets. Taking the ipsilateral silent period into account, this fits with an assumption that activity is not available from the stimulated muscle, but it is still difficult to identify the exact nature of how the brain has perceived an attempted to adapt to the perturbation.

As earlier discussed, the important factor is whether there is a target specific response, and the fact that this was not observed has several possible explanations. The first is that the efference copy, and hence the state estimate, has been disrupted, but the exact effect in terms of target response was too small to resolve fully in this form of the experiment. The second possibility is that, assuming OFCT is correct, the efference copy does not arise in M1, and that a target specific correction based on a perceived perturbation could be achieved via stimulation of other motor areas. In particular (Desmurget et al., 2009) induced belief of movement via stimulation of parietal cortex areas and movement without awareness through stimulation of premotor areas, potentially linking them to creation of efference copy.

However, there were two flaws in the design of this experiment which contributed to the decision not to pursue it. The first was a practical barrier present with stimulation; it was difficult to maintain a constant coil position throughout the duration of the experiment (8 blocks each lasting 8 minutes). The small number of TMS trials in each block meant that any 'missed' trials had a disproportionate effect on the overall result and increasing the time of the experiment would merely have compounded the problem (and lost subject concentration). This issue could have potentially been overcome by changing the experimental design, but a further problem existed in the subject's awareness of a perturbation occurring. In the visual perturbation experiment, subjects were not consciously aware of the exact nature of the perturbation, leading to reflex correction via optimal feedback. Here, TMS is not easy to hide, resulting in subjects being aware of trials that are different from the norm, and creating interference with the simple model of mismatch between predicted and real sensory feedback. Therefore the data here is inconclusive, as the creation of the perceived perturbation could potentially be affecting how it is conceptualised and dealt with.

6.4.3 SMA stimulation

SMA stimulation was also attempted, the area having been reported to be involved in the creation of the efference copy and hence potentially influence learning and adaptation protocols (Haggard and Whitford, 2004, Nachev et al., 2008). However, it proved difficult to find a level of TMS where SMA was stimulated, but M1 was not. As a result, m-waves were present in a significant number of trials, obscuring any potential effect arising from SMA stimulation. Therefore I decided not to pursue this line of thinking.

6.5 Conclusion

Experimental design flaws made the results observed here inconclusive. Therefore I decided that based on the lack of any clear effects that could be worth pursuing and the design flaws within the experiment, this line of investigation was not worth pursuing within the time constraints of a PhD.

CHAPTER 7 - MCI MODELLING

In which I look at models used to understand data presented in Chapters 3-5. The first, used to look at adaptation to global rotations and the effect of M1 and cerebellar stimulation on that adaptation, is a multi-process adaptive model. The second, used to look local rotations, is a reward modulated Hebbian learning algorithm.

7.1 Modelling global perturbations

7.1.1 A multi-rate adaptive model

In Chapter 1 it was discussed that motor adaptation is a more complex process that can be described by a single state model. Effects such as savings, anterograde interference and spontaneous recovery are present in real adaptation, but cannot be accounted for so simply. (Smith et al., 2006) proposed a two state model in which two neurally distinct processes drive adaptation. It has successfully been shown to describe effects in reaching movement (Sing and Smith, 2010) and saccade adaptation tasks (Ethier et al., 2008). In this section I took this model and applied it the experiments described in Chapter 5.

The model describes adaptation as the result of two processes acting on differing timescales: a fast process that reacts strongly to error, but retains information poorly, and a slow process that retains information, but with little immediate response to error.

The model assumes that a perturbation of the system results in an error that then drives the evolution of the two learning processes, each with their own rates of learning and retention (Sing and Smith, 2010). It can be described with:

$$e(n) = P(n) - x(n)$$

Eq. 7.2

$$x(n) = x_{fast}(n) + x_{slow}(n)$$

Eq. 7.3

$$x_{fast}(n+1) = A_{fast} \cdot x_{fast}(n) + B_{fast} \cdot e(n)$$

Eq. 7.4

$$x_{slow}(n+1) = A_{slow} \cdot x_{slow}(n) + B_{slow} \cdot e(n)$$

Eq. 7.5

$$A_{fast} < A_{slow}; B_{fast} > B_{slow}$$

Where $e(n)$ is the error on trial *n* (0 if no visual feedback is available)

