# Contributions of Cortical and Subcortical Circuits to Reaction Times and Excitability Levels in Complex Tasks

by

Michael Daniel Kennefick

BHSc, The University of Ottawa, 2008

BHK, The University of Ottawa, 2012

MSc, The University of Ottawa, 2014

A THESIS SUBMITTED IN PARTICAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPY

in

The College of Graduate Studies

(Interdisciplinary Graduate Studies)

THE UNIVERSITY OF BRITISH COLUMBIA

(Okanagan)

OCTOBER 2018

The following individuals certify that they have read, and recommend to the College of Graduate Studies for acceptance, a thesis/dissertation entitled:

CONTRIBUTIONS OF CORTICAL AND SUBCORTICAL CIRCUITS TO REACTION TIMES AND EXCITABILITY LEVELS IN COMPLEX TASKS

submitted by Michael Kennefick in partial fulfillment of the requirements of

the degree of Doctor of Philosophy.

Dr. Paul van Donkelaar, School of Health and Exercise Sciences

**Co-Supervisor**

Dr. Chris McNeil, School of Health and Exercise Sciences

**Co-Supervisor**

Dr. Gordon Binsted, School of Health and Exercise Sciences

**Supervisory Committee Member**

Dr. Brian Dalton, School of Health and Exercise Sciences

**Supervisory Committee Member**

Dr. Miriam Spering, Department of Ophthalmology and Visual Sciences

**University Examiner**

Dr. Aimee Nelson, Department of Kinesiology, McMaster University

**External Examiner**

**Abstract**

The way humans interact with their environment can range from simple reaching and grasping movements to remarkably complex movement patterns. Complexity increases reaction time (RT) and alters the excitability of the motor system. However, this area of research lacks a detailed description of the locus of the processes involved in the successful preparation and execution of complex movements. As the motor system can be influenced by cortical, spinal, and peripheral components, the overall purpose across the four studies of this thesis was to assess separately how they contribute to complex movement preparation and execution. The purpose of study 1 was to describe how movement complexity affected whole-body anticipatory postural adjustments (APAs). In this study, it was shown that APA onset times increased prior to an imperative stimulus (IS) as movements became more complex, demonstrating the motor system integrated movement complexity into a global motor plan. To isolate corticospinal contributions to this motor plan, study 2 used transcranial magnetic stimulation (TMS) to demonstrate that motor evoked potentials (MEPs) increased as a consequence of movement complexity. Study 3 used a combination of TMS and transmastoid stimulation to assess the cortical and spinal contributions to the increase of the MEP. This study demonstrated that increases in MEP due to movement complexity were mediated at the spinal level. Furthermore, it was shown that motoneuron excitability increases at least 50% earlier than previously described in the literature. As the spinal cord also receives descending input independent of cortical influence (e.g. extrapyramidal pathways), the purpose of study 4 was to examine if the vestibulomotor system had a role in the preparation of complex movements. This study demonstrated that vestibular-evoked responses are greater during the preparation of complex movements in both the upper and lower limbs. Prior to this study, the vestibulomotor pathway was shown to be involved in the online control of arm movements; however, this demonstrates the vestibulomotor pathway is also

involved in the preparation of movement. Overall, this thesis demonstrates a complex interaction of multiple elements of the motor system in the execution of movement.

**Lay Summary**

Understanding how humans produce complex movements requires a better characterization of the regions of the body responsible for movement production. The motor cortex within the brain initiates movement, but the descending command can be altered at many sites between the brain and muscle (motor output). This includes the spinal cord itself, or input from the vestibular system (which is responsible for relaying information regarding balance to the brain and spinal cord). Study 1 showed that postural responses are altered by movement complexity. Study 2 demonstrated that an increase in movement complexity leads to an increase in the excitability of the motor pathway. However, study 3 demonstrated the information required for complex movement production is delivered to the central nervous system at some level below the motor cortex, perhaps by the vestibular system, as revealed by study 4. The interaction between these areas as it relates to movement production is discussed.

**Preface**

Chapters 2-5 are based on work conducted at the University of British Columbia Okanagan. The methods in chapter 2 were approved by the the University of British Columbia's Behavioural Research Ethics Board (H11-02368) and the methods in chapters 3-5 were approved the University of British Columbia's Clinical Research Ethics Board (H17-00796).

A version of chapter 2 has been accepted for publication. Kennefick, M., Wright, A.D., Smirl, J.D., van Donkelaar, P (2018). Anticipatory postural adjustments as a function of response complexity in simple reaction time tasks. Neuroscience Letters 684: 1-5. MK and PvD were responsible for the design of the study. MK performed data collection. MK and ADW performed the analyses. MK wrote the manuscript. All authors had full access to the data, interpreted the data, and critically revised the manuscript before reviewing and approving the final version. Reprinted with permission from Elsevier.

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**Glossary**

| Definition | Abbreviation |
|---|---|
| AMT | Active motor threshold |
| AP | Anterior-posterior |
| APA | Anticipatory postural adjustment |
| CE | Corticospinal excitability |
| CMEP | Cervicomedullary motor evoked potential |
| CNS | Central nervous system |
| EMG | Electromyograph |
| EVS | Electrical vestibular stimulation |
| GVS | Galvanic vestibular stimulation |
| IS | Imperative stimulus |
| MEP | Motor evoked potential |
| ML | Medial-lateral |
| MT | Movement time |
| PMd | Dorsal premotor cortex |
| RMT | Resting motor threshold |
| rTMS | Repetitive transcranial magnetic stimulation |
| SAS | Startling acoustic stimulus |
| TMS | Transcranial magnetic stimulation |

**Acknowledgements**

I am certain this thesis, let alone the journey that has been the past 4 years, would not have been possible without the help of many others. I would first like to thank all past and present members of the Sport Concussion Research Lab, with particular thanks to Sandy Wright, Colin Wallace, Jon Smirl, and Joel Burma for their contributions to this work and to my overall doctoral experience, in addition to Rhyan McKay who only graced our lab space for a short while.

I had the privilege of having two distinguished researchers as co-supervisors on this journey. Dr. van Donkelaar, your guidance during my first years allowed me to seamlessly integrate into my new environment and community. Your faith in my ability and work ethic undoubtedly enhanced my experience as a doctoral student. Dr. McNeil, I will forever be in awe of your meticulous attention to detail. You do not accept anything less than excellent writing, and because of this I owe much of my growth as a writer to you. I would furthermore like to thank you both for giving me the opportunity to take part in research projects outside of typical academia.

I am eternally grateful to my family for providing me with endless love and support. Moving 4000 kilometres away was never going to be easy, but it never felt like I was too far away.

**Dedication**

For Sophie

Your birth brought me tremendous joy at a time of maximal frustration. You will never realize the incredible effect you had on the family at this time, but I hope you can always read these words and feel how special you are to us all.

## Chapter 1: Introduction

### The motor pathway

The initiating and execution of movement takes time. This suggests the brain processes information in one or more steps and at a finite speed. The process of movement execution can be described in two parts: the foreperiod and the response time. Schmidt and Lee (2011) have described the foreperiod as the interval between a warning signal and the presentation of an imperative stimulus (IS), each of which can be presented in a variety of modalities (e.g. auditory, visual, or tactile). The response time can be broken down into two distinct time intervals; the reaction time (RT) and the movement time intervals. The RT is the interval between the presentation of the IS and the onset of movement (i.e. the onset of muscle activity; premotor RT), which is thought to present the central processes involved in making a response. The movement time is typically defined as the interval between the end of the RT interval and the completion of movement, which can range anywhere from a few milliseconds (ms) to several minutes, or even hours. As RT reflects the central processes associated with making a response, the processes contributing to increases or decrease in RT have long been of interest to scientists. One way to probe these processes is to artificially stimulate the brain, and to measure the resultant motor output. While this input/output relationship may seem straightforward, the manner in which scientists interpret this relationship requires a profound understanding of how the brain functions.

The mammalian motor pathway incorporates several different descending systems (Lemon, 2008). The best described descending system is undoubtedly the corticospinal tract, which is a complex system mainly involved in the cortical control of segmental activity (Lemon, 2008; Lemon & Griffiths, 2005). Specifically, this system is heavily implicated in the control of

afferent inputs, spinal reflexes and motoneuron activity (Lemon & Griffiths, 2005), and thus is paramount to the mediation of voluntary movements (see Welniarz, Dusart, & Roze, 2017 for a review). Our current knowledge of descending pathways is primarily the result of Hans Kuypers's life work (Lemon, 2008), to which he dedicated to localizing where the various descending pathways terminated (Kuypers & Brinkman, 1970). The majority of corticospinal tract axons originate from pyramidal cells located in the inferior part of cortical layer V in the primary motor and sensory cortices, with other cortical regions making smaller contributions (Nudo & Masterton, 1990). Aside from the corticospinal tract, Kuypers (1981) separated the remaining descending pathways into two groups: group A (ventromedial) and group B (dorsolateral) brainstem pathways. Belonging to the reticulospinal, tectospinal and vestibulospinal descending pathways, group A fibres arise from the brainstem reticular formation, superior colliculus, and the vestibular complex. These fibres are considered to be a bilateral postural control system for head, neck, trunk and proximal limb movements (Lawrence & Kuypers, 1968). Group B fibres belong to the rubrospinal pathway, which Kuypers (1981) considered to provide additional capacity for flexion-based movements involving more distal limb segments.

These descending systems have since become colloquially known as pyramidal and extrapyramidal systems (or tracts; described below). In the interest of simplicity, this thesis will hereafter describe the descending systems as the "motor pathway", which incorporates both the pyramidal and extrapyramidal tracts.

### The pyramidal tract

The pyramidal tract incorporates both the corticospinal and corticobulbar tracts and is known as pyramidal tract because it crosses-over at the level of the pyramids in the medulla. It

contains motoneuron fibres extending to the spinal cord (corticospinal tract) or to the brainstem (corticobulbar tract) (Rea, 2015). The corticospinal tract contains approximately one million axons, 40% of which originate from the motor cortex, through the subcortical white matter, the internal capsule, the cerebral peduncle, the pons and the medulla. At the pyramids, approximately 90% of the axons cross the spinal cord to form the lateral and medial (ventral) corticospinal tract. Ultimately, the corticospinal tract makes monosynaptic or indirect connections with motoneurons in the ventral horn of the spinal cord and innervates muscle to elicit movements (Kandel, Schwartz, & Jessell, 2000). The information contained in the corticospinal tract does not travel unaltered. It is heavily modulated by a stream of tactile, visual and proprioceptive information necessary for accurate voluntary movement. Furthermore, motor cortex output is influenced by other motor areas such as the basal ganglia and the cerebellum (Kandel et al., 2000).

**Extrapyramidal tracts**

Extrapyramidal tracts coordinate, and process motor commands performed at a subconscious level via multiple projections to the motor pathway. First, they project to the motor cortex, modulating activity in the pyramidal tracts. Second, they project to cranial nerve nuclei, coordinating reflexive response activities linked to visual, auditory and equilibrium input. Finally, they project to the tectospinal, rubrospinal, reticulospinal and vestibulospinal motor pathways of the spinal cord (Waldman, 2009). The vestibulomotor pathway functions to maintain accuracy in three specific types of behaviours; (1) the control of gaze, (2) the production of compensatory neck and limb movements to maintain postural equilibrium, and (3) complex voluntary tasks, such as reaching. The vestibular system encodes self-motion relating to the head in space, thus providing essential information for the stabilization of gaze, and the

control of balance and posture. The vestibular apparatus contains two types of sensors: the first are three semicircular canals, which sense angular acceleration in three dimensions, and the second are two otolith organs (the saccule and the utricle), which sense linear accelerations in three dimensions. Afferent fibres of the vestibulocochlear nerve (cranial nerve VIII) carry signals from receptors cells of the sensory organs to the vestibular nuclei, which project to neural structures controlling eyes movements, posture, and balance, as well as neural structures involved in the computation of self-motion (Cullen, 2012).

Gaze and posture can be influenced by various reflexes, such as the vestibulo-ocular and vestibulospinal reflexes. Gaze, or head motions purposefully made to voluntarily redirect the visual axis, can be rapid (gaze shifts) or slow (gaze pursuit). These are coordinated sequences of eye and head movements that are made towards a target of interest (Cullen, Huterer, Braidwood, & Sylvestre, 2004). Humans can maintain stable gaze when moving through the world via the vestibulo-ocular reflex, which produces compensatory eye movements of equal and opposite magnitude to head rotations. This reflex is arguably the fastest human behaviour, responding to head movement in as little as 6 ms (Huterer & Cullen, 2002). The vestibulospinal reflex coordinates head and neck movements with the trunk and body to maintain the upright position of the head. This reflex is mediated by vestibular afferents to the vestibular nuclei, which in turn project to motoneurons (Cullen, 2012).

In addition to the vestibular system's involvement in the control of gaze and postural equilibrium, recent evidence has demonstrated the brain uses vestibular information for the online correction of planned movement trajectories (Day & Reynolds, 2005). Accurate reaching requires the nervous system to compensate for forces, such as Coriolis or centrifugal forces, that require humans to rapidly adapt and plan compensatory movements (Bockisch & Haslwanter,

2007). These adaptations have been shown in a variety of upper limb movements, for example reaching towards either earth-fixed targets while seated (Bresciani, Blouin, Popov, Sarlegna, et al., 2002; Mars, Archambault, & Feldman, 2003; Moreau-Debord, Martin, Landry, & Green, 2014; Smith & Reynolds, 2017) or standing (Bresciani, Blouin, Popov, Bourdin, et al., 2002. Importantly, adaptations to different movement conditions establishes a task dependency of the vestibular response during movement.

## The motor pathway: stimulation techniques

Merton and Morton (1980) were the first researchers to stimulate the brain without opening the skull, by using electrodes to penetrate it electrically. Similar to electrical stimulation of the exposed motor cortex of monkeys (Phillips & Porter, 1977), a brief high-voltage pulse is passed between electrodes affixed to the scalp. A single stimulus to the scalp elicits several descending volleys in the corticospinal tract either as a single direct (D) wave or transsynaptically via multiple sequential indirect (I) activation waves in pyramidal tract neurons. These waves can be distinguished from one another based on their latencies. The D-wave represents the earliest descending volley, while the I-wave(s) represents the later volley(s) (Patton & Amassian, 1954).

### Transcranial magnetic stimulation

In the early 1980s, transcranial magnetic stimulation (TMS) of the brain appeared and promised to be a major advancement in brain stimulation. Instead of using electrodes to generate electrical currents in the brain, TMS activates the brain using the principles of electromagnetic induction to generate electrical currents non-invasively (Barker, Freeston, Jalinous, Merton, & Morton, 1985). The first magnetic stimulation experiments were conducted by Polson and colleagues (1982) who used a prototype time-varying magnetic field machine designed to induce

an electrical current in the vicinity of a nerve, thereby activating it. TMS began replacing electrical stimulation in a research setting due in large part to three advantages: The first was its ability to penetrate bony structures such as the skull, which has between 8 and 15 times the resistance to electricity compared to soft tissue (Adrian & Yamagiwa, 1935), with relative ease (Barker & Jalinous, 1985). The second was its ability to stimulate the brain at lower stimulation intensities than required for electrical stimulation, which minimized the level of discomfort to the participant. The third was that TMS does not require any kind of physical or electrical contact with the body; stimulation can be achieved with the coil tens of millimetres from the body (Barker, Freeston, Jalinous, & Jarratt, 1987). Like electrical stimulation, TMS can evoke descending corticospinal tract activity in response to stimulation of the motor cortex; however, unlike electrical stimulation, magnetic stimulation does not easily produce a D-wave. The differences between electrical and magnetic stimulation appear to be due to the orientation of the axis of the neuron relative to the lines of stimulating current; i.e., stimulation in the horizontal plane with TMS might explain the lack of D-wave production (Day et al., 1989).

Application of TMS over the motor cortex evokes a compound short-latency excitatory response captured by the electromyogram (EMG) in a target muscle termed a motor evoked potential (MEP). This evoked potential can be used as an index of corticospinal excitability (CE; Rothwell, 1997). The latency of the MEP represents the conduction time of neural impulses from the motor cortex to target muscles, determined by corticospinal projections, summation of descending volleys converging on spinal motoneurons, and the conduction time along the axons of peripheral motoneurons (Bestmann & Krakauer, 2015). The MEP importantly consists of both cortical and spinal (Taylor, 2006), as well as peripheral components (Stefan, Kunesch, Cohen, Benecke, & Classen, 2000). If one wishes to isolate cortical and spinal contributions to the MEP,

stimulation of the corticospinal tract below the level of the motor cortex is required. This type of stimulation can be used to isolate motoneuron excitability by way of a cervicomedullary motor evoked potential (CMEP; Taylor, 2006).