$P(n)$ is the perturbation applied on trial *n*

$x(n)$ is the net motor output on trial *n*

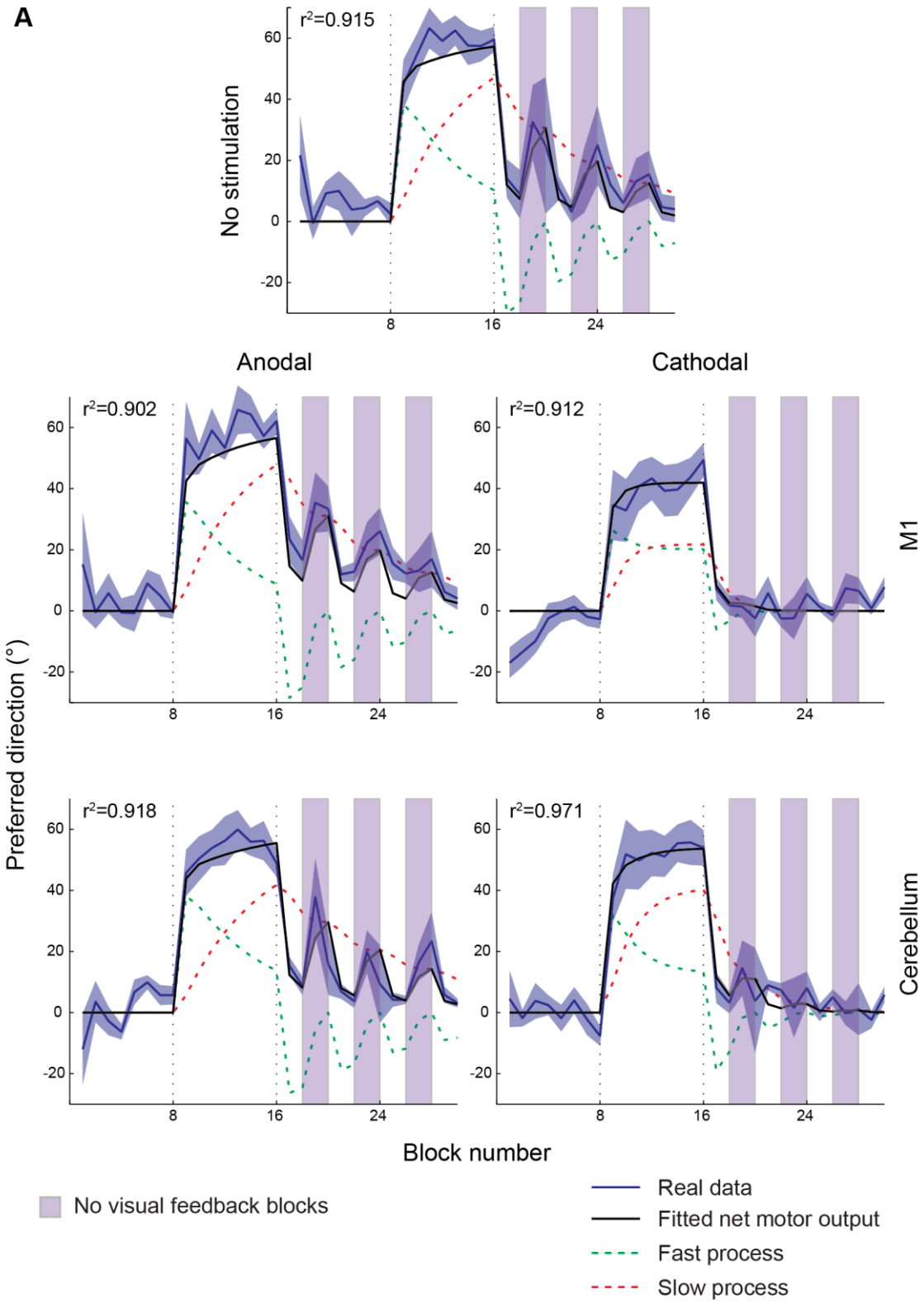
x_{fast}, x_{slow} are internal states that contribute to the net motor output and

A, B denote respectively the retention and learning factors

The collected data can be modelled by providing the perturbation/visual feedback structure of the task. The model determines the values of the fast and slow components of the learning and retention factors which result in a net motor output that best fits each dataset (no stimulation, anodal/cathodal stimulation of M1/cerebellum).

7.2 Results

I fitted each set of modelled global rotation data to the corresponding real dataset using an Excel Solver Evolutionary algorithm minimizing a least squares measure. The results of both the fitted curves and the associated values are shown in Figure 7.1.