A common way to determine the intensity of a TMS pulse used during an experimental protocol is to normalize stimulator output to the intensity necessary to evoke a small MEP. This response, termed the motor threshold, is generally lower for distal compared to proximal muscles (Rossini et al., 1994), highly variable across individuals, but remarkably constant for a given individual (Ziemann & Hallett, 2000). Because of this variability, most TMS researchers attempt to correct for this by normalizing TMS intensity as a proportion of an individual's motor threshold (McConnell et al., 2001). In healthy participants, the MEP amplitude increases with increasing stimulus intensity. This stimulus-response relationship is described by a sigmoid curve that starts as a flat line, deviating from zero once resting motor threshold (RMT) is reached (Groppa, Oliviero, Eisen, Quartarone, Cohen, Mall, Kaelin-Lang, Mima, Rossi, Thickbroom, Rossini, Ziemann, Valls-Sole, et al., 2012). Motor threshold can be measured while a participant is at rest (RMT), or when the participant is weakly contracting a target muscle, known as the active motor threshold (AMT). As the target muscle is preactivated during AMT, it transitions from the flat portion of the sigmoid curve earlier than RMT, thus requiring a lower stimulus intensity. However, neither RMT or AMT consider the maximal electrical potential (Mmax) of the target muscle and do not allow for comparable portions of the motoneuron pool to be measured across participants. The experiments in the current thesis have normalized all relevant stimuli to a percentage of the Mmax, indicating modifications at the corticospinal level (Davranche, Temesi, Verges, & Hasbroucq, 2015). In this technique, current is increased gradually with successive stimuli until the M-wave reached a plateau (Mmax). Once a plateau

was established, an additional two stimuli were delivered at that current to establish a mean Mmax value.

**Transmastoid stimulation**

Transmastoid stimulation is a non-invasive type of electrical stimulation of the corticospinal tract that elicits a short-latency excitatory response in a target muscle termed the cervicomedullary motor evoked potential (CMEP) and is dependent on the excitability of the motoneuron pool. In contrast to cortical stimulation (i.e. TMS), which elicits multiple descending volleys that can cause motoneurons to fire more than once (Day et al., 1987; Rothwell, Thompson, Day, Boyd, & Marsden, 1991), transmastoid stimulation evokes a single descending volley down the corticospinal tract. Importantly, collision studies have demonstrated that both the MEP and CMEP travel in many of the same corticospinal axons (Gandevia, Petersen, Butler, & Taylor, 1999; Taylor, Petersen, Butler, & Gandevia, 2002; Ugawa, Rothwell, Day, Thompson, & Marsden, 1991). Transmastoid stimulation is typically accomplished by passing a brief high-voltage between electrodes stuck to the skin in the groove between the mastoid process and the occiput (Taylor & Gandevia, 2004). As reviewed by McNeil and colleagues (2013), there are two aspects of CMEPs that make transmastoid stimulation the most direct method for testing motoneuron excitability in a conscious human (Martin, Butler, Gandevia, & Taylor, 2008). First, as mentioned above, the CMEP has a large monosynaptic component in the upper limb. Second, the descending signals are not subject to conventional presynaptic inhibition at the level of the motoneurons (Jackson, Baker, & Fetz, 2006; Nielsen & Petersen, 1994). This represents a marked improvement over other measures of motoneuron excitability, such as H-reflex. The H-reflex is the result of peripheral nerve stimulation (Magladery & McDougal, 1950) which produces action potentials that travel along afferent fibres until they reach motoneurons (Groppa,

Oliviero, Eisen, Quartarone, Cohen, Mall, Kaelin-Lang, Mima, Rossi, Thickbroom, Rossini, Ziemann, Valls-Solé, et al., 2012). However, the H-reflex is not an ideal measure of motoneuron excitability because the response can be influenced by Ib (Marchand-Pauvert, Nicolas, Burke, & Pierrot-Deseilligny, 2002), recurrent, or presynaptic inhibition (Hultborn, Meunier, Pierrot-Deseilligny, & Shindo, 1987), and post-activation depression (Crone & Nielsen, 1989).

**Galvanic vestibular stimulation**

As reviewed by Cohen and colleagues (2011), Luigi Galvani spent 20 years performing experiments attempting to demonstrate the electrical conductivity of nerves and muscles prior to the publication of his major collection of work in 1791. The first published work dedicated to probing the function of the vestibular system was physiologist Johann Purkyne's dissertation in 1820, where he described that galvanic current flowing through the head disrupted balance and equilibrium. During the Franco-Prussian War (1870-1871), Eduard Hitzig noted that nystagmus, or the rapid involuntary movement of the eyes, was a consequence of the application of electrical current to the brains of dogs and humans. This demonstrated that two outputs of the vestibular system could be modulated by galvanic stimulation. However, it was not until Josef Breuer in 1875 that these phenomena were shown to be of galvanic origin (see Fitzpatrick & Day, 2004 for a review). Nearly 230 years after Galvani's publication, the non-invasive technique used to stimulate vestibular nerves still carries his name. Galvanic vestibular stimulation, or GVS, has been used to activate vestibular nerve fibres by applying DC currents through the skin, over the mastoid processes (Cohen et al., 2011). This stimulus, also known as electrical vestibular stimulation (EVS), is most commonly delivered between two electrodes. When applied for as little as 1-2 s, a person sways if they are standing, or perceive an illusory movement if they are not (Fitzpatrick & Day, 2004).

There is considerable debate as to whether EVS primarily or exclusively activates the otolith system, or if the otolith and semicircular canal systems are equivalently activated (Cohen et al., 2011). While EVS induces the non-selective activation of central vestibular neurons related to both the otolith and semicircular canal systems (Courjon, Precht, & Sirkin, 1987; Ezure, Cohen, & Wilson, 1983; Peterson, Fukushima, Hirai, Schor, & Wilson, 1980; Wilson, Peterson, Fukushima, Hirai, & Uchino, 1979), the sensation of rocking/pitching, tilting of the head and/or body, and ocular torsion favour otolith system activation (Bent, Bolton, & Macefield, 2006; MacDougall, Brizuela, Burgess, Curthoys, & Halmagyi, 2005; Séverac Cauquil, Faldon, Popov, Day, & Bronstein, 2003; Watson et al., 1998; Zink, Steddin, Weiss, Brandt, & Dieterich, 1997). In contrast, the absence of nystagmus favours semicircular canal activation (Bernard Cohen, Suzuki, & Bender, 1965; Guedry, 1974). This thesis, however, is not interested in exploring the origin of the induced response. When standing with the head and feet facing forward, as is the case in chapter 5 (study 4), the balance response to EVS is directed medial-laterally (Fitzpatrick & Day, 2004). This medial-lateral movement is the response of interest in this thesis. Electrical vestibular stimulation evokes a virtual signal of head rotation (Day & Fitzpatrick, 2005; Peters, Blouin, Dalton, & Inglis, 2016; Peters, Rasman, Inglis, & Blouin, 2015) interpreted as an unexpected vestibular perturbation by the CNS. The elicited whole-body compensatory postural response (Britton, Day, Brown, & Rothwell, 1993; Fitzpatrick & Day, 2004) may be regulated by the vestibulospinal tract via necessary musculature (Rea, 2015). The vestibular apparatus thus provides the information required for balance by encoding information concerning the orientation and the motion of the of the head in relation to the external world (Fitzpatrick & Day, 2004). Spatial transformation of vestibular signals can be assessed using an isolated vestibular error while the balance system is engaged

(Britton et al., 1993; Lund & Broberg, 1983; Pastor, Day, & Marsden, 1993). Electrical vestibular stimulation is therefore a simple tool that delivers a pure disturbance to directly probe vestibular function and the balance system (Fitzpatrick & Day, 2004).

## The motor pathway: movement preparation

As a human prepares to perform a voluntary movement, activity over motor areas increases 2000 ms to 1000 ms preceding movement onset. This so-called Bereitschaftspotential or "readiness potential" is an indication the brain is preparing to execute a movement (Deecke, 1996). These preparatory properties at the neural level are indicative of an increasing level of neural activation related to the process of motor preparation and can be further probed using stimulation techniques such as TMS or transmastoid stimulation. The resultant output of these techniques can give researchers a better understanding of how humans prepare for simple and complex movements. The studies contained within this thesis exclusively use a simple RT paradigm, in which a single movement or movement sequence is produced in response to a single stimulus. As to be made is known in advance, it can be preplanned. This contrasts with a choice RT paradigm in which there are multiple stimuli, each requiring a different response. Given that a participant does not know which stimulus will be presented, they cannot preprogram their response.

### Preparatory responses

In his seminal review, Massion (1992) described how internal and external constraints contribute to skillful motor performance. External constraints refer to those imposed by the environment, such as gravitational forces, while internal constraints refer to those concerned with the body, such as the inertial characteristics of the body segments and the internal forces

associated with muscular contractions. The central organization of motor performance takes into account these constraints to perform complex multi-joint movements via multiple parallel commands (Arbib, 1981). One of the major difficulties with attempting to investigate the organization of movement is the internal forces arising from muscular contractions disturb reference values, such as the centre of gravity of the body. To counteract this, Belen'kii and colleagues (1967) demonstrated that in producing a movement, an anticipatory response is elicited 50-100 ms prior to prime mover activation. This anticipatory response was interpreted as a feedforward command aimed at minimizing the equilibrium disturbance associated with the production of movement. Much research has been conducted since this pioneering study; however, Massion's original definition of this phenomenon still holds. He defined this response as an anticipatory postural adjustment, or APA, which constitutes a general type of postural movement that stabilizes posture and equilibrium prior to the initiation of a movement.

If the APA is a general type of movement meant to stabilize posture and equilibrium prior to the initiation of a movement, different movements should elicit different stabilization strategies. Indeed, Friedli and colleagues (1988) examined how bilaterally symmetric, rapid elbow flexion or extension movements influenced ground reaction forces. Not surprisingly, patterns of ground reaction forces were found to be directionally opposite in the elbow flexion compared to the elbow extension movement and can thus be considered to be specified by the dynamics of the upcoming focal movement. The authors concluded that postural adjustments must counterbalance translational and rotational elements resulting from focal movements with the singular goal of preventing the body from falling and maintaining the relationship of the various body segments to each other. Lee and colleagues (1987) expanded on this interpretation by correlating pre-movement EMG to the magnitude of a dynamic disturbance associated with

arm movements over an eight-fold range of speeds. EMG data indicated a strong relationship between postural muscles and arm acceleration, consistent with the idea that anticipatory EMG activity in postural muscles help maintain posture against self-generated disturbances. Furthermore, the recruitment order of postural and focal muscles appeared to be dictated by the behavioural demands of the task. For fast visually-guided movements, the hamstrings and deltoid muscles were recruited at the same time, whereas for fast self-paced fast movements, the hamstrings were recruited prior to the deltoids. This task-dependency was also explored by Benvenuti and colleagues (1997) when they sought to determine if APAs were modified when the same focal movement was made in either a self-paced condition or a RT-based condition. They found the interval between the onset of postural EMG and the onset of focal EMG was shorter when the movement was triggered by an external stimulus, compared to when the movement was self-paced. Overall, these studies show the CNS can vary the timing of postural and focal commands depending on the task at hand.

One way to explore the contribution of the CNS to postural responses is to measure if these responses are influenced by *central set* effects. Central set can be defined as a general readiness of the body to anticipate varying stimulus and task conditions (Schmidt, 1982). The central set can be influenced by planning aspects of the response in advance, which can decrease the time needed for the CNS to transform a stimulus into an appropriate response (Greene, 1972). Horak and colleagues (1989) postulated that if APAs are influenced by central set, responses to a given postural perturbation should differ if the same perturbation was presented repeatedly (expectedly) or randomly (unexpectedly). They demonstrated that in addition to torque and EMG response magnitudes being scaled by sensory information coding velocity and amplitude of displacement, magnitudes of APAs were modulated by central set based on prior

experience. That is, participants tuned their initial APA amplitude based on immediate prior experience when the perturbation was expected. Furthermore, there was an over or undershoot in the magnitude of APAs when perturbations unexpectedly changed, demonstrating further task-dependent modifications of APAs.

**Preparatory excitability**

Previous studies on non-human primates have shown that instructions regarding an upcoming movement results in anticipatory activity in the motor cortex. These changes in activity persist for several seconds as the monkey awaits the cue to begin the movement. During the foreperiod of the task, 61% of pyramidal tract neurons modulated their discharge patterns according to the nature of the instruction. For example, if the upcoming movement was a push movement, activity in the neurons that usually discharge during push movements increased. Conversely, activity in the neurons that usually discharge during pull movements decreased (Tanji & Evarts, 1976). In humans, Touge and colleagues (1998) used TMS to demonstrate excitability of motor cortical projections to agonist muscles decreased as early as 100 ms after the warning, or "get ready" stimulus and continued until the presentation of the IS, 500 ms later. Similarly, Hasbroucq and colleagues (1997) found that MEPs decreased progressively during the first 333ms of a short (500ms) foreperiod. This may be the result of inhibition within the motor cortex that acts to prevent the premature release of a response during the foreperiod of a RT task (Stinear, Coxon, & Byblow, 2009). Indeed, Prut and Fetz (1999) suggested that inhibitory modulations may reflect a general "braking" mechanism in which the tendency to initiate a movement during the foreperiod is suppressed and the "brake" is released once the IS appears and movement is initiated. Following the IS, or during the RT interval, MEPs elicited by both electrical stimulation and TMS have been shown to increase in amplitude. This robust effect has

been reproduced in several studies using a simple RT paradigm, beginning approximately 100 ms prior to EMG onset (Chen, Yaseen, Cohen, & Hallett, 1998; Hoshiyama et al., 1996; Kennefick, Maslovat, Chua, & Carlsen, 2016; Pascual-Leone, Brasil-Neto, Valls-Solé, Cohen, & Hallett, 1992; Pascual-Leone, Valls-Solé, et al., 1992; Tarkka, McKay, Sherwood, & Dimitrijevic, 1995; Tomberg & Caramia, 1991).

**Movement complexity and excitability levels**

In addition to a general increase in excitability prior to movement onset, the complexity of an upcoming movement can also affect the preparatory state of the motor system. In their seminal experiment, Henry and Rogers (1960) sought to understand how the complexity of a movement affected RT. Their experiment consisted of three simple RT tasks, each with a varying number of movement components. In the first movement (A), the participants lifted their finger from a button only a few millimeters. The second movement (B) involved the participant lifting their finger from the button and then grasping a hanging tennis ball approximately 30 cm ahead of the starting position. The third movement (C) made use of a second hanging tennis ball mounted 30 cm lateral to the first tennis ball. The participant lifted their finger, reached forward and upward to strike the second tennis ball with the back of his or her hand, then reversed direction to touch a second button, before striking the first tennis ball. Results demonstrated that RT for the least complex of the three movements, movement (A), was faster than the second most complex movement, movement B, by 36 ms. Furthermore, movement B was faster than the most complex movement (movement C), by an additional 13 ms.

The effect that movement complexity has on RT was further investigated by Klapp and colleagues (2003; 1974). In these studies, there was an alteration of the complexity of the movements themselves, as opposed to an alteration of the number of movement components (c.f.

Henry & Rogers, 1960). This was accomplished using Morse code "dit" and "dah," button presses, where "dit" was a short (press-release) simple button press and "dah" was a long (press-hold-release). Klapp (2003) further added the notion of "INT" and "SEQ", where INT was related to the internal programming of a movement and can be thought of as single "dit" or "dah" movement chunks, whereas SEQ related to a sequence of chunks and can be thought of as a series of individual "dit" or "dah" movements. Single-chunk responses require INT but do not require SEQ because there is no movement sequence. INT is assumed to occur prior to the IS in a simple RT paradigm because the response is preprogrammed. As the response cannot be preprogrammed in a choice RT paradigm, INT is assumed to occur following the IS. Therefore, if programming INT requires more time for a complex response, then choice RT will depend on response complexity, whereas simple RT will not. This RT pattern is known as the *choice-up-simple-flat* pattern. Multiple-chunk movements are more difficult to interpret because both INT and SEQ are involved. In these movements, simple RT increases as a function of the number of chunks, but choice RT does not. This is opposite to what is seen in the choice-up-simple-flat pattern and is termed *simple-up-choice-flat*. The simple-up-choice-flat pattern can be demonstrated in a manual button press task when the number of chunks (dits and dahs) increases. This task results in an increase in simple RT, but no increase in choice RT. Therefore, simple RT is assumed to depend on the number of chunks, and not on the chunk's internal complexities.

The timing structure of a movement has also been shown to affect RTs. This was demonstrated by Franks and colleagues (1998) who asked participants to complete a reciprocal extension/flexion movement with and without a 250 ms pause at the reversal of the movement. Results indicated that RT for the extension/flexion movement was significantly shorter when the pause was inserted into the movement profile, and that RTs for the paused movement were the

same as those seen when participants performed a simple extension movement with no reversal. When the length of the pause was reduced to 100 ms, participants were unable to preprogram the timing of the pause which resulted in no differences in RTs between paused and continuous movements. It was the authors' contention that participants made use of an extended pause at reversal to subsequently program the upcoming flexion movement; however, the nature of the processing of the internal features occurring during this pause could not be investigated. In an extension of Klapp's work, Maslovat and colleagues (2014) varied the complexity of a key-press movement by having participants perform either single element or multiple element key-press sequences with varying isochronous or non-isochronous timing structures. They demonstrated that in non-isochronous movements, the length of the first interval (i.e between key-press one and two) had a profound effect on overall RTs. For example, when the length of the first interval was long (450 ms), overall RTs were shorter than when the first interval was short (150 ms). The authors suggested participants may have only prepared the first movement component (first button press) in advance, with the remaining components prepared online. This is an important finding as it indicates simple RT may also reflect the preparation of the timing of movement chunk onsets.