A
No stimulation
r²=0.915
Anodal
Cathodal
r²=0.902
r²=0.912
M1
r²=0.918
r²=0.971
Cerebellum
Preferred direction (°)
Block number
No visual feedback blocks
Real data
Fitted net motor output
Fast process
Slow process

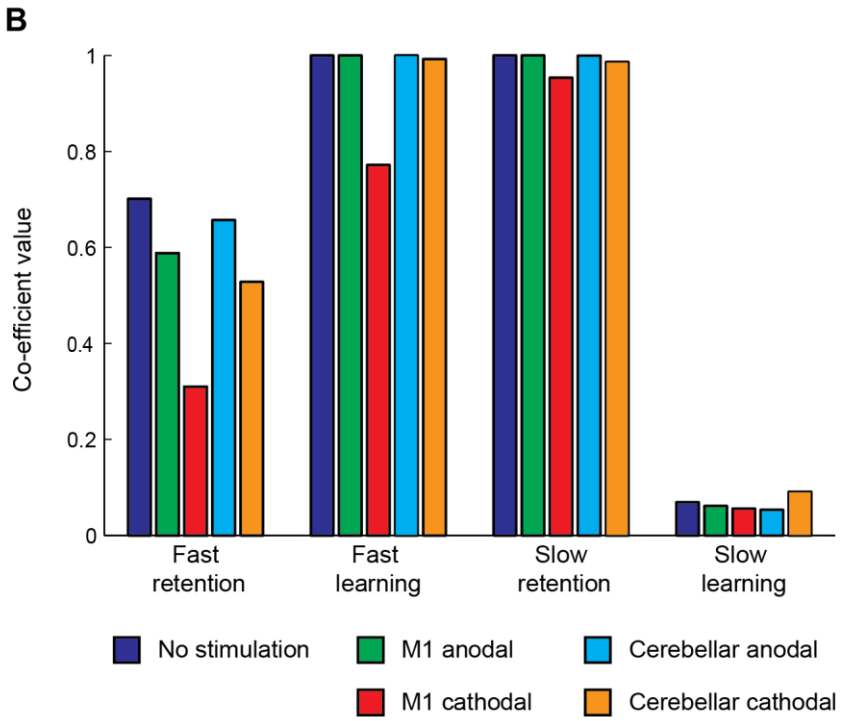


Figure 7.1 - Fitted data for global perturbations and comparison of learning and retention factors

A – Real and fitted datasets for the global rotation task in Chapter 5. Conditions are; No stimulation, Anodal/Cathodal stimulation of M1 and Anodal/Cathodal stimulation of the cerebellum. Each graph shows the individual contributions of the fast and slow processes and the net motor output fitted against the data presented in Chapter 5.

B – Comparison of fast and slow components of the learning and retention factors from the fits shown in Figure 7.1A.

Small changes in the slow retention co-efficient have a large impact on net motor output. Under cathodal stimulation of M1 the reduction in slow retention is small, but the effect on the decay of the slow process is enough to vastly reduce the appearance of spontaneous recovery. A similar effect was seen under cathodal stimulation of the cerebellum, with a small change in the slow retention resulting in a depression of the spontaneous recovery (although not to the same extent).

The lowered fast learning component under cathodal stimulation of M1 results in a lack of decay of the fast process during the Adapt phase, and hence a very small negative response in the same process upon the return to the initial mapping.

In order to look at the contribution of each process to the variation seen between the conditions, I found the fast/slow component values that best fitted all conditions taken together, then looked at solely varying either the fast or slow process and finally comparing the co-efficient of determination for each case. Fitting the fast/slow components to all models take together ensures that deviations that could be explained with the same model exploring a different space are not taken as a sign of the model itself being insufficient (as would be possible by using the No stimulation fit to assess the other conditions). The result is shown in Figure 7.2.

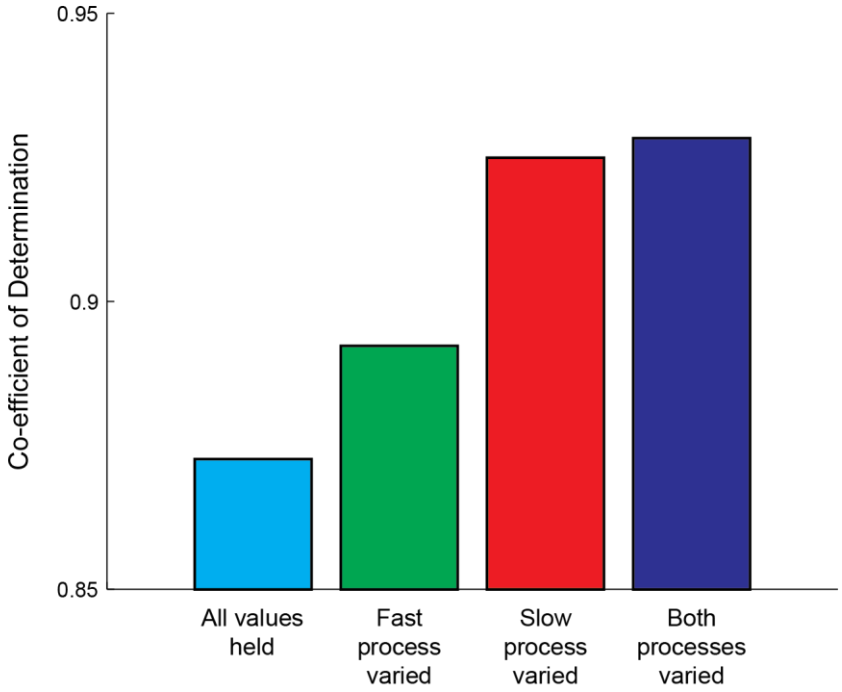


Figure 7.2 – Co-efficients of determination for varying model fits

The chart shows the co-efficient of determination calculated over all the conditions shown in Figure 7.1A taken together. 'All values held' refers to the optimal fast/slow process factors when fitting over all conditions. The fast and slow process was then individually varied for each condition while holding the alternate process stable. Finally, the optimal factors found for Figure 7.1 were used.

Varying the fast process does not improve much over the initial held values, but varying the slow process accounts for nearly all of the improvement observed when both process factors are varied for each individual condition. This indicates that the majority of the variation between conditions observed in Figure 7.1A can be explained solely by an effect on the slow process. This is particularly relevant when considering the effect of cathodal stimulation over M1, the condition in which the greatest variation from the no stimulation condition is observed.

7.3 Discussion

Multiple adaptive processes describe adaptation to abstract sensorimotor mappings

The first important point to make is that this model describes adaptation to abstract mappings extremely well. In previous work, the multi-rate model has been used to describe adaptation to tasks in which the null state (the equivalent of the initial mapping in the tasks described here) is natural behaviour. Here I have shown that the same model can be used to describe adaptation and de-adaptation to tasks which are both novel and non-naturalistic.

The effect of stimulation on multiple adaptive processes

There are two main conclusions that can be made from modelling the effect of tDCS on this task. Firstly, with respect to anodal vs. cathodal stimulation, in general cathodal stimulation is associated with lowered rates of learning and retention compared to anodal/no stimulation. Secondly, regarding M1 vs. cerebellar stimulation, stimulation of each area results in similar changes, but those changes are more pronounced in M1.

Looking more specifically at the fits achieved here, there are two key points that I wish to discuss. Firstly, the effect of cathodal stimulation of M1 (i.e. the reduced adaptation during the Adapt phase and the loss of the after-effect and the spontaneous recovery during the Probe phase) can be attributed to an effect solely on the slow process. rTMS of M1 has been previously shown to specifically affect the slow adaptive process during reaching movements (Richardson et al., 2006, Hadipour-Niktarash et al., 2007). In

Chapter 5 it was discussed that these results potentially contradicted (Galea et al., 2011), in which M1 stimulation resulted only in an effect on retention. The modelling here implies that the studies are compatible, but that the differentiation between M1 and the cerebellum (and indeed, slow and fast adaptation processes) cannot be considered as simply as a direct retention/adaptation split.

It is also of note that an effect on the slow process has also been achieved via stimulation of the posterior parietal cortex (Della-Maggiore et al., 2004). (Tunik et al., 2007) suggested that, instead of being anatomically segregated, distinct adaptive processes could be attributed to differing functional interaction within standard sensorimotor circuits. Therefore the contribution of other areas to effects on a global rotation is an area in which further investigation could prove useful.