**Movement complexity and the excitability of the motor pathway**

As described above, the effect that movement complexity has on RTs is well established. However, the effect that movement complexity has on the excitability of the motor pathway is much less defined. Flament and colleagues (1993) investigated the effects of an isolated index finger abduction (simple) and a variety of static gripping (complex) tasks on CE, in which the grip was held at 5% of MVC. Results indicated that in every subject, MEPs were greater in at least one of the complex gripping tasks compared to that of the simple finger abduction.

Abbruzzese and colleagues (1996) used TMS during sequential finger movements of varying complexities in a non-RT task. In theses tasks, participants were required to execute a simple repetitive or complex sequential movement, or to mentally simulate the same simple or complex movement. Results indicated the size of MEPs increased during both the real and imagined complex compared to simple sequential movements. Roosink and Zijdewind (2010) investigated CE during the execution of a simple and a complex finger-tapping sequence in a non-RT task. Two finger sequence tasks consisted of a simple index-index-middle-middle-ring-ring-little-little finger sequence, and a complex task index-index-ring-ring-index-little-middle-ring fingers. Results indicated that MEPs were greater during the complex finger sequence compared to the simple finger sequence.

While the three studies mentioned above demonstrated task dependent increases in CE based on movement complexity, this is not an unequivocal finding. In a simple RT paradigm, Kennefick and colleagues (2016) had participants complete a button-press movement of a single telegraph key using their right index finger. In the simple movement, participants were required to press the telegraph key once for a duration of 150 ms, while the complex movement required three 150 ms key presses, the first two separated by 150 ms and the second and third separated by 450 ms. The 150 ms button presses can be considered as the “dit” movements described by Klapp. Results indicated that while MEP size increased in both the simple and complex movements after the IS, the simple movement reached higher levels of excitability 75 ms prior to EMG onset. The decreased excitability in the complex movement was attributed to the specific timing structure imposed on the participants.

**Safety, application and ethical considerations of stimulation techniques**

There is an extremely small risk (~1 in 50,000) of producing an epileptic fit with TMS. There have been fewer than 20 events reported since the technique was developed in 1985 and most of these occurred in patients taking pro-epileptogenic medications and some are believed to represent fainting rather than a seizure. All stimulation within this thesis complied with published safety guidelines developed in collaboration with the Safety of TMS Consensus Group which includes clinicians and researchers from around the world (Rossi, Hallett, Rossini, Pascual-Leone, & Safety, 2009). These guidelines set safe standards for the frequency, intensity and duration of stimuli. After large numbers of stimuli some people (fewer than 1 in 20) complain of a mild-headache lasting up to several hours due to scalp muscle contraction and can be treated with standard non-prescription medications (e.g. acetaminophen).

Transmastoid stimulation is achieved with isolated and grounded electric stimulators designed specifically for humans. Some participants perceive these stimuli to be uncomfortable (e.g., a pain rating of 2-4 out of 10) but they are very brief and cause no injury.

There are no known risks associated with electrical vestibular stimulation. Some participants who are highly susceptible to motion sickness may experience mild nausea, light-headedness or dizziness for a brief period (up to 1 hour) following the experiment.

## Thesis objectives and summary of studies

The specific objective of this thesis was to use an experimental research design to test the hypothesis that various regions of the motor system interact to produce complex movements. The results of this work will be incorporated within a broader discussion of the mechanistic foundations of human movement production.

## Specific aims and hypotheses

### Chapter 2 (study 1)

**Primary aim:** To characterize the extent to which movement complexity modulates APA metrics in a manner analogous to those observed in a primary effector in a simple RT task.

**Hypothesis:** Increased movement complexity was hypothesized to prolong onsets of the APAs and alter APA velocity profiles.

### Chapter 3 (study 2)

**Primary aim:** To examine how corticospinal excitability is affected by a step-wise increase in the complexity of a movement in a simple RT paradigm.

**Hypothesis:** Reaction times would be lengthened in the more complex movements, which would be mirrored by an increase in MEP amplitude as the movements became more complex.

### Chapter 4 (study 3)

**Primary aim:** The first aim was to establish a time-course of motoneuron excitability prior to the onset of complex movements in a simple RT task. The second aim was to describe the task-dependent effect of complex movements on cortical and spinal excitability.

**Hypothesis:** Both cortical and spinal excitability would increase prior to movement onset, as well as in response to movement complexity.

### Chapter 5 (study 4)

**Primary aim:** To examine the contribution of the vestibulomotor system to the preparation of complex movements in a simple RT task.

**Hypothesis:** Reaction times would be lengthened in the more complex movement conditions, which would be mirrored by a task-dependant increase in the vestibular-evoked response in both upper and lower limb musculature.

## Chapter 2: Anticipatory postural adjustments as a function of response complexity in simple reaction time tasks

### Background

The first groundbreaking study on postural adjustments was undertaken by Belen'kii and colleagues (1967), in which they proposed that muscles in the lower limb were activated during the preparation for voluntary movement in order to maintain balance prior to new movement situations. In his seminal review, Massion (1992) described how *internal constraints* – inertial characteristics of the body segments and the internal forces associated with muscular contractions – and *external constraints* (gravitational forces) contribute to skillful motor performance. The central organization of movement takes into account these constraints to perform complex multi-joint movements, with multiple parallel commands coordinated and integrated towards generating one fluid motion (Arbib, 1981). To facilitate this process, the CNS preplans postural responses to accommodate internal and external constraints. Massion (1992) defined this response as an APA, which constitutes a general type of response for stabilizing posture prior to movement initiation.

Reaching and grasping can disturb balance unless a compensatory movement is initiated prior to extension of the arm. Friedli and colleagues (1988) examined how rapid, bilaterally symmetric elbow flexion or extension movements influenced ground reaction forces (reflective of APAs). Not surprisingly, ground reaction forces were directionally opposite in elbow flexion and extension movements, suggesting postural adjustments are specified by the dynamics of the upcoming focal movement (Friedli et al., 1988). In addition, Horak and colleagues (1989) have demonstrated that APA characteristics differ if the same perturbation is expectedly or unexpectedly presented. The authors observed a systematic over- or undershoot in APA

magnitude when perturbations were changed unexpectedly. Furthermore, a gradual reduction in APA magnitude was observed when the perturbation condition became predictable. Collectively these findings indicate APAs are shaped by characteristics of the perturbation as well as prior experience.

If an APA is a general type of modifiable adjustment that stabilizes posture prior to the initiation of a movement, different movements should elicit different stabilization strategies. Indeed, APAs have been shown to be adaptable to the spatial and temporal requirements of an upper limb task (Aruin & Latash, 1995). As such, a simple single component movement should elicit a different postural strategy than a complex movement requiring multiple components and multiple movement reversals, even if the initial component is the same as that generated in the simple movement. Henry and Rogers' (1960) seminal experiment was designed to probe the effect of movement complexity on RT. Their experiment consisted of three simple RT tasks, each with a varying number of movement components. They demonstrated that reaction time lengthened as the complexity of the movement was increased, suggesting that RT is sensitive to movement preparation processes. Importantly, as a simple RT paradigm informs participants of all required movement prior to the IS, they could be prepared in advance. Thus, this task could also be used to investigate APA behaviour across progressively more complex movements.

The influence of task complexity on APA dynamics in a simple RT task is unknown. The primary purpose of this study was to characterize the extent to which task complexity modulates APA metrics. Increased task complexity was hypothesized to prolong RT of the APAs and alter APA velocity profiles.

## Methods

### Participants.

Thirteen (8 male, age range 21-37) healthy, self-declared right-handed participants with normal or corrected-to-normal vision, and no history of neurological, sensory, or motor disorders participated in this study. Testing of each participant took place in a single session and required ~1.5 hours to complete. All participants provided written informed consent prior to beginning data collection. The study was approved by the University of British Columbia's Behavioural Research Ethics Board (H11-02368).

### Experimental set-up and task.

The participant stood without shoes, with feet shoulder-width apart on a force platform (NDI True Impulse, Waterloo, Canada) in front of the KINARM End-Point Lab (BKIN Technologies Ltd., Kingston, Canada) and used their right hand to grasp the right manipulandum linked to the robotic motors. Arm movements were performed in the horizontal plane in response to targets presented on an augmented reality display. Participants were informed the upcoming task was a simple RT task consisting of a ballistic arm movement for one of three movement conditions. Prior to the IS, the visual display indicated which of the three movement conditions was to be performed. In the 1-target condition, movement was directed anteriorly (straight ahead) and terminated at the first target (A in Figure 1). In the 2-target condition, the participant reached the first target and performed a reversal in the posterior direction and to the right before terminating their movement at the second target (B in Figure 1). The 3-target condition involved a second reversal after reaching the second target, requiring an anterior (straight ahead) movement to reach the final target (C in Figure 1). Importantly, regardless of the final target position, the initial movement (i.e., home position to target one) was identical across all

movement conditions, in line with Henry and Rogers' original experiment (Henry & Rogers, 1960). Each trial required the participant to first reach the home position, represented by a red dot that was positioned 19 cm in front of the participant's right arm. Following a random foreperiod (1000-3000 ms), the home position marker turned green (IS), signaling the participant to initiate the movement. All targets were the same size (visual radius of 0.5 cm) and changed from white to green when reached successfully. Movement onset was defined as the moment when the centre of the cursor left the home position. Following the completion of a practice block consisting of 10 trials for each condition, participants completed 150 trials (50 per complexity condition, presented randomly).

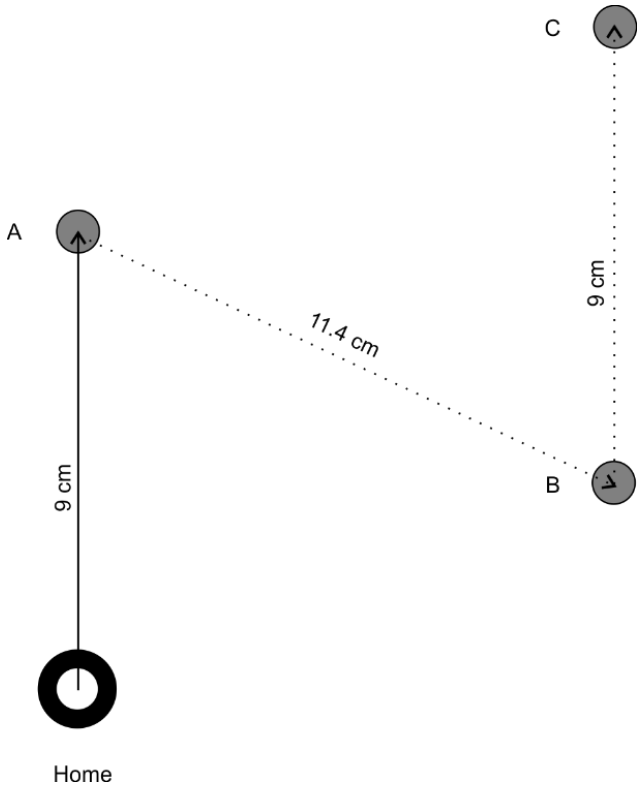


**Figure 1**. Visual representation of the behavioural task implemented with the KINARM system.

**Recording equipment and data reduction.**

The KINARM recorded displacement and acceleration at each robotic joint angle, as well as force/torque in 6 degrees of freedom. Reaction time of the arm was defined as the time interval between the presentation of the IS and the time at which the participant left the home position. Initial MT was defined as the time interval between the time when the participant left the home position and the time at which the first target was reached (Figure 1: A), across all movement conditions.

The force plate collected forces in, and moments around the X (left-right), Y (forward-backward) and Z (vertical) directions in relation to the centre of the plate, which allowed for the calculation of centre-of-pressure (COP) displacements and velocities in both the anterior-posterior (AP) and medial-lateral (ML) directions using a custom written MATLAB script (vR2013a, Mathworks Inc, Natick, MA). All COP related signals were processed using a fourth-order, dual-pass digital Butterworth filter with a 5 Hz low-pass cutoff frequency. Displacements in COP were calculated with respect to the baseline value defined as the average position during the 500 to 300 ms interval prior to the IS (Slijper, Latash, & Mordkoff, 2002). The AP position of the COP ($COP_{AP}$) was calculated as $M_x/F_z$, whereas the ML position was calculated as $COP_{ML} = -M_y/F_z$. These measures took into account the distance between the surface of the force plate and its geometric center. Due to inter-trial, as well as inter-participant variability potentially caused by the availability of differing postural strategies (Lowrey, Nashed, & Scott, 2017), APA onset time ($APA_{onset}$) was measured by taking the time point at which the COP displacement changed by 3 SD from the mean, calculated during the most stable baseline period prior to movement onset. APA onset times were measured in relation to movement onset as this best represents the time course of the developing APA with respect to the complexity of the

upcoming movement. Participants who did not demonstrate APA onset changes as defined above were excluded from this analysis (N=2). The following characteristics describing $COP_{AP}$ and $COP_{ML}$ trajectories were calculated (see Slijper et al., 2002):

1. $APA_{onset}$: APA onset time prior to arm movement onset, expressed in ms

2. $\Delta COP_{rate}$: Average rate of anticipatory COP displacements from -100 to +50 ms in relation to movement onset, corrected for its average rate of change from -500 to -300 ms, expressed in cm/s.

Negative values in $COP_{AP}$ indicated a posterior shift in COP, whereas negative values in $COP_{ML}$ indicate a rightward shift in COP.

**Statistical analysis.**

Data were analyzed using repeated-measures analyses of variance (RM-ANOVA). All analyses were conducted using SPSS version 23 (SPSS Inc., Chicago, IL, USA). For all RM-ANOVAs, Greenhouse-Geiser Epsilon was used to adjust degrees of freedom for violations of sphericity when necessary. Post-hoc tests were performed using Bonferroni-corrected paired samples Student's *t*-tests to compare across conditions. Differences with an adjusted $p < 0.05$ were considered significant. Other statistical parameters presented are effect sizes using the partial-eta squared ($\eta_p^2$) metric and mean differences (M). Data are presented as mean ± SD.

## Results

**Arm movements.**

A one-way RM-ANOVA was performed to determine if RT and MT differed across task complexity (Table 1). Results revealed a significant main effect ($F(2,24) = 13.8$, $p < 0.001$, $\eta_p^2 = 0.534$) wherein RT was faster in the 1- versus 2-movement condition ($M$ = -11.8 ms, 95% CI [-20.9, -2.55], $p = 0.012$), as well as in the 1- versus 3-movement condition ($M$ = -18.6 ms, 95% CI [-31.7, -5.37], $p = 0.006$). Furthermore, RT was faster in the 2- versus 3-movement condition ($M$

= -6.80 ms, 95% CI [-9.70, -1.79], $p$ = 0.005). While complexity affects RT, it did not affect MT evidenced by the absence of a main effect ($F$(2,24) = 0.074, $p$ =0.929, $\eta_p^2$ = 0.006).

**Table 1.** Mean reaction and movement times across the 3 movement complexities. All values are expressed in ms and parentheses indicate standard deviations.

| | **1 Movement** | **2 Movement** | **3 Movement** |
|---|---|---|---|
| **Reaction Time (ms)** | 350.8 (33.9) | 362.6 (35.1)* | 369.4 (37.4)*,** |
| **Movement Time (ms)** | 156.5 (39.9) | 155.2 (56.4) | 158.9 (64.0) |

*denotes an RT significantly slower than the 1-movement condition. **denotes an RT significantly slower than the 2-movement condition. All significant p-values < 0.006.

**Centre of pressure metrics.**

To determine whether COP characteristics were influenced by task complexity, one-way RM-ANOVAs were conducted for $APA_{onset}$ and $\Delta COP_{rate}$ in the AP and ML directions.

**$APA_{onset}$:** In the AP direction (Figure 2a), the analysis revealed a main effect of task complexity ($F$(2,20) = 3.859, $p$ =0.038, $\eta_p^2$ = 0.278) with no significant post-hoc differences (all $p$ > 0.11). In the ML direction (Figure 2b), a main effect of task complexity was observed ($F$(2,20) = 9.065, $p$ =0.002, $\eta_p^2$ = 0.475) with an earlier onset of APA in the 3-movement versus 1-movement condition ($M$ = 31 ms, 95% CI [-58.3, -3.72], $p$ = 0.026), and in the 3- versus 2-movement condition ($M$ = 22.8 ms, 95% CI [-36.5, -9.16], $p$ = 0.002).

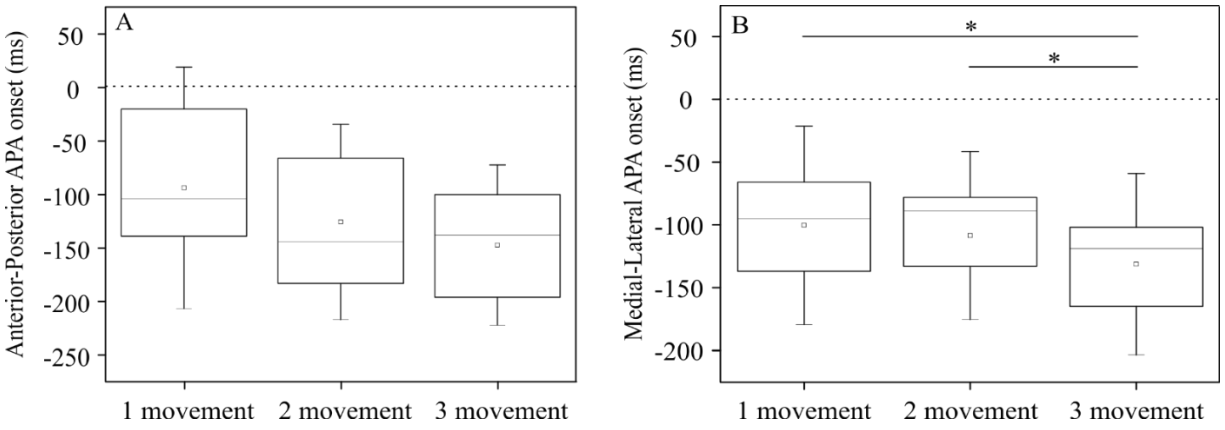


**Figure 2.** Boxplot of the mean onset time of the COP ($APA_{onset}$) prior to movement onset in the AP (A) and ML (B) directions across the 3 complexity levels. Box boundaries represent the 25$^{th}$ and 75$^{th}$ percentiles, solid horizontal lines represent medians, the small squares within the box represent means, and error bars represent the standard deviation. The dashed lines at 0 ms represent the onset of hand movement. A single asterisk (*) denotes a significant decrease in onset times between task complexity conditions.