Modelling local perturbation structures

A major limitation of this model for this task is that it cannot be translated to a local perturbation in its current form. Since only one error signal is available, and that error does not include noise, the model has no means of distinguishing the two sets of muscles that have been rotated. Further to this, the lack of noise means that there is no associated cost for incorrect solutions, and therefore the current model is not capable of identifying a remapping solution as being closer to the optimum than a re-aiming one.

In Chapter 5, I identified two forms of adaptation, referred to as classic and modular adaptation, with one of the key features of modular adaptation being that it did not demonstrate classic effects such as spontaneous recovery. However, cathodal stimulation of M1 and cerebellum resulted in spontaneous recovery occurring in the context of a local rotation. Since this is an effect which arises due to the interaction of multiple processes, it would be beneficial to extend this model to a point where it is capable of disassociating sets of muscles.

7.4 Conclusion

Adaptation to a global perturbation in an abstract MCI task is well described by a two-state model with adaptive processes acting on different timescales. The model also

replicates performance under stimulation of M1 and the cerebellum, in particular the effect of cathodal stimulation of M1, reducing both adaptation and spontaneous recovery, can be modelled as a specific effect on a slow adaptive process under a scenario in which multiple processes are contributing with adaptation. This fits with previous research locating M1 as the potential site for a slow process.

CHAPTER 8 - GENERAL DISCUSSION

In which I summarise the results achieved as part of this thesis and discuss the implications and future directions of the work.

8.1 Summary

MCIs provide the ability to explore questions of motor control from a different perspective from naturalistic movement tasks by allowing the creation of abstract sensorimotor tasks. In this thesis I have used multiple MCI tasks to investigate the ability of the motor system to learn abstract mappings, and adapt to differently structured perturbations. In particular, this is the first work in which locally structured perturbations (where subsets of contributing muscles are perturbed in different ways) are investigated. I have examined how subjects perform when faced with local perturbations, how the form of adaptation differs in comparison to the standard global adaptation, the strategies that subjects use in order to deal with the perturbation, how M1 and the cerebellum contribute to the use of those strategies and how M1 and the cerebellum are involved in the underlying adaptive processes involved in the two forms of perturbation (global and local).

8.2 The use of the MCI as a motor task

MCIs and BCIs are similar in their basic function, and both allow the investigation of the nature of motor control while freed from biomechanical restraints. However, MCIs can be used to investigate similar questions without the need for invasive procedures.

In Chapter 1, I discussed three key feature of the MCI that make it particularly useful as a tool for studying motor learning and adaptation. To recap, these are:

1) The ability to create novel, abstract sensorimotor mappings

2) The ability to precisely define the relationship between activation of individual effectors and overall outcome.

3) The ability to create perturbations that affect a subset of contributing muscles.

Further to point 2, in the tasks used here the contributions of the effectors are simple and easily described. Through this, we avoid the complex mathematics associated with both describing behaviour and determining optimal performance. Even with such simple movements as reaching, the maths governing the limb biomechanics quickly becomes extremely complex. In an abstract task with a small number of contributing effectors (importantly, the only units that can contribute at all) the problem of increasingly complex equations is sidestepped.

8.2.1 Performance of MCI tasks

Subjects were able to learn novel, abstract mappings within a very short time frame (approx. 20 minutes), and exploit task redundancy by using multiple muscles to complete the task – in line with models of minimizing signal-dependent noise. The redundancy of the task also created a choice for subjects in terms of how they adapt to perturbations. When presented with perturbations to the original mapping, subjects used various strategies to adapt – resulting in the shifting of the PD or the increase/decrease of individual muscle activity. The choice of strategy is dependent on the individual perturbation scheme and provides an insight into the mechanism behind adaptation.

In Chapter 3, I showed that subjects can find the optimal solutions in novel, abstract motor tasks even when those solutions are difficult to find and not necessary for task completion. The exploration to find those solutions was biased by naturalistic muscle relationships, but they ultimately did not constrain the ability to find the optimal solutions. This indicates that motor primitives act as priors, but are not hardwired constraints on the motor system. However, it is relevant to this point that this work was done using hand muscles as the basis of control and it has been previously noted that finger movements require a high degree of flexibility and specialization, making it difficult to provide any definitive comment on the existence of muscle synergies (Tresch and Jarc, 2009).

8.2.2 The cortical and cerebellar contributions to global and local adaptation

Subjects were able to adapt both to consistent perturbations of a muscle-DoA mapping (global), and to perturbations that affected a subset of the muscles used (local).

In Chapter 5, I looked at the differing nature of global and local adaptation. I showed that adaptation to a global perturbation resulted in the presence of an after-effect and spontaneous recovery of the adapted state, both hallmarks of classical adaptation. Under a local perturbation, neither of these effects were present, indicating different processes underlying the two forms of adaptation. I suggested that the two differed in their relationship to the internal model, with global adaptation resulting in alterations to a single internal model, and local adaptation resulting in creation of a new model.

I also demonstrated differing effects on global and local adaptation via stimulation of M1 and the cerebellum. Cathodal stimulation of M1 detrimentally affected adaptation to a global perturbation, while cathodal stimulation of the cerebellum detrimentally affected adaptation to a local perturbation. This reinforces the idea that the two forms of adaptation are driven via different processes and further to this suggests that those processes are dependent on the respective areas.

I conceptualised this idea in the form of a two-stream model, with a global stream consisting of a fast and slow process, both to some extent dependent on M1, and a local stream consisting of a modular process, dependent on the cerebellum. This model accounted for some of the effects observed under stimulation, but it is clear that as adaptation increases in complexity, multiple adaptive processes driven from different sites are revealed, and cannot be described by simple one/two process models.

8.2.3 Motor strategies

The use of the term ‘motor strategy’ in previous literature has been used to refer to conscious use of an explicit, specific and independent technique for (e.g.) adapting to a perturbation. (Taylor and Ivry, 2012) describe an experiment in which subjects were instructed to aim at an imaginary target in order to compensate for a perturbation, with this activity described as an explicit motor strategy.

Here, the term ‘strategy’ is used to refer to the way in which muscles are used in relation to one another in an MCI task. Importantly, in none of the tasks were subjects given an explicit strategy to follow and were just told to maximize either success rate or score. The strategies described exist in a spectrum ranging from the global re-aiming strategy, to the local re-mapping strategy.

In Chapter 4 I showed that motor strategy use can be biased by direct current stimulation of M1 and the cerebellum, highlighting the fast that anodal stimulation had the effect of pushing the stimulated hand towards a more global solution. This is particularly interesting as it demonstrates that increasing excitability, and thus enhancing the learning rate (as demonstrated in Chapter 5 under global perturbations) may not necessarily be beneficial for improved motor task performance in the case of complex tasks, as it appears to reinforce inappropriate learning.

8.2.4 Bimanual vs. unimanual tasks and tDCS

Comparing the local perturbation conditions (without stimulation) between Chapters 3-5, it is interesting to note that subjects are more successful at finding a remapping solution in the unimanual version of the task, as opposed to the bimanual version. (Although the two cannot be directly compared, as the task structure is different, and the bimanual task is effectively the unimanual task occurring in both hands simultaneously, making it more complex by nature). It would be interesting to look further at the comparison of a no stimulation within hand task in the score-based paradigm, with the prediction being that the effect observed in the success-based paradigm (within hand reaching the remapping solution faster than across hand) would be emphasised, and to determine whether it is inherent to the bimanual structure that a greater level of re-aiming is observed compared to the unimanual structure.

In terms of stimulation, tDCS during performance of a unimanual task resulted in site specific effects on adaptation depending on the form of adaptation, whereas in the case of a bimanual task, stimulation of M1 and cerebellum had the same overall effect. There are two important points to make here regarding the comparison between the two tasks; the first is that the extent to which remapping had been achieved was different, with a fuller remapping solution being present in the unimanual task under the no stimulation

condition. If multiple processes are contributing to the adaptation, then it is possible that the relative contributions of those processes (and hence the corresponding brain areas) are different between the two tasks at the point where stimulation was applied. Secondly, stimulation in the bimanual task was intended to look at an effect within performance of a single condition, as opposed to the cross-condition comparison of the unimanual task. Since each hand cannot be thought of in isolation, it is difficult to directly compare the effect of stimulation on muscle use in MCI tasks here.

8.2.5 MCI application to prosthetics

With regards to the hierarchy of adaptation discussed in Chapter 3, MCIs are based on signals extracted from a higher level of control, and as such myoelectric control is easier and faster to learn than brain control. As a result, the use of EMG signals recorded from the periphery of the nervous system is the preferred option when attempting to return a degree motor control to patients. This is particularly relevant in the case of amputee patients, as the muscles themselves are not available, but the output signals are still accessible (Kuiken et al., 2007).