**$\Delta COP_{rate}$.** In the AP direction (Figure 3a), there was a task complexity main effect ($F(1.08,13.1) = 6.00$, $p = 0.045$, $\eta_p^2 = 0.286$) with no significant post-hoc differences (all $p > 0.083$). In the ML direction (Figure 3b), there was also a main effect of task complexity ($F(2,24) = 8.52$, $p = 0.002$, $\eta_p^2 = 0.415$) wherein the rate of displacement was greater in the 2-movement versus 1-movement condition ($M = 3.58$ cm/s, 95% CI [0.525, 6.64], $p = 0.021$), as well as in the 3-tversus 1-movement condition ($M = 4.37$ cm/s, 95% CI [0.525, 6.64], $p = 0.038$).

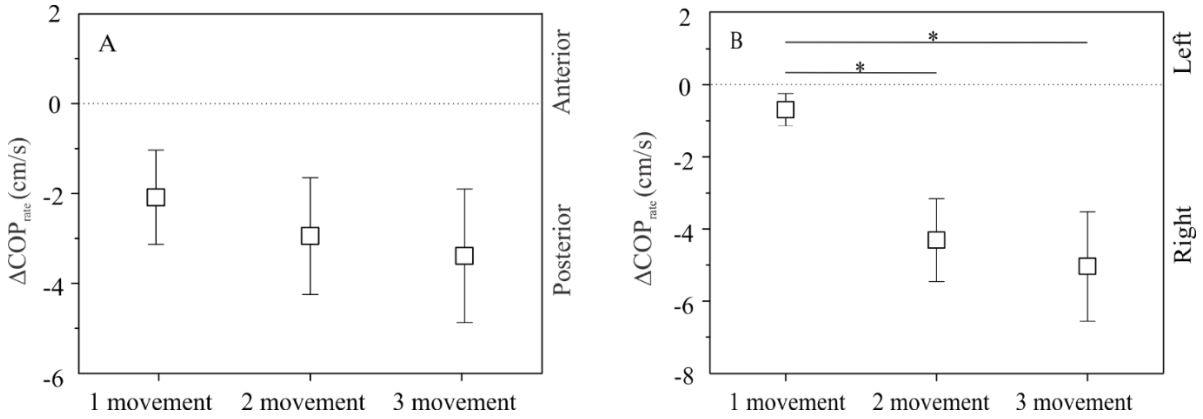


**Figure 3**. Mean rate of anticipatory COP displacements from -100 to +50 ms, corrected for its average rate of change from -500 to -300 ms (ΔCOPrate). The dashed lines at 0 represent baseline COP position in either the AP (a) or ML (b) directions. The filled in boxes represent means, and error bars represent standard error. A single asterisk (*) denotes a significant decrease in onset times between task complexity conditions.

**Discussion**

The purpose of this study was to determine if task complexity modulates APA. Previous work has shown primary effector RT increases as a task becomes more complex. This occurs regardless of whether the task requires a gross motor skill such as reaching, wherein RT differences were attributed to additional sequencing (Henry & Rogers, 1960); or a fine motor skill such as a button press, in which RT differences were attributed to sequencing requirements (Klapp, 1995). The results of the current study demonstrate complexity was successfully manipulated: simple RT increased as the movement became more complex (Table 1) while standing. Furthermore, there were no differences in MT to the first target. The current results also revealed APA characteristics are also modulated by task complexity (Figures 2 and 3).

Anticipatory postural adjustments have been defined as a general type of movement aiming to minimize postural disturbances, with direct evidence demonstrating they are planned *prior to* voluntary movement initiation (Massion, 1992). An effective technique to probe if a

movement is preplanned is to use a startling acoustic stimulus (SAS) to elicit the same movement but at a shorter latency. For example, Carlsen and colleagues (2004) demonstrated SAS reduced premotor RT by ~70 ms when the control IS (84 dB) was replaced with a 124 dB startle tone. In the context of APAs, Valls-Solé and colleagues (1999) demonstrated that participants who quickly rose on their tiptoes in response to a control visual IS versus a 130 dB SAS had shorter latencies to EMG onset and to movement initiation when the SAS was presented. Indeed, MacKinnon and colleagues (2007) demonstrated a similar effect during stepping trials, a SAS released the APA sequence with a shorter latency.

The APA response serves to stabilize posture prior to voluntary movement onset (Massion, 1992). Within the current study, all dependent measures were affected by the complexity manipulation. Analogous to the increased RTs with increased complexity of arm movement in Henry and Rogers (1960), we demonstrated a strong effect of complexity on the RT of APAs. Whereas there was a main effect of complexity in the AP direction (Figure 2a), the most robust effect of complexity on RTs was in the ML direction (Figure 2b). In particular, the onset of APAs in the ML direction occurred 131 ms prior to movement onset in the most complex (3-component) movement, compared to 109 ms in the second most (2-component) movement and 100 ms in the simplest (1-component) movement. Furthermore, the rate of COP displacement ($\Delta COP_{rate}$; Figures 3a and 3b) was incrementally faster as movement complexity was increased. At first glance, the displacement rates may seem small; however, the small displacements in COP were likely a byproduct of the stance width, or the haptic feedback participants received from the robotic handle they were always grasping during testing trials. This type of effect has previously been demonstrated by Jeka and Lackner (1995) in a study in which they reported that fingertip contact of a surface can reduce postural sway by 50%. The

current data indicate differential preparation of APAs in relation to the complexity of the upcoming task, irrespective of an identical first movement phase (i.e., Figure 1: home position to target 1). Importantly, these findings demonstrate that all movement segments were incorporated into APA planning during movement preparation, specifically evidenced by the lengthened APA onset times relating to the ML shift in APAs in preparation for a target reach that included a rightward component. Thus, simple movements requiring a single component (i.e. reaching to target 1) require a different postural strategy than complex movements requiring multiple components (i.e. continuing the movement to targets 2 and 3) irrespective of the initial aspect of the arm movement being identical across the 3 complexity conditions.

As reviewed by Massion and colleagues (2004), there is an extensive literature describing the coordination of both posture and movement within the CNS for the ultimate purpose of achieving a specific movement goal. A major issue arises in multi-joint movements, wherein the movement of one body segment influences the movement of all segments in the kinematic chain. While the current investigation is the first to specifically examine the effect of task complexity on postural responses, a recent study by Lowrey and colleagues (2017) examined task-dependent postural responses to mechanical perturbations. In their study, participants had their hands perturbed shortly after they initiated movements to either a circular target (1.5 cm diameter) or a rectangular target (1.5 cm width, 30 cm length). Similar to the current study, task-dependent differences in COP were evident, as there were greater corrections to the mechanical perturbations to the circular versus rectangular target, evidenced by higher peak COP and greater COP velocity traces. Weerdesteyn and colleagues (2008) instructed participants to either recover or not recover their balance after being released from a tether at a 15 degree angle. Importantly, postural adjustments were seen even when participants were instructed to fall. The results

demonstrated early and pronounced differences between instructional sets, as response amplitudes were greater when participants were instructed to recover balance. This finding indicates task demands influence responses to a perturbation by adjusting gain settings, which result in differential scaling of response amplitudes across muscles. To that end, it appears these automated responses can be downregulated by the CNS. The results of the current study further confirm this notion. There is a scaling in magnitude of APAs in relation to task complexity (Figure 3), consistent with the fact that APAs are dependent on behavioural context. Furthermore, the delayed APA onset times with increasing task complexity (Figure 2) demonstrate an earlier implementation of the tailored motor plan with increased complexity of the task at hand. Despite an identical initial movement being performed across all conditions, the CNS planned the APAs such that subsequent movements would allow participants to maintain postural equilibrium while successfully completing the reaching task.

The way in which task complexity is manipulated can provide further insight into how APAs are planned. As described previously, the current study uses the classic Henry and Rogers RT-based complexity manipulation (Henry & Rogers, 1960). Their interpretation of the complexity effect was based on a computer analogy, known as the "memory drum theory". This theory outlined how more complex responses require a larger program, thus requiring an increased amount of time to retrieve the movement program from memory. Similarly, Fitts (1954) developed a law which predicted increasing MT as a function of an increasing index of difficulty, defined as the ratio between the distance to a target and the width of that target. In a study by Berrigan and colleagues (2006), a greater rearward COP displacement was associated with an increasing difficulty index during a single arm extension movement to a single target. This was coupled with an increase in primary effector RT as the difficulty index increased,

demonstrating a clear complexity manipulation. The current results extend this notion using a series of more complex movements – rather than one movement with smaller targets – to demonstrate movement complexity also alters APA magnitudes. The complexity manipulation of Berrigan and colleagues (Berrigan et al., 2006) probed the speed-accuracy trade-off between an increasing index of difficulty and the speed at which the accompanying movement can be performed in relation to COP behaviour. In contrast, the current study had an identical index of difficulty (i.e., same sized targets) across all target conditions, indicating there was no speed-accuracy trade-off, and was consistent with the original Henry and Rogers view of complexity (1960). Importantly, no differences in MT of the initial movement segment were observed across the different task complexity conditions, indicating effects were isolated to the preparatory phase and not execution phase. Thus, the findings of the current study coupled with those of Berrigan and colleagues (Berrigan et al., 2006) provide robust complexity-based manipulation of APAs, demonstrating how a simple manipulation can have profound effects on whole-body preparation for upcoming movements.

**Summary**

In conclusion, the current findings indicate movement complexity affects the planning of APAs to successfully complete reaching movements while maintaining balance. Manipulating movement complexity by adding additional elements resulted in systematic delays in both the primary effector RT and APA metrics. Furthermore, the findings provide a novel description of how movement complexity affects full-body human preparation strategies.

## Chapter 3: Corticospinal Excitability is Enhanced with Increasing Movement Component

Chapter 2 demonstrated that movement complexity can be integrated into a global motor plan that stabilizes posture prior to the initiation of movement. The simple addition of movement components elicited delayed responses in both the primary effector and the APA, which establishes that movement preparation strategies can be altered by movement complexity. However, chapter 2 did not allow for the determination of the origin of these preparatory processes. Chapter 3 attempts to start this discussion.

### Background

As a human prepares to perform a voluntary movement, brain activity increases in the motor areas during the 2000 ms prior to movement onset (Deecke, 1996). There have been several models proposed to describe the processes involved in the preparation for, and initiation of, movement (Carpenter & Williams, 1995; Hanes & Schall, 1996; Nazir & Jacobs, 1991). In the "cell assembly model" (Wickens, Hyland, & Anson, 1994), a group of cortical motor neurons related to performance of the desired action (known as a "cell assembly") are brought closer to threshold, then held, in preparation of the motor response. The preparation for a desired motor response influences the excitability of the motor pathway and can be quantified using TMS.

Transcranial magnetic stimulation provides a safe, painless and non-invasive technique to activate the motor cortex and, via the MEP recorded in the EMG of a target muscle, assess CE (Kobayashi & Pascual-Leone, 2003). The size of the MEP is influenced by both cortical and spinal (Taylor, 2006), as well as peripheral, excitability (Stefan et al., 2000). Furthermore, the size of the MEP is sensitive to cognitive processes external to the motor cortex, such as decision making. For example, Hadar and colleagues (2016) demonstrated MEP amplitude can indicate an association between a decision and an immediate action during a perceptual discrimination task.

The manner in which the motor pathway prepares for a forthcoming movement can be altered by movement complexity. In their seminal experiment, Henry and Rogers (1960) demonstrated that RT to an IS increased with the number of movement components. The authors interpreted the lengthened RTs as a complexity effect, related to an increased amount of time required to program and retrieve a motor response from memory. This fundamental work provided a foundation for numerous interpretations of how complexity affects movement production. For example, Klapp (1995) proposed the hierarchical sequencing of movement components is still programmable following the presentation of the IS, resulting in longer RTs. Furthermore, Maslovat and colleagues (2014) proposed that simple RT is indicative of the time required to organize the timing basis for the initiation of movement components.

In addition to lengthened RTs, complexity manipulations induce robust alterations in the excitability of the motor pathway. Flament and colleagues (1993) demonstrated that MEPs were greater during a static gripping (complex) task compared to an isolated finger abduction (simple) movement. Additionally, Abbruzzese and colleagues (1996) used sequential finger movements of varying complexity in a non-RT task to demonstrate that MEPs increased during real and imagined sequential movements. Likewise, Roosink and Zijdewind (2010) noted a complex finger sequence elicited greater MEPs compared to a simple finger sequence. However, an increase in MEP size with movement complexity is not a universal finding, as Kennefick and colleagues (2016) revealed recently that a sequential button-press task requiring a specific timing pattern led to a complexity-related *decrease* in MEP size.

Given the conflicting evidence cited above, the purpose of the current study was to examine how the motor pathway is affected by a step-wise increase in the complexity of a movement in a simple RT paradigm, similar to Henry and Rogers (1960). It was hypothesized

that RTs would be lengthened in the more complex movements, which would be closely mirrored by an increase in MEP amplitudes as the movements became more complex.

## Materials and Methods

### Participants.

Fifteen (9 female, age range 20-38) healthy, self-declared right-handed participants with normal or corrected-to-normal vision, and no history of neurological, sensory, or motor disorders participated in this study. Testing of each participant took place in a single session and required approximately 1.5 hours to complete. The study was conducted in accordance with ethical guidelines and was approved by the University of British Columbia's Clinical Research Ethics Board (CREB approval: H17-00796) and conformed to the guidelines of the Declaration of Helsinki, except for registration in a database.

### Experimental design.

Participants were seated in front of the KINARM End-Point Lab (BKIN Technologies Ltd., Kingston, Canada) and grasped the right manipulandum, linked to robotic motors, with their right hand. Arm movements were performed in the horizontal plane in response to targets presented on an augmented reality display. Participants were informed the upcoming task was a simple RT task consisting of a ballistic arm movement for one of three movement conditions. Prior to the IS, the visual display indicated which of the three movement conditions was to be performed. In the 1-target condition, movement was directed anteriorly (straight ahead) and terminated at the first target (A in Figure 1). In the 2-target condition, the participant reached the first target and performed a reversal in the posterior direction and to the right before terminating their movement at the second target (B in Figure 1). The 3-target condition involved a second

reversal after reaching the second target, requiring an anterior (straight ahead) movement to reach the final target (C in Figure 1). Importantly, regardless of the final target position, the initial movement (i.e., home position to target one) was identical across all movement conditions, in line with Henry and Rogers' original experiment (Henry & Rogers, 1960). Each trial required the participant to first reach the home position, represented by a red dot that was positioned 19 cm in front of the participant's right arm. Following a random foreperiod (1000-3000 ms), the home position marker turned green (imperative stimulus), signaling the participant to initiate the movement. All targets were the same size (visual radius of 0.5 cm) and changed from white to green when reached successfully.

Prior to testing, participants completed a practice block consisting of 10 trials for each condition. Mean premotor RT was calculated for each condition, after excluding the fastest and slowest trials. Premotor RT was defined as the time between the IS and the onset of EMG activity. Movement time was also calculated and defined as the time between leaving the home position and hitting target A. Testing trials were identical to those of the practice trials, with the exception that TMS was presented at six time points following the IS (0, 50, 60, 70, 80 or 90% of each participant's premotor RTs). Testing consisted of 144 trials separated into 4 blocks of 36. Each block included 12 trials for each condition (i.e. 2 trials at each of the 6 TMS stimulation points for the 1-, 2-, and 3-movement conditions).

**Recording Equipment.**

Velocity and acceleration of the right manipulandum were sampled by the KINARM at 1000 Hz. Surface EMG data were recorded via adhesive Ag-AgCl electrodes (10mm diameter, Cleartrace; ConMed, Utica, NY), with the active lead positioned over the triceps brachii muscle belly and the reference over the distal tendon. Data were recorded using a 16-bit A/D converter

(CED Power1401-3; Cambridge Electronic Design Ltd, Cambridge, UK) and Spike2 software (version 7.10; Cambridge Electronic Design). Signals were sampled at 2000 Hz, amplified (×100) and bandpass filtered (16-1000 Hz) using CED 1902 amplifiers (Cambridge Electronic Design Ltd., Cambridge, UK).

**Electrical stimulation.**

To determine the EMG response to simultaneous activation of the entire triceps brachii motoneuron pool, electrical stimulation was applied to the brachial plexus to evoke the maximal compound muscle action potential (Mmax). Single stimuli were delivered by a constant-current electrical stimulation (DS7AH; Digitimer Ltd, Welwyn Garden City, UK) at a pulse duration of 200 μs and continuously variable voltage between 100 and 400 V. The cathode and anode (adhesive Ag-AgCl electrodes; Cleartrace) were placed over the supraclavicular fossa and acromion, respectively. Stimuli were delivered as the participant held the manipulandum at the home position and prepared as if to move. Current was increased gradually with successive stimuli until the M-wave reached a plateau (Mmax). Once a plateau was established, an additional two stimuli were delivered at that current to establish a mean Mmax value.

**Transcranial Magnetic Stimulation.**

To elicit a MEP from triceps brachii, TMS was applied to the motor cortex using a circular coil (13.5 cm outer diameter) attached to a Magstim $200^2$ stimulation (Magstim, Dyfed, UK). The coil was held over the vertex, with the handle pointing backwards. Stimulus intensity was set to elicit a MEP amplitude of ~10% Mmax.

**Data analysis.**

All measures were analyzed offline using Signal software (version 6.03, Cambridge Electronic Design). The amplitude of the $M_{max}$ and MEPs were measured between the initial deflection from the baseline to the second crossing of the horizontal axis (Martin, Gandevia, & Taylor, 2006). Voluntary EMG measures included the root mean square (RMS) of the signal both in the 100 ms prior to ($EMG_{BACKGROUND}$), mean integrated EMG over the first 100 ms of muscular activity ($EMG_{100}$), as well as premotor RT (time between the IS and EMG onset) and silent period (time between TMS pulse and EMG onset) duration. Finally, both peak velocity and acceleration of the right hand were measured from the KINARM, using custom-written MATLAB scripts. Dependent measures greater than 2 standard deviations from each individual's overall mean were removed from the analysis. Overall, data from 272 trials (13%) were removed from the analysis.

**Statistical analysis.**

Data were analyzed using repeated-measures analyses of variance (RM-ANOVA). All analyses were conducted using SPSS version 23 (SPSS Inc., Chicago, IL, USA). Unless otherwise stated, all RM-ANOVAs were run as 3 (movement complexity) × 6 (TMS time) comparisons. For all RM-ANOVAs, Greenhouse-Geiser Epsilon was used to adjust degrees of freedom for violations of sphericity, when necessary. In the event of a significant interaction, simple main effects were assessed. Post-hoc tests were performed using Bonferroni corrected paired samples Student's *t*-tests, where appropriate. Differences with a $p<0.05$ were considered significant. Data are presented as mean ± SD.

## Results

### Response time measures.

To determine if the complexity manipulation led to differences in premotor RT, a one-way RM ANOVA was performed. The analysis (Figure 4) revealed a significant main effect of complexity ($F(2,26) = 21.7$, $p < 0.001$, $\eta_p^2 = 0.626$). The post-hoc analysis indicated that there was a progressive increase in premotor RT with complexity. Specifically, RT was faster for the 1- than 2-movement condition ($M$ = -29.6 ms, 95% CI [-49.1, -10.1], $p = 0.003$), 1- than 3-movement condition ($M$ = -43.8 ms, 95% CI [-66.3, -21.3], $p < 0.001$), and for the 2- than 3-movement condition ($M$ = -14.3 ms, 95% CI [-26.7, -1.83], $p = 0.023$). The same analysis was performed on MT data, and revealed no main effect of complexity ($F(2,24) = 0.064$, $p = 0.938$, $\eta_p^2 = 0.005$).

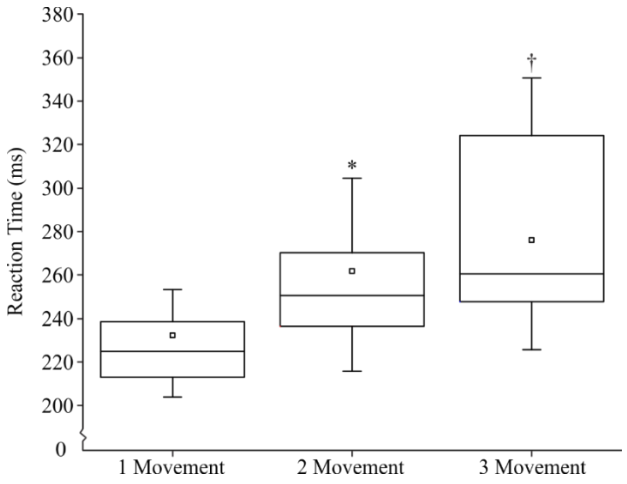


**Figure 4**. Boxplot of the mean premotor RT across the 3 complexity levels. Box boundaries represent the 25th and 75th percentiles, solid horizontal lines represent medians, the small squares within the box represent means, and error bars represent the farthest outliers within 1.5 times the inter-quartile range from the box boundaries. The single asterisk (*) denotes a significantly slower RT compared to the 1-movement condition. The single dagger (†) denotes a significantly slower RT compared to both the 1- and 2- movement conditions.

**Motor Evoked Potentials.**

Peak-to-peak amplitude Mmax values across the group of participants was 24.9 ± 3.8 mV. A 3 (movement complexity) × 6 (TMS time) RM ANOVA was performed to determine if MEP differences existed among the three task complexities over time (Figure 5).

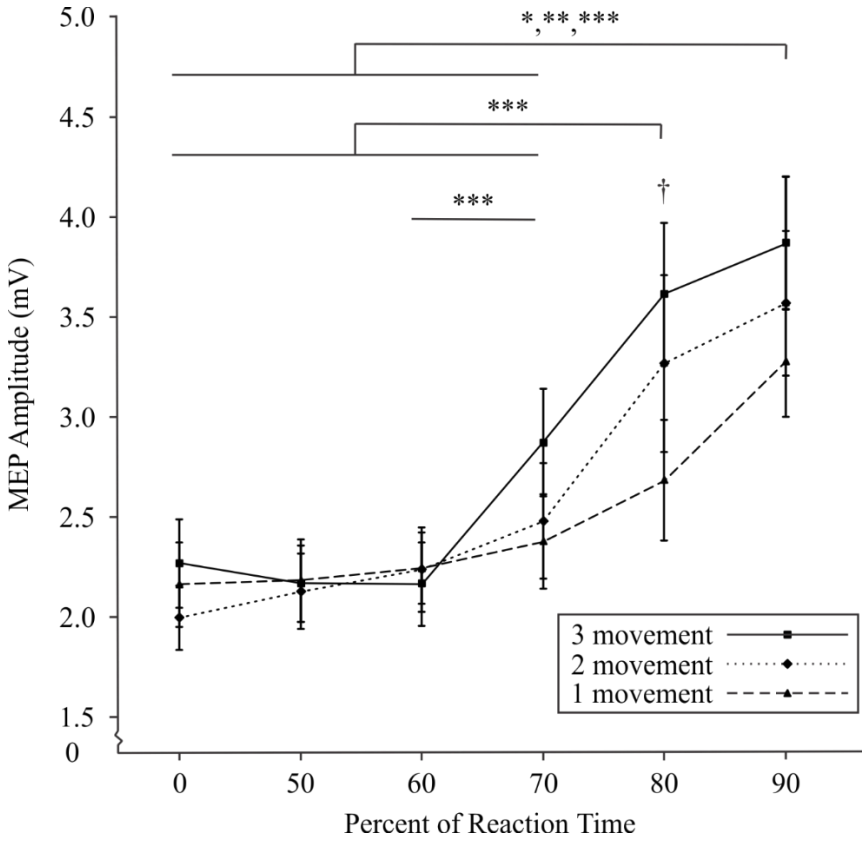


**Figure 5**. Mean MEP amplitudes across the 3 movement complexity levels. Asterisks denote significant increases in MEP amplitudes over time in the 1-movement (*), 2-movement (**) and 3-movement (***) conditions. The single dagger (†) denotes a significant increase in MEP amplitude between the 1- and 3-movement conditions at 80% of RT. Error bars represent standard error of the mean.

The analysis revealed a main effect of complexity ($F(1.28,16.7) = 4.233$, $p = 0.047$) and time ($F(1.44,18.8) = 24.3$, $p < 0.001$) as well as an interaction between complexity and time

($F(4.72,61.4) = 3.12$, $p = 0.016$). Therefore, the effect of complexity was assessed at each time point (% RT) and the effect of time was assessed separately for each condition. Post-hoc tests revealed mean MEP amplitude was 35% (95% CI [0.193,1.67]) greater in the 3-movement as opposed to the 1-movement movement condition at 80% RT, ($F(2,26) = 7.40$, $p = 0.003$). With respect to time, in the 1-movement condition, mean MEP amplitude was at least 38% (95% CI [0.164, 1.64]) greater at 90% RT than all other time points ($F(5,65) = 11.4$, all $p$s <0.001), except at 80% RT. Similarly, in the 2-movement condition, mean MEP amplitude was at least 44% (95% CI [0.265,1.91]) greater at 90% RT than all other time points ($F(5,65) = 13.1$, all $p$s <0.011), except at 80% RT. In the 3-movement condition, mean MEP amplitude was at least 35% (95% CI [0.012,1.99]) greater at 90% RT than all other time points ($F(5,65) = 22.9$, all $p$s <0.046), except at 80% RT. Representative individual EMG traces from a single participant in each of the three movement conditions at 0% RT are shown in Figure 6.

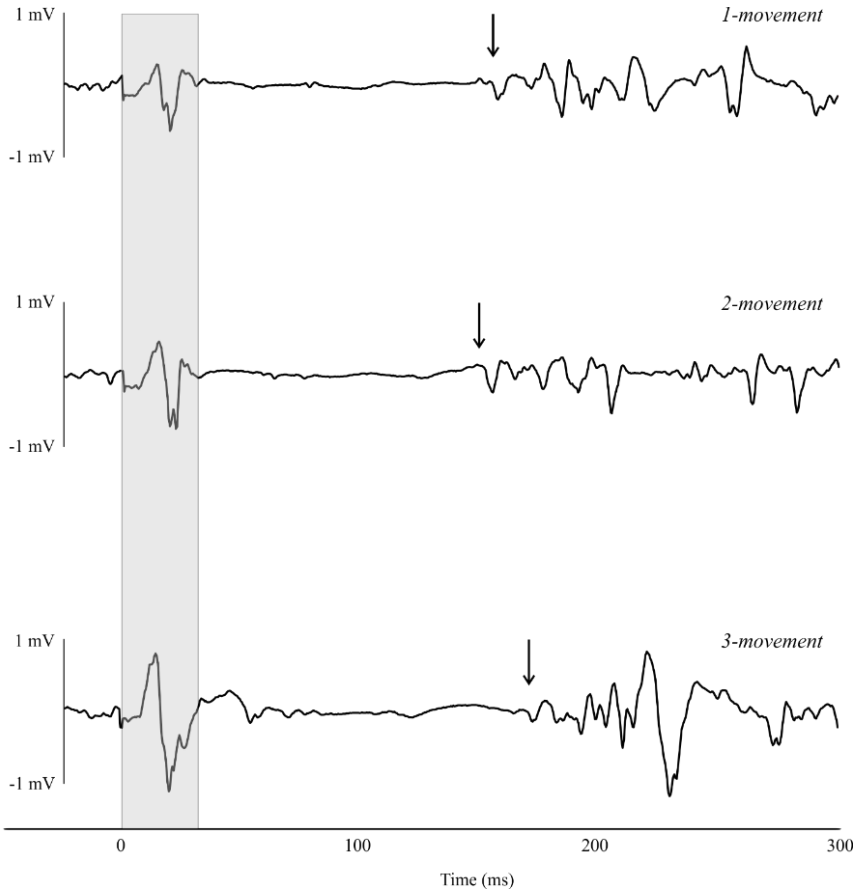


**Figure 6**. Representative EMG traces from a single participant in the 1-, 2-, and 3-movement conditions. The shaded box highlights the MEP. In all trials, the TMS pulse was delivered at 0% RT (i.e., at the time of the imperative stimulus), represented by the left edge of the shaded box. Time to voluntary EMG onset (premotor RT) is indicated in each condition by an arrow.

**Voluntary electromyographical measures.**

Background EMG was compared among the three task complexities in the 100ms prior to the TMS stimulus (Figure 7). This analysis revealed that there was no main effect of complexity ($F(2,26) = 1.13$, $p = 0.340$) or an interaction ($F(2.27,29.5) = 2.30$, $p = 0.112$). There was a main effect of time ($F(1.37,17.8) = 5.48$, $p = 0.023$); however, the post-hoc analysis revealed no further differences.

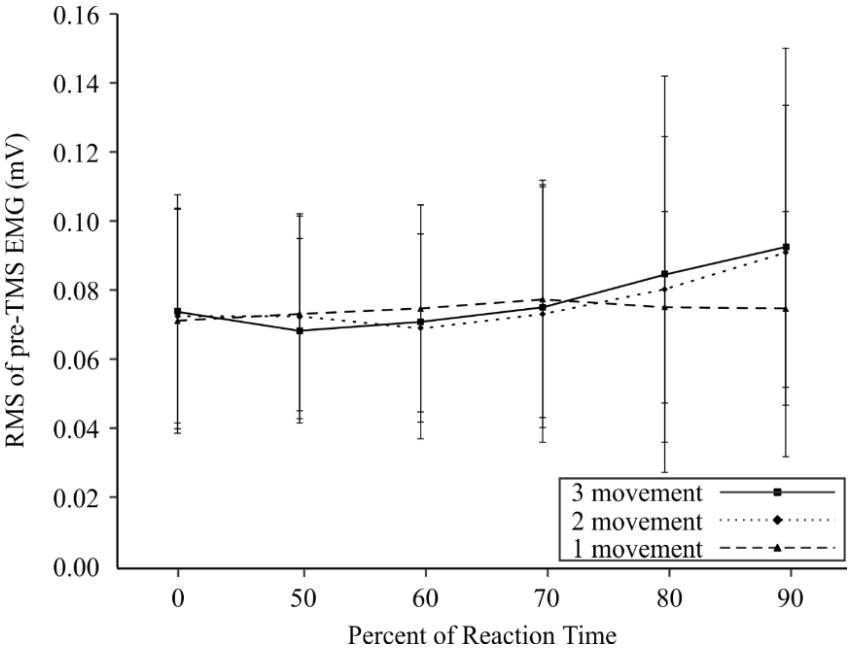


**Figure 7.** The Root Mean Square (RMS) of the pre-TMS EMG across the 3 movement complexities. Error bars represent standard error of the mean.

The mean integrated muscular activity over the first 100 ms ($EMG_{100}$) of the voluntary agonist burst was analysed to determine if differences existed between the three task complexities (Figure 8). There were significant main effects for complexity ($F(2,28) = 6.13$, $p = 0.006$) and time ($F(2.11,6.07) = 3.50$, $p = 0.041$) but no interaction ($F(5.17,72.4) = 1.22$, $p = 0.307$). The post-hoc analysis demonstrated $EMG_{100}$ in the 3-movement condition was 9% and 7% lower than the 1-movement (95% CI [-1.51, -0.131 mV], $p = 0.018$) and 2-movement (95% CI [-1.16, -0.021 mV], $p = 0.041$) complexity conditions, respectively. No post-hoc differences were found (all $p$s > 0.414) over time. The ratio of the RMS values between the agonist (triceps brachii) and the antagonist (biceps brachii) muscles were compared to determine if differences in the first 100 ms of voluntary EMG ($EMG_{RMS}$) existed between the three task complexities over time. This analysis was specifically run to determine if a change in the ratio in

muscular activity could have contributed to the movement of the right arm. The analysis revealed that there were no main effects of complexity ($F(2,24) = 0.508$, $p = 0.608$) or time ($F(2,24) = 1.22$, $p = 0.309$, as well as no interaction effect ($F(2,24) = 0.888$, $p = 0.547$).

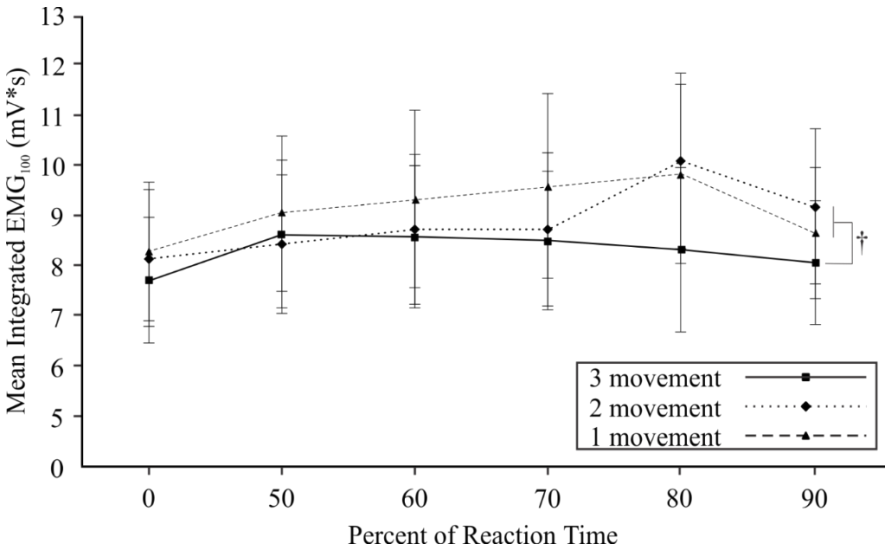


**Figure 8.** The mean integrated EMG of the first 100 ms ($EMG_{100}$) of agonist burst across the 3 movement complexities. The single dagger (†) denotes a significantly lower mean value for the 3- compared to 1- and 2-movement complexities. Error bars represent standard error of the mean

The length of the silent period was analyzed to determine if differences existed among the three task complexities prior to the onset of the initial agonist EMG burst (Figure 9). There was a trend towards a significant main effect for complexity ($F(2,26) = 3.33$, $p = 0.052$) and a significant main effect of time ($F(5,70) = 2.46$, $p = 0.042$). These were superseded by a significant two-way interaction between complexity and time ($F(4.28,55.7) = 2.60$, $p = 0.042$). Therefore, simple main effects were run across complexity and time. Mean silent duration was 8 (95% CI [0.002, 0.014]) ms longer in the 3-movement as opposed to the 1-movement movement condition at 50% RT ($F(2,26) = 5.60$, $p = 0.01$). There were also significant simple main effects

at 60% RT ($F(2, 26) = 3.37$, $p = 0.05$) and 70% of RT ($F(2,26) = 4.85$, $p = 0.016$); however, no post-hoc differences were found (all $p$s > 0.058*)* among movement complexities. There was a decrease in silent period duration over time in both the 1-movement ($F(5,65) = 3.30$, $p = 0.01$) and 3-movement conditions ($F(5,65) = 2.49$, $p = 0.04$); however, no post-hoc differences were found (all $p$s > 0.096).

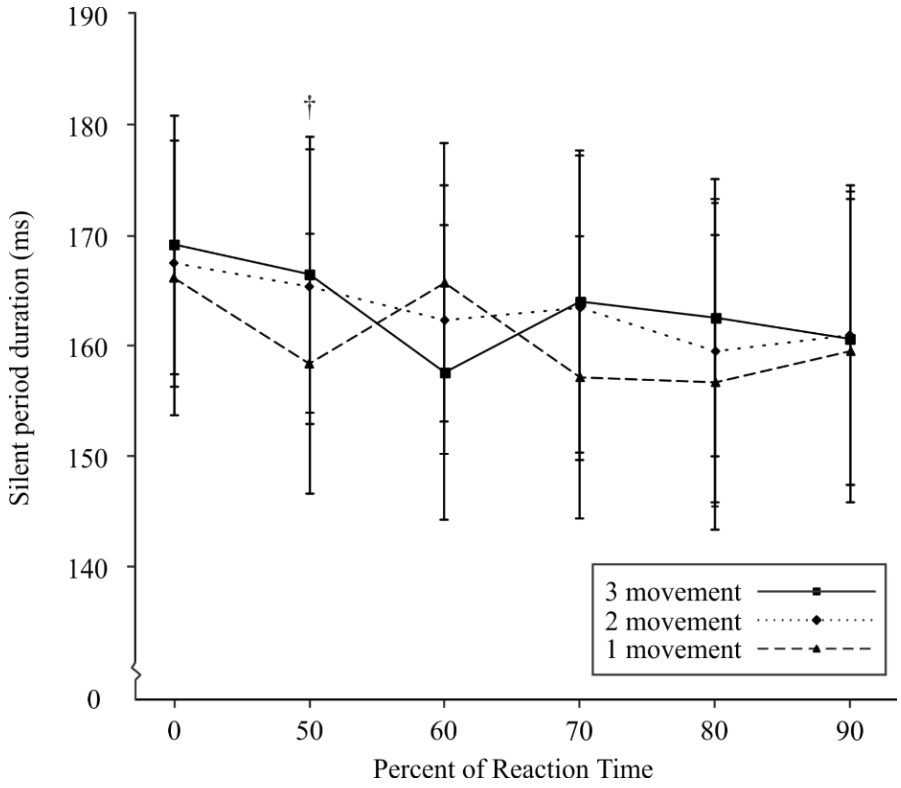


**Figure 9.** Silent period duration across the 3 movement complexity conditions. The single dagger (†) denotes that silent period duration was longer for the 3- than 1-movement condition at 50% of RT. Error bars represent standard error of the mean.

**Kinematic measures.**

Both the peak acceleration and peak velocity of the KINARM handle were analysed to determine the effect of movement complexity on the functional output of the arm. The peak acceleration (Figure 10) analysis revealed a main effect for movement complexity ($F(2,26) =$

4.02, $p$ =0.03); however, no post-hoc differences were found. Furthermore, no effect of time ($F$(2.61,33.9) = 0.826, $p$ =0.474) or interaction ($F$(4.30,55.8) = 0.883, $p$ =0.486) was found. With regards to peak velocity, there was a trend for a movement complexity ($F$(2,26) = 3.25, $p$ =0.055), but no main effect of time ($F$(2.15,28.0) = 1.091, $p$ =0.353) or interaction ($F$(10, 130) = 0.377, $p$ =0.955).

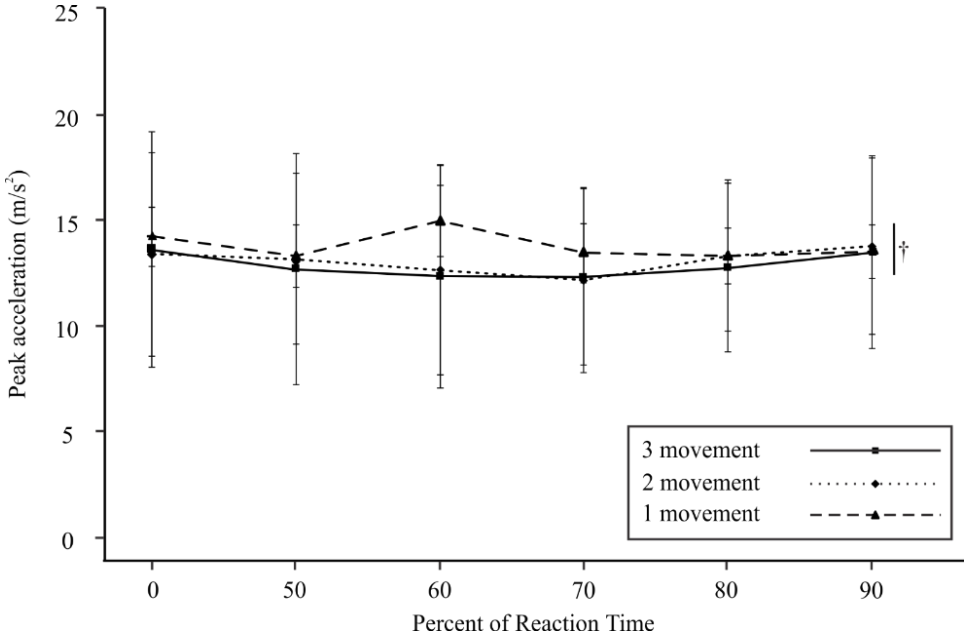


**Figure 10.** Peak acceleration ($m/s^2$) of the right arm across the 3 movement complexity conditions. The single dagger (†) denotes a significant main effect of complexity. Error bars represent standard error of the mean.

## Discussion

The purpose of this study was to examine how step-wise manipulation of response complexity during a movement task affects excitability of the motor pathway in a simple RT task. The major finding was that CE increased with complexity (figure 5), without an effect of complexity on the level of background EMG in the preparation phase prior to movement.

Prior studies have used a variety of tasks to demonstrate CE can be affected by an increase in complexity (e.g., Abbruzzese et al., 1996; Flament et al., 1993; Kennefick et al., 2016; Roosink & Zijdewind, 2010); however, interpretation is made difficult by other elements of the task. A simple RT task is the only paradigm that allows participants to prepare fully for upcoming movements and thereby accentuate different preparation strategies between simple and complex movements. Three of the aforementioned studies were not performed with an RT paradigm (Abbruzzese et al., 1996; Flament et al., 1993; Roosink & Zijdewind, 2010), while the fourth (Kennefick et al., 2016) imposed a specific timing on the elements of the complex task. Further, to best assess the effect of complexity on CE, the initial movement should be identical across all conditions. This was not the case for two of these studies (Abbruzzese et al., 1996; Flament et al., 1993). The current study avoided these previous limitations by using a simple RT paradigm in which the initial movement was always directed to the same target (Figure 1 – target A) and complexity was increased in a stepwise manner.

Previous TMS studies have shown a decrease in CE during the preparatory phase of movement production (Hasbroucq et al., 1997; Touge et al., 1998). This inhibition has been postulated to prevent the premature release of a response during the foreperiod of a RT task (Stinear et al., 2009). For example, the inhibition could act as a general "braking" mechanism and suppress the tendency to initiate a movement, which is released once the IS appears (Prut & Fetz, 1999). However, recent studies indicate that a general braking mechanism is unlikely. Using a Go/NoGo task in mice, Hasegawa and colleagues (2017) found the preparation for an intended movement was characterized by the selective suppression of certain motor circuits but increased activity in so-called "build-up neurons" in the motor cortex. Using TMS in humans, Hannah and colleagues (2018) demonstrated that a specific set of excitatory inputs to

corticospinal neurons (responsible for late I-waves) are suppressed during motor preparation, while others remain unaffected. Interestingly, an increase in preparatory suppression was accompanied by a reduction in RT. This finding would not be expected if a general "braking" mechanism existed, as this form of suppression would lengthen RTs. The results of the current study agree with this interpretation, as RT was shortest in the simplest movement condition and was accompanied by a suppression in CE compared to the most complex task. This suggests the complexity effect responsible for lengthened RTs in the original Henry and Rogers' (1960) experiment may be due in part to reduced suppression of specific motor circuitry, while other circuitry is responsible for the increase in CE seen with more complex movements.

It is important to note that changes in MEPs are not an exclusive representation of cortically-mediated processes. For example, during weak (Hess, Mills, & Murray, 1987), moderate (McNeil, Giesebrecht, Gandevia, & Taylor, 2011) and maximal (McNeil, Martin, Gandevia, & Taylor, 2009) contractions, changes in MEPs has been attributed to altered motoneuron excitability. Furthermore, recent evidence (Yacyshyn, Woo, Price, & McNeil, 2016) shows that the reduction of motoneuron excitability after TMS can last beyond 150 ms, so the spinal portion of the silent period may last much longer than previously proposed (Fuhr, Agostino, & Hallett, 1991; Inghilleri, Berardelli, Cruccu, & Manfredi, 1993). The current study demonstrated the silent period was longest in the most complex, 3-component movement (Figure 9), suggesting that corticospinal inhibition increases with complexity. In addition to cortical and spinal influences, peripheral excitability has been shown to affect the size of the MEP. (Stefan et al., 2000). There is no reason to anticipate a peripheral influence for the present MEP dataset; however, we opted to measure Mmax in the same experimental design with a subset of participants (n=3). Although a sample size of three participants offers little statistical power,

there is no indication that peripheral excitability affects movement complexity ($p = 0.975$). However, importantly, we cannot deduce if the complexity effects on the MEP occur at a cortical or spinal level (or both).

We also found that with increasing movement complexity there was both a decrease in the initial burst of agonist EMG (Figure 8) and the peak acceleration of the movement (Figure 10). These effects occurred despite the absence of an impact of complexity on MT. Following initiation of the movement, participants may have adopted online control strategies to navigate through the more complex conditions, indicating that some movement components may not have been fully preprogrammed. This has previously been shown for a repetitive elbow extension/flexion task that increased complexity by increasing the number of cycles (movement reversals) following the IS (van Donkelaar & Franks, 1991). With increasing complexity, there was an increase in the ratio of the duration of agonist muscular activity in relation to duration of angular displacement, indicative of online control. Furthermore, Maslovat and colleagues (2014) had participants perform single element key-press or multiple element key-press sequences with either an isochronous or non-isochronous timing structure in a simple RT paradigm, thereby manipulating both complexity and timing structure. They demonstrated that simple RT can increase when the timing structure of the initiation of a movement is manipulated, even when complexity (movement components) is not increased. This indicates that some elements of movement can be preprogrammed, while others are controlled online.

The corticospinal tract is responsible for a broad cortical modulation of motoneuron output (Lemon & Griffiths, 2005) but other cortical structures influence both the motor cortex and the motoneurons. For example, Dum and Strick (2002) have shown that premotor areas have direct and indirect (via motor cortex) connections with motoneurons that are capable of

influencing movement. Studies in nonhuman primates (see Churchland, Yu, Ryu, Santhanam, & Shenoy, 2006) have demonstrated that firing rate variability in the premotor cortex declines between target onset and movement onset, which has been hypothesized to reflect the progress of motor preparation. Based on this work, Klein-Flügge and colleagues (2013) measured the variability of CE prior to movement onset, which should track the state of action preparation. The authors noted a decrease in variability of CE contralateral to the responding hand prior to movement onset that was specific to a chosen action and hypothesized to be analogous to the firing rate variability seen in non-human primates. Furthermore, Groppa and colleagues (2012) used dual-site TMS during relaxation to probe ipsilateral cortico-cortical connections between the left dorsal premotor cortex (PMd) and the hand representation on the motor cortex. They reported a facilitation of MEPs in the contralateral first dorsal interosseous muscle at an interstimulus interval of 2.8 ms. Importantly, activity in PMd reflects stages in the specification and selection of movement (Cisek & Kalaska, 2005). This recent evidence demonstrates that CE can also be influenced by action selection processes originating from premotor areas and warrants further investigation.

**Summary**

The current study addressed methodological limitations in other studies to demonstrate that CE prior to movement onset is influenced by the complexity of the planned task. The key findings from this investigation indicate that the movement complexity manipulation lead to increases in RTs, as well as MEP amplitudes. This increase in excitability was coupled with decreases in voluntary EMG and kinematic variables after movement onset. These results suggest that, inline with recent literature, suppression of CE excitability is inversely related to RT.

## Chapter 4: The Time Course of Motoneuron Excitability During the Preparation and Execution of Complex Movements

Chapter 2 (study 1) demonstrated that movement preparation processes can be altered by movement complexity; however, it could not determine where within the motor pathway these alterations occurred. Chapter 3 (study 2) determined CE could be also be altered by movement complexity, as the complexity manipulation lead to increases in both RTs and MEP amplitudes. Importantly, chapter 3 (study 2) confirmed that it was possible to capture excitability changes due to complexity within the motor pathway; however, it was not possible to isolate whether these changes were cortically or segmentally mediated. Chapter 4 (study 3) disentangles this mediation.

### Background

How the brain controls volitional movement has long been debated and is still not fully resolved. Output from the primary motor cortex (M1) is the impetus for goal-direct movements; however, it is important to consider that M1 output is influenced by numerous cortical and subcortical inputs. Further, M1 output can be modulated at multiple subcortical sites as it travels along the motor pathway toward the target muscle (see Scott, 2003 for a review). In humans, the excitability of the motor pathway to a target muscle is often probed using TMS, which activates the motor cortex and produces a short-latency excitatory response in the electromyogram (EMG). This *motor evoked potential* (MEP) reflects the responsiveness of neurons at cortical, spinal and peripheral levels (Taylor, Butler, & Gandevia, 1999). Thus, in order to isolate the contribution of these components to a change in MEP size, the motor pathway must be probed at one or more sites below the level of the motor cortex, under the same conditions. Prior to movement onset during a simple RT task, a change in peripheral excitability (as measured by the

maximal compound muscle action potential, Mmax) is unlikely, which makes it justifiable to attribute a change in the MEP to altered corticospinal excitability (CE). To test for a cortical component to any change in CE, it is necessary to normalize the MEP to a measure of motoneuron excitability. Stimulation of the corticospinal tract at the level of the mastoids (Ugawa et al. 1991) yields the cervicomedullary motor evoked potential (CMEP), the most direct means to assess motoneuron excitability in humans (Martin et al. 2008). Notably, the CMEP is not subject to the presynaptic inhibition that limits the utility of the H-reflex as a measure of motoneuron excitability (Nielsen & Petersen 1994).

In a simple RT paradigm, CE has been shown to gradually increase ~100 ms prior to EMG onset (Chen et al., 1998; Hoshiyama et al., 1996; Pascual-Leone, Brasil-Neto, et al., 1992; Pascual-Leone, Valls-Solé, et al., 1992; Tarkka et al., 1995; Tomberg & Caramia, 1991). None of these studies included a measure of motoneuron excitability so it was not possible to separate CE into cortical and spinal components. The one study to consider spinal contributions to the increase in MEP size prior to movement (rapid wrist flexion) found that the H-reflex only increased with the onset of EMG, which led the authors to attribute the facilitation of the MEP to cortical mechanisms (MacKinnon & Rothwell 2000). Conversely, studies using static contractions demonstrate a progressive facilitation of the H-reflex, beginning ~50 ms prior to movement onset (Day, Rothwell, & Marsden, 1983; Gottlieb, Agarwal, & Stark, 1970; Pierrot-Deseilligny, Lacert, & Cathala, 1971).

In their seminal experiment, Henry and Rogers (1960) demonstrated that simple RT increases with an increasing number of movement components. Complex motor behaviours have also been shown to alter other behavioural output metrics such as CE (Abbruzzese et al., 1996; Flament et al., 1993; Greenhouse, Saks, Hoang, & Ivry, 2015; Kennefick et al., 2016; Roosink &

Zijdewind, 2010), in a task dependent manner. While CE has been shown to be sensitive to complex movements, no studies have investigated the specific role of motoneuron excitability in complex movements. Therefore, the purpose of the current study was two-fold. The first purpose was to establish a time-course of motoneuron excitability prior to the onset of movement in a simple RT task. The second purpose was to describe the task dependent effect of complex movements on motoneuron and cortical excitability. It was hypothesized that both cortical and motoneuron excitability would increase prior to movement onset, as well as in response to movement complexity.

## Materials and Methods

### Participants.

Twenty healthy (11 females; age range 18-42), self-declared right-handed participants with normal or corrected-to-normal vision, and no history of neurological, sensory, or motor disorders participated in this study. Testing of each participant took place during a single session and required approximately 1.5 hours to complete. The study was conducted in accordance with ethical guidelines and was approved by the University of British Columbia's Clinical Research Ethics Board (CREB approval: H17-00796) and conformed to the guidelines of the Declaration of Helsinki, except for registration in a database.

### Experimental set-up.

From a seated position, the participant used their right hand to grasp the right manipulandum of a KINARM End-Point Lab (BKIN Technologies Ltd., Kingston, Canada). Surface EMG data were recorded via adhesive Ag-AgCl electrodes (10mm diameter, Cleartrace; ConMed, Utica, NY), with the active lead positioned over the triceps brachii muscle belly and the reference over the distal tendon. Data were recorded using a 16-bit A/D converter (CED

Power1401-3; Cambridge Electronic Design Ltd, Cambridge, UK) and Spike2 software (version 7.10; Cambridge Electronic Design). Signals were sampled at 2000 Hz, amplified (×100) and bandpass filtered (16-1000 Hz) using CED 1902 amplifiers (Cambridge Electronic Design Ltd., Cambridge, UK).

**Task details.**

Arm movements were performed in the horizontal plane in response to targets presented on an augmented reality display. Participants were informed that the upcoming task was a simple RT task consisting of a ballistic arm movement for one of three movement conditions. Prior to the IS, the visual display indicated which of the three movement conditions was to be performed. In the 1-target condition, movement was directed anteriorly (straight ahead) and terminated at the first target (A in Figure 1). In the 2-target condition, the participant reached the first target and performed a reversal in the posterior direction and to the right before terminating their movement at the second target (B in Figure 1). The 3-target condition involved a second reversal after reaching the second target, requiring an anterior (straight ahead) movement to reach the final target (C in Figure 1). Importantly, regardless of the final target position, the initial movement (i.e., home position to target one) was identical across all movement conditions, in line with Henry and Rogers' original experiment (Henry & Rogers, 1960). Each trial required the participant to first reach the home position, represented by a red dot that was positioned 19 cm in front of the participant's right arm. Following a random foreperiod (1000-3000 ms), the home position marker turned green (imperative stimulus), signaling the participant to initiate the movement. All targets were the same size (visual radius of 0.5 cm) and changed from white to green when reached successfully.

**Brachial plexus stimulation.**

To determine the EMG response to simultaneous activation of the entire triceps brachii motoneuron pool, electrical stimulation was applied to the brachial plexus to evoke the maximal compound muscle action potential (Mmax). Single stimuli were delivered by a constant-current electrical stimulator (DS7AH; Digitimer Ltd, Welwyn Garden City, UK) at a pulse duration of 200 μs and continuously variable voltage between 100 and 400 V. The cathode and anode (adhesive Ag-AgCl electrodes; Cleartrace) were placed over the supraclavicular fossa and acromion, respectively. Stimuli were delivered as the participant held the manipulandum at the home position and prepared as if to move. Current was increased gradually with successive stimuli until the M-wave reached a plateau (Mmax). Once a plateau was established, an additional two stimuli were delivered at that current to establish a mean Mmax value.

**Transmastoid stimulation.**

To elicit a CMEP from the triceps brachii, the corticospinal tract was stimulated with a high-voltage electrical current (DS7AH; 200 μs pulse duration, 100–400 V) passed between adhesive Ag–AgCl electrodes fixed to the skin ~1 cm superior and medial to the mastoid processes (Gandevia et al., 1999; Ugawa et al., 1991). Stimulus intensity was set to elicit a CMEP amplitude equivalent to ~10% of the Mmax obtained under the same conditions (i.e., at the home position, prepared to move).

**Transcranial magnetic stimulation.**

To elicit a MEP from triceps brachii, TMS was applied to the motor cortex using a circular coil (13.5 cm outer diameter) attached to a Magstim $200^2$ stimulation (Magstim, Dyfed, UK). The coil was held over the vertex, with the handle pointing backwards. Stimulus intensity

was set to elicit a MEP amplitude equivalent to ~10% of the Mmax obtained under the same conditions (i.e., at the home position, prepared to move).

**Experimental procedures.**

Data collection began with the establishment of mean premotor RT (the time between the IS and the onset of EMG activity) for each level of complexity. In separate blocks for each condition (performed in order of ascending complexity), participants completed 10 practice trials. The fastest and slowest trials were excluded, and a mean was calculated based on the remaining eight trials. Next, Mmax was determined and stimulus intensities were set for transmastoid stimulation and TMS. After a brief rest, the main protocol began. Testing trials were identical to those of the practice trials, with the exception that either TMS or transmastoid stimulation was pseudo-randomly presented at four time points following the IS (0, 70, 80 or 90% of each participant's premotor RTs). Testing consisted of 144 trials separated into 3 blocks of 48. Each block included 24 trials for each stimulation type (TMS and transmastoid stimulation) across each level of complexity (i.e. 2 trials at each of the 4 stimulation points for the 1-, 2-, and 3-movement conditions with both TMS and transmastoid stimulation).

**Data analysis.**

All measures were analyzed offline using Signal software (version 6.03, Cambridge Electronic Design). Root mean square (RMS) of the background voluntary EMG was measured in the 100 ms prior to the TMS or transmastoid stimulation pulses. The amplitude of each evoked potential ($M_{max}$, CMEP and MEP) was measured between the initial deflection from the baseline to the second crossing of the horizontal axis (Martin et al., 2006). To determine if motoneuron or corticospinal excitability was altered by complexity or the percentage of premotor RT, for each

participant, CMEP and MEP amplitudes were expressed relative to their respective baselines (0% RT) across movement complexities. For comparison to previous work, absolute MEP amplitude was also used to evaluate CE in each condition. To assess the cortical contribution to any changes in CE, mean MEP amplitude was normalized to the mean CMEP amplitude obtained under the same conditions (e.g., MEP at baseline/CMEP at baseline). For both CMEPs and MEPs, potentials were removed from the analysis if they had an amplitude greater than two standard deviations from each individual's overall mean. Furthermore, if the RMS EMG was greater than two standard deviations from each individual's overall mean, the entire trial was removed from the analysis. Overall, data from 100 trials (3.9% of all trials) were removed from the analysis.

### Statistical analysis.

Data were analyzed using repeated-measures analyses of variance (RM-ANOVA). All analyses were conducted using SPSS version 23 (SPSS Inc., Chicago, IL, USA). RMS EMG was analyzed using a 2 (stimulation type) x 3 (movement complexity) × 4 (stimulation time) three-way RM-ANOVA. Evoked potentials were analyzed using 3 (movement complexity) × 4 (stimulation time) two-way RM-ANOVAs. For all RM-ANOVAs, Greenhouse-Geiser Epsilon was used to adjust degrees of freedom for violations of sphericity, when necessary. Post-hoc tests were performed using Bonferroni corrected paired samples Student's *t*-tests, where appropriate. Differences with a $p<0.05$ were considered significant. Data are presented as mean ± SD.

## Results

### Control measures.

Across participants, the mean peak-to-peak amplitude of Mmax was 25.2 ± 5.25 mV. Measured prior to testing, while the participant held the manipulandum at the home position and

prepared to move, the targeted ~10% MEP and CMEP amplitudes were 2.40 ± 0.64 mV (9.5% of Mmax) and 2.51 ± 0.58 mV (10.0 % of Mmax), respectively.

**Reaction time measures.**

To determine the effect movement complexity had on premotor RT, a one-way RM ANOVA was performed. The analysis (Figure 11) revealed a significant main effect of complexity ($F(1.14, 20.5) = 12.4$, $p < 0.001$, $\eta_p^2 = 0.408$). The post-hoc analysis indicated that premotor RT was faster for the 1-movement condition compared to both the 2-movement ($M$ = 37.4 ms, 95% CI [9.51, 65.3], $p$ = 0.002) and 3-movement conditions ($M$ = 41.7 ms, 95% CI [11.6, 71.9], $p$ = 0.002). However, RT did not increase from the 2- to 3-movement condition ($M$ = 4.32 ms, 95% CI [-4.84, 13.5], $p$ = 0.668).

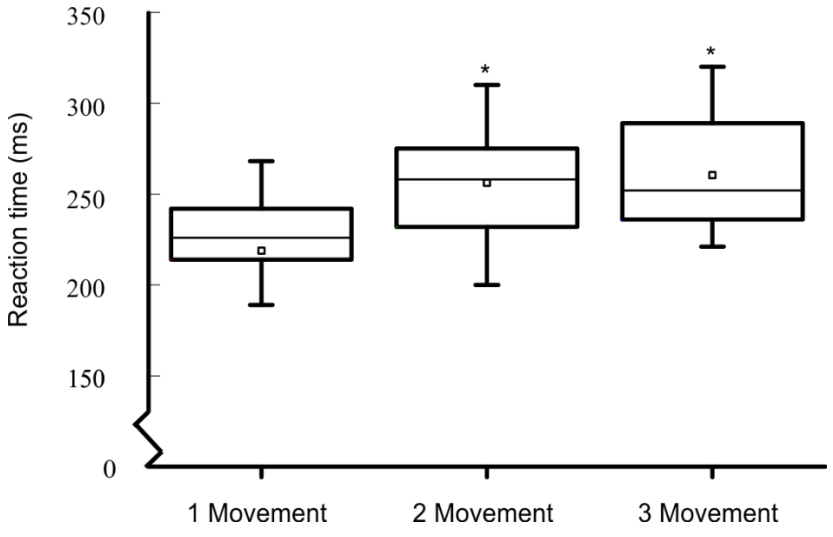


**Figure 11.** Boxplot of the mean premotor RT across the 3 complexity levels. Box boundaries represent the 25th and 75th percentiles, solid horizontal lines represent medians, the small squares within the box represent means, and error bars represent the farthest outliers within 1.5 times the inter-quartile range from the box boundaries. The asterisk (*) denotes a significantly slower RT compared to the 1-movement condition.

**Voluntary EMG.**

There was minimal RMS EMG under any conditions (Figure 12), indicating that the triceps brachii muscle was almost completely relaxed prior to TMS or transmastoid stimulation. The analysis revealed no main effects of stimulus intensity ($F(1,17) = 0.034$, $p = 0.856$, $\eta_p^2 = 0.002$), complexity ($F(2,34) = 0.021$, $p = 0.979$, $\eta_p^2 = 0.001$), or time ($F(1.23, 20.9) = 2.47$, $p = 0.126$, $\eta_p^2 = 0.127$).

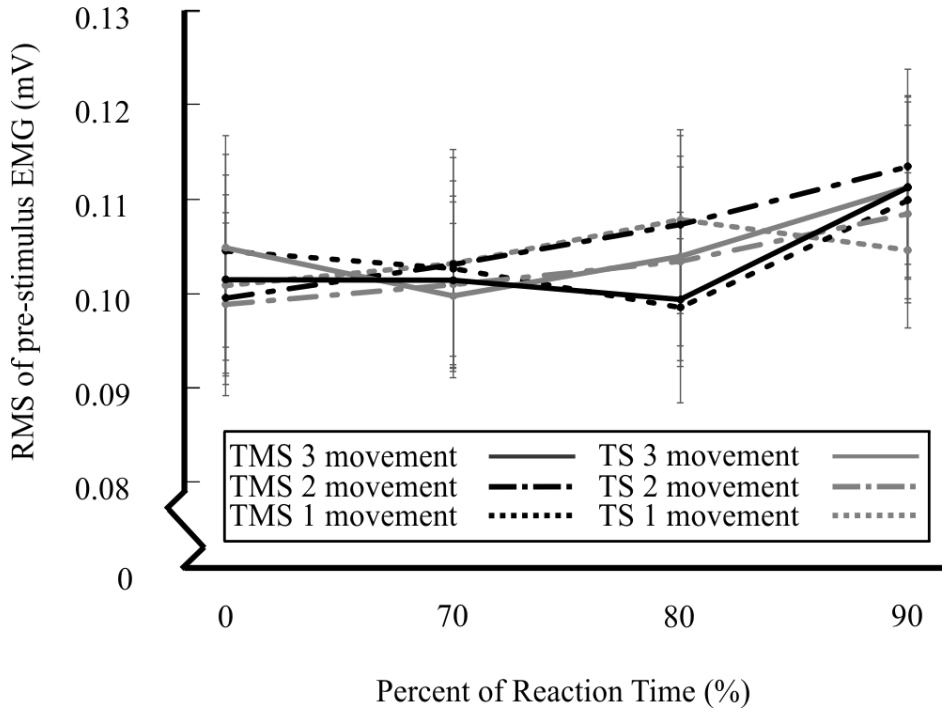


**Figure 12.** The Root Mean Square (RMS) of the voluntary EMG 100 ms prior to transmastoid stimulation (TS; gray lines) or transcranial magnetic stimulation (TMS; black lines) across the 3 movement complexities. Error bars represent standard error of the mean.

**Evoked Potentials.**

Mean values for all raw data in absolute units are summarized in Table 2. As this study used a simple RT paradigm, participants knew which movement they were to perform when the IS was presented. To test if complexity could affect motoneuron or corticospinal excitability as

early as the IS, a 2 (stimulus type) x 3 (movement complexity) two-way RM-ANOVA was performed for absolute MEP and CMEP amplitudes at 0% RT.

**Table 2.** Raw data for all experimentally measured responses.

| | **1-movement complexity** | **2-movement complexity** | **3-movement complexity** |
|---|---|---|---|
| **Reaction time (ms)** | 229 (23) | 256 (31) | 261 (30) |
| **Peak-to-peak MEP amplitude (mV)** | | | |
| *0 % RT* | 2.85 (1.65) | 2.89 (1.66) | 2.86 (1.62) |
| *70% RT* | 3.21 (2.01) | 3.60 (2.40) | 3.41 (2.51) |
| *80% RT* | 3.67 (2.51) | 3.90 (2.55) | 3.75 (2.68) |
| *90% RT* | 4.13 (2.96) | 4.69 (3.81) | 4.07 (2.91) |
| **Peak-to-peak CMEP amplitude (mV)** | | | |
| *0 % RT* | 2.03 (0.91) | 1.99 (0.87) | 1.94 (0.93) |
| *70% RT* | 2.17 (1.05) | 2.57 (1.57) | 2.61 (1.39) |
| *80% RT* | 2.85 (1.51) | 3.12 (2.13) | 2.92 (2.15) |
| *90% RT* | 3.23 (2.39) | 3.75 (2.73) | 3.34 (2.29) |
| **RMS of 100ms prior to TMS pulse (mV)** | | | |
| *0 % RT* | 0.105 (0.04) | 0.100 (0.03) | 0.101 (0.04) |
| *70% RT* | 0.103 (0.04) | 0.103 (0.04) | 0.101 (0.04) |
| *80% RT* | 0.099 (0.04) | 0.107 (0.04) | 0.100 (0.03) |
| *90% RT* | 0.110 (0.04) | 0.113 (0.04) | 0.111 (0.04) |
| **RMS of 100ms prior to Transmastoid pulse (mV)** | | | |
| *0 % RT* | 0.101 (0.04) | 0.100 (0.04) | 0.105 (0.05) |
| *70% RT* | 0.103 (0.05) | 0.100 (0.04) | 0.100 (0.03) |
| *80% RT* | 0.108 (0.03) | 0.103 (0.04) | 0.104 (0.04) |
| *90% RT* | 0.104 (0.03) | 0.108 (0.04) | 0.111 (0.04) |
| **RMS of agonist burst (100 ms) in the TMS condition (mV)** | | | |
| *0 % RT* | 0.60 (0.45) | 0.51 (0.43) | 0.54 (0.46) |
| *70% RT* | 0.67 (0.46) | 0.61 (0.46) | 0.60 (0.46) |
| *80% RT* | 0.71 (0.50) | 0.60 (0.49) | 0.63 (0.48) |
| *90% RT* | 0.49 (0.49) | 0.60 (0.44) | 0.61 (0.39) |
| **RMS of agonist burst (100 ms) in the Transmastoid stimulation condition (mV)** | | | |
| *0 % RT* | 0.64 (0.37) | 0.53 (0.33) | 0.61 (0.49) |
| *70% RT* | 0.75 (0.44) | 0.67 (0.44) | 0.66 (0.43) |
| *80% RT* | 0.77 (0.46) | 0.76 (0.49) | 0.69 (0.44) |
| *90% RT* | 0.81 (0.48) | 0.74 (0.45) | 0.72 (0.45) |

The analysis of the evoked potentials revealed a main effect for stimulation type ($F(1,17) = 8.00$, $p = 0.012$, $\eta_p^2 = 0.320$) but not movement complexity ($F(1.32,22.4) = 0.083$, $p = 0.842$, $\eta_p^2 = 0.005$), which indicates that complexity of the upcoming movement does not influence motoneuron or corticospinal excitability at the timing of the IS. Representative individual EMG traces from a single participant in each movement condition at 0% RT are shown in Figure 13. Despite the excellent matching of the MEP and CMEP during set-up (9.5 vs. 10.0% of Mmax, respectively), the MEP amplitude was larger than that of the CMEP at 0% RT (2.9 vs. 2.0 mV, respectively). Although this finding was unwanted, the potentials represent a similar proportion of the motoneuron pool.

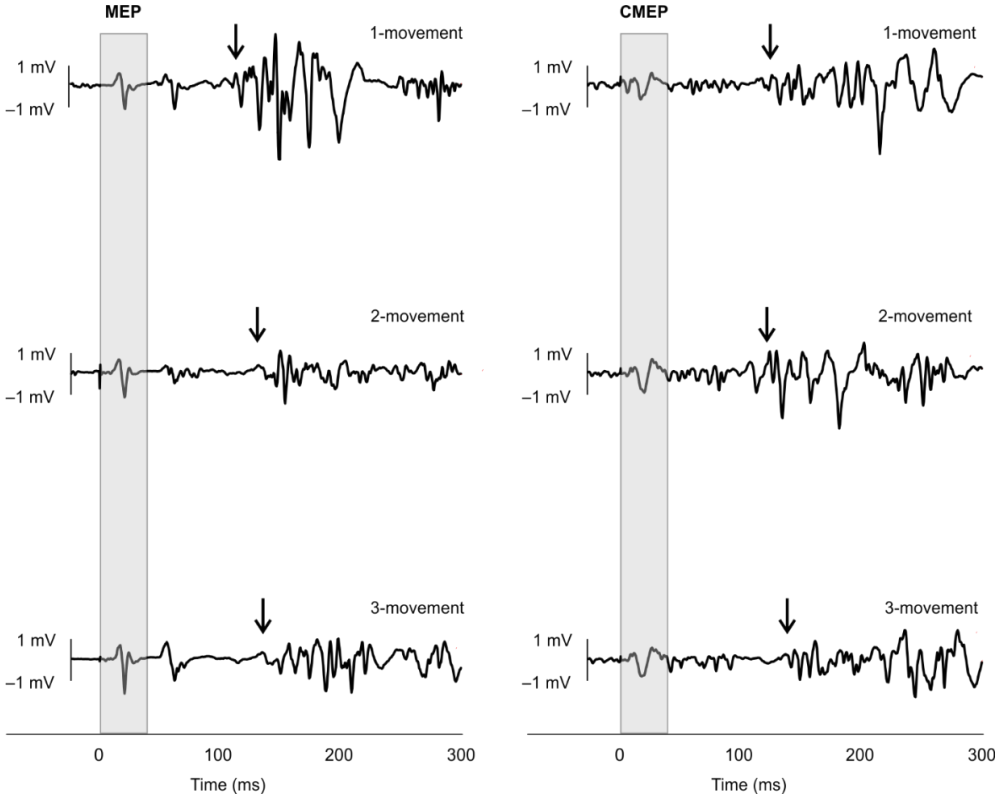


Figure 13. Representative EMG traces from a single participant in the 1-, 2-, and 3-movement conditions for both TMS (left) and TS (right) conditions. The shaded box highlights the MEP or CMEP. In all trials, the TMS pulse was delivered at 0% RT (i.e., at the time of the imperative stimulus), represented by the left edge of the shaded box. Time to voluntary EMG onset (premotor RT) is indicated in each condition by an arrow.

Prior to normalizing the MEP to the CMEP to isolate cortical excitability, CMEP and MEP amplitudes were both expressed as a percentage of the 0% RT in their respective conditions to determine the effect of movement complexity on motoneuron excitability (CMEP) and CE (MEP). The analysis of the CMEP (Figure 14) revealed a main effect of complexity ($F(2,34) = 3.89$, $p = 0.030$, $\eta_p^2 = 0.186$) and time ($F(1.59,28.8) = 17.0$, $p < 0.001$, $\eta_p^2 = 0.500$) but no interaction ($F(2.70,45.9) = 1.90$ $p = 0.149$, $\eta_p^2 = 0.100$). The post-hoc analysis indicated a trend for greater motoneuron excitability in the 3-movement compared to 1-movement condition ($M$ = 12.8%, 95% CI [-0.083, 25.7], $p = 0.052$) and in the 2- compared to 1-movement condition ($M$ = 13.3%, 95% CI [-1.32, 29.0], $p = 0.080$). Furthermore, the post-hoc analysis of for the time effect revealed that motoneuron excitability increased between the baseline condition (0% RT) and all subsequent time points (all p-values < 0.037). There was also an increase between the 70% RT time point and all subsequent time points (all p-values < 0.044).

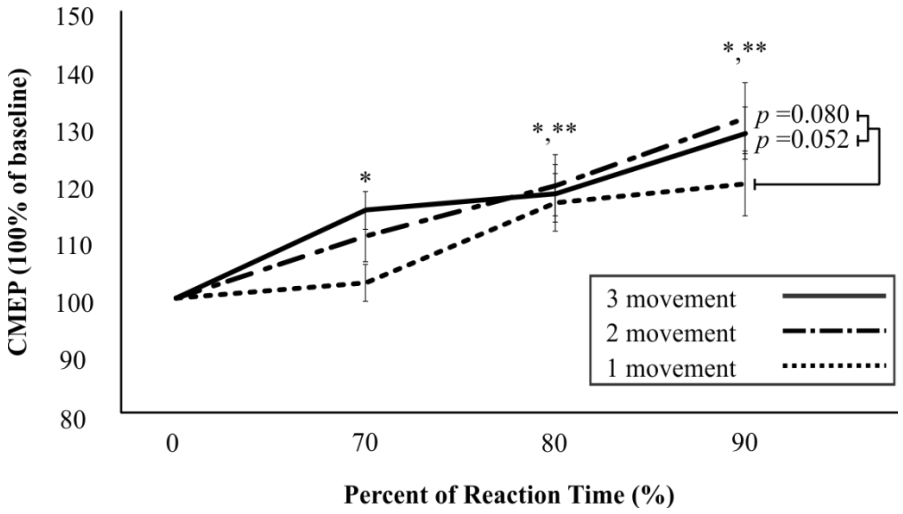


**Figure 14.** CMEP amplitude expressed as a percentage of the 0% RT condition in each movement condition. A single asterisk (*) denotes a significant increase in motoneuron excitability from 0% RT. Two asterisks (**) denotes a significant increase in motoneuron excitability from 70% RT. A main effect for movement complexity was detected and the inserted post-hoc p-values depict trends between the 1- and 2-movement conditions ($p$ =0.080) in addition to the 1- and 3-movement conditions ($p$ =0.052). Error bars represent standard error of the mean.

The analysis of the MEP (Figure 15) did not reveal a main effect of complexity ($F$(2,34) = 0.682, $p$ =0.512, $\eta_p^2$ = 0.039), nor did it reveal an interaction ($F$(6,102) = 0.362, $p$ =0.902, $\eta_p^2$ = 0.021); however, there was a main effect of time ($F$(1.98,33.7) = 14.8, $p$ <0.001, $\eta_p^2$ = 0.465). The post-hoc analysis revealed an increase in CE from baseline (0% RT) at both 80% RT ($M$ = 29.9 %, 95% CI [7.49,52.5], $p$ = 0.006) and 90% RT ($M$ = 44.7 %, 95% CI [15.8,73.7], $p$ = 0.001). This increase likely occurred earlier (e.g. at 70% RT; however, this increase from 0% RT had a Bonferroni-corrected value of $p$ = 0.051). Furthermore, there was an increase in CE between 70% RT and 90% RT ($M$ = 28.9 %, 95% CI [7.45,50.3], $p$ = 0.005). When the absolute MEP amplitude was analyzed to reflect previous work, there was a main effect of complexity ($F$(2,34) = 5.23, $p$ =0.011, $\eta_p^2$ = 0.235) and time ($F$(1.59,27.1) = 8.63, $p$ =0.002, $\eta_p^2$ = 0.337), but no interaction ($F$(3.00,51.1) = 0.770, $p$ =0.517, $\eta_p^2$ = 0.043). The post-hoc analysis indicated that CE was greater in the 2-movement compared to 3-movement condition ($M$ = 0.249 mV, 95% CI [0.019, 0.479], $p$ = 0.032) and nearly in the 2- than 1-movement condition ($M$ = 0.302 mV, 95% CI [-0.017, 0.621], $p$ = 0.067).

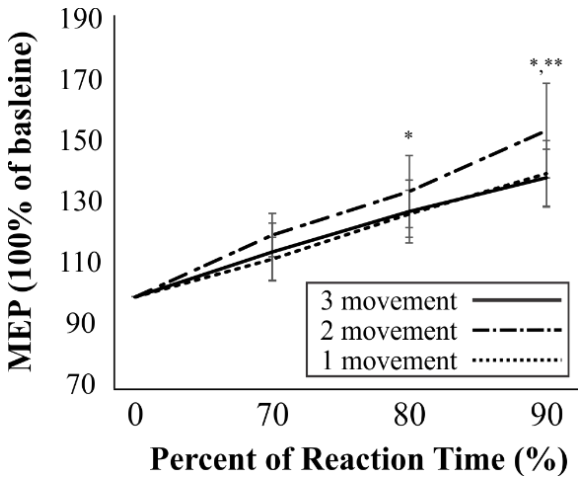


**Figure 15.** MEP amplitude expressed as a percentage of the 0% RT condition in each movement condition. A single asterisk (*) denotes a significant increase in corticospinal excitability from 0% RT. Two asterisks (**) denotes a significant increase in corticospinal excitability from 70% RT. Error bars represent standard error of the mean.

When normalized to the CMEP collected under the same conditions, the MEP had no main effect of complexity ($F(1.48, 25.2) = 1.86$, $p = 0.183$, $\eta_p^2 = 0.098$) or time ($F(3,51) = 1.207$, $p = 0.317$, $\eta_p^2 = 0.066$), as well as no interaction ($F(6,102) = 1.36$, $p = 0.236$) (Figure 16). Hence, although absolute MEPs showed a main effect of complexity, this analysis suggests that CE alterations due to complexity were not mediated primarily at the cortical level.

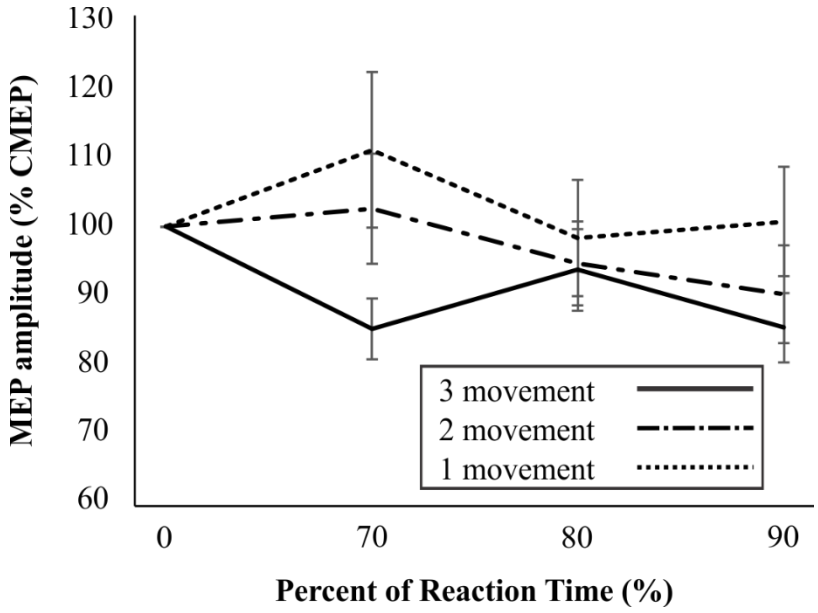


**Figure 16.** Mean MEP amplitude expressed as a percentage of mean CMEP amplitude. No differences were found for any comparisons. Error bars represent standard error of the mean.

## Discussion

The purpose of this study was to establish a time-course for the excitability of motoneurons prior to the onset of movement and to determine if movement complexity affects motoneuron and cortical excitability in a simple RT task. The first major finding of this study was an increase in the excitability of motoneurons as movement onset approaches (Figure 14). This increase in excitability occurred with minimal RMS EMG prior to the IS, under any conditions (Figure 12). This indicated that the triceps brachii muscle was almost completely

relaxed prior to both TMS or transmastoid stimulation. Furthermore, the analysis revealed that at baseline (0% RT), evoked potentials were unchanged between movement complexity conditions (Table 2). The increase in motoneuron excitability conflicts with the only previous study to assess spinal excitability prior to movement (MacKinnon & Rothwell 2000). This disparity is likely due to two factors. This first is the technique used to measure spinal excitability. In the previous study, the H-reflex was used; however, the H-reflex, but not the CMEP, could be influenced by presynaptic inhibition (Hultborn et al., 1987) during preparatory processes. Thus, any increases in motoneuron excitability may have been masked by presynaptic inhibition. The second factor is that CE only increased ~10 ms prior to EMG onset in the previous study, a finding which was at odds to the existing literature that showed increases in CE ~80-100 ms prior to EMG onset (Chen et al., 1998; Hoshiyama et al., 1996; Pascual-Leone, Brasil-Neto, et al., 1992; Pascual-Leone, Valls-Solé, et al., 1992; Tarkka et al., 1995; Tomberg & Caramia, 1991). As demonstrated in Figures 14 and 15, our data indicate that motor pathway excitability was increased at 70-80% RT; i.e., our data support these earlier works.

Indeed, when pooled across complexities, the CMEP amplitude at the earliest interval tested (70% RT) was 23% greater than the value at 0% RT (Figure 12). To translate this relative time to an absolute time before movement onset, we used the following equation for each participant at each level of complexity: time before movement = [mean RT − (mean RT × 0.7)]. Group means for the 1-, 2-, and 3-target conditions were 69±7, 77±9 and 79±9 ms. Hence, we can conclude that motoneuron excitability is increased at least 75 ms prior to movement onset in a simple RT task. As we did not test earlier intervals, it is not possible to state when the increase in motoneuron excitability first occurred. This increase in motoneuron excitability at ~75 ms prior to movement is at least 50% earlier than the ~50 ms estimated by facilitation of the H-

reflex during preparation for an isometric contraction (Day et al., 1983; Gottlieb et al., 1970; Pierrot-Deseilligny et al., 1971). Importantly, these studies were not performed in a simple RT paradigm. This is a major disadvantage in the assessment of preparatory processes because a simple RT paradigm is the only one that allows participants to prepare fully for upcoming movements. Besides the difference in task (RT vs. non-RT), the discrepency from previous studies may also be due to contraction type (dynamic vs. static).

The second purpose of this study was to determine if motoneuron excitability, cortical excitability or both contribute to task dependent increases in CE during preparation for complex movements. Previous studies have demonstrated that CE increases as task complexity increases during preparation for both static (Abbruzzese et al., 1996; Flament et al., 1993; Roosink & Zijdewind, 2010) and dynamic (chapter 3, study 2) movements; however, no previous studies have examined motoneuronal excitability influences on this response. As shown in Table 2, this is the first study to implicate spinal processes in the preparation for complex movements. While the analysis only revealed a main effect for complexity, there were robust post-hoc trends for greater motoneuron excitability in the 3-movement compared to 1-movement condition ($p$ = 0.052) and in the 2- compared to 1-movement condition ($p$ = 0.080). Furthermore, when the MEP amplitude was normalized to the CMEP amplitude (Figure 16), the normalized MEP values were consistent over the RT interval, suggesting negligible cortical contribution to the increase in motor pathway excitability over time, or with increased movement complexity.

The corticospinal tract is responsible for a broad cortical modulation of motoneuron output. Specifically, this tract is heavily implicated in the control of afferent inputs, spinal reflexes and motoneuron activity (Lemon & Griffiths, 2005). While the corticospinal tract is paramount to the mediation of voluntary movements (see Welniarz et al., 2017 for a review),

other cortical structures influence both the motor cortex and the motoneurons. For example, Dum and Strick (2002) have shown that premotor areas have direct and indirect (via motor cortex) connections with spinal motoneurons that are capable of influencing movement. While changes in neural activity are largely considered to be reflective of "tuning" for a particular response, Kaufmann and colleagues (2016) demonstrated that during the transition from movement preparation to execution, increases in neural activity may be indicative of *when* movement is to be made, rather than *which* movement is to be made. This was based on observations within M1 and dorsal premotor cortex that revealed large "un-tuned" or task invariant responses that may play an important role in movement. Furthermore, neural activity in M1 may include information relating to spatial goals, hand motion, joint motion, force output and EMG activity (Scott, 2003). Thus, while the M1 initiates the response, movement complexity may not increase the excitability of the motor cortex per se.

**Summary**

The purpose of this study was to establish the time-course of motoneuron excitability prior to the onset of movement in a simple RT task. The second purpose was to describe the task dependent effect of movement complexity on motoneuron and cortical excitability. The current study addressed methodological limitations in previous studies to establish that, in the preparation phase before a movement, motoneuron excitability increases at least 50% earlier than previously measured. We also observed a significant increase in CMEP amplitude with increasing complexity. When the MEP amplitude was normalized to the CMEP amplitude, the data suggested minimal influence of cortical excitability to previously observed increases in CE with movement complexity. It seems that movement complexity-based increases in CE may

involve a contribution