Further to this, I have demonstrated that (at least in terms of distal and proximal muscles) a high degree of flexibility is available in terms of how muscles relate to each, regardless of naturalistic use. This indicates that future prosthetics may not have to be based entirely on replicating natural behaviour, and biofeedback based designs that will ultimately allow a greater level of control could be learned by patients.

8.3 Future directions

The adaptability of the MCI task means that there is a huge array of experiments that could potentially be performed using it, a small range of which I have presented here. In this section I wish to discuss future work that could be performed, firstly specifically related to the experiments described here and secondly in a more general sense.

8.3.1 Extension of experiments

The experiments here have all focused on a small group of muscles, specifically distal hand and wrist muscles. However, no such limitation exists for MCI study. The varying degree to which different groups of muscles can move beyond their naturalistic use has already been investigated to some extent by (Radhakrishnan et al., 2008) and (de Rugy et al., 2012), but this work was still limited to arm muscles. Therefore there is a wide range of muscle use in abstract tasks that has yet to be investigated (the most obvious being muscles in the leg, due to the potential practical application to myoelectric based prosthetic limbs).

At specific points during the experimental chapters I discussed future work that could be undertaken, or would need to be in order to verify predictions based on the results here. A brief recap follows:

In Chapter 4, it was noted that in the no stimulation version of the bimanual task, subjects continued to utilise a re-aiming solution upon the return to the initial mapping. This is particularly interesting, because if effort is indeed the focus of the cost function, then this would be considered a sub-optimal solution occurring after the optimal solution has been experienced. There are several possible explanations, the penalty is not great enough to induce a return to the optimal solution, the motor system is biased towards correct solutions, regardless of whether they are optimal, or there is some aspect to the cost function that is being optimized that results in the re-aiming solution being considered optimal. As suggested in Chapter 4, a potential starting point for investigating this question would be looking at the extent to which re-aiming/remapping occurs when the perturbation takes place within hand as opposed to across both hands.

In Chapter 5, experiment 5.1, I did not find any evidence of structural learning. However, it was noted that the design of experiment could have been altered in order to create conditions in which structural learning effects were more likely to be observed, specifically by changing the final phase to a local perturbation and determining whether previously experiencing a local structure was beneficial to adaptation.

Also in Chapter 5 I discussed the integration of dual adaptation and models of fast and slow processes with the two stream internal model switching I described there. A

potential path for continuing this work would be the progression of PD in an experiment where the DoA switched repeatedly between multiple global or local perturbations.

Finally, with regards to the modelling in Chapter 7, the next step would be modelling local perturbations. The difficulty of doing so with the current multi-rate adaptive model was discussed in that chapter, so the extension would require either updates to the model, or new techniques (such as reward-based algorithms (Legenstein et al., 2010)) would be required. A further continuation of the work would be replicating the features of the hierarchy based adaptation experiment, potentially through the use of hierarchical Bayesian modelling. The attractive feature of this is the ability to use likelihoods of outcomes, ideal for a system in which the controller descends through a hierarchy of what is considered 'most likely' (Braun et al., 2010b, Kemp and Tenenbaum, 2008).

8.3.2 Other brain areas

Posterior parietal cortex

Posterior parietal cortical (PPC) areas have been noted to be involved in adaptation to visuomotor rotations (Tanaka et al., 2009, Krakauer et al., 2004). (Graydon et al., 2005) showed early activation during learning of a visuomotor rotation, indicating a relationship to acquisition of a transformation. Although here I have focused on processes that are potentially M1 and cerebellum dependent, it is likely that the processes encompass multi-area networks within the brain and it is important not to neglect the contributions of areas such as PPC. In addition, PPC has been linked to awareness of movement (Desmurget et al., 2009) and could be relevant to the efference copy creation discussed in Chapter 6.

The basal ganglia

The basal ganglia is thought to be involved in the reward based aspects of motor learning (reinforcement learning) (Doya, 2000) and has been essentially ignored by this work. The reason for this is simply the difficulty of stimulating the area. Since it is not located near the surface of the brain (like the cerebellum and M1) tDCS is not an option (certainly not as a non-invasive technique). Therefore, looking at the effect of the basal

ganglia on strategy usage in this work was not possible, hence its absence. However, there are opportunities to study the contribution of the basal ganglia in the form of patient groups, for example the basal ganglia is highly affected in Parkinson's disease (Obeso et al., 2008) and future work could potentially look at the ability of these groups to control MCIs.

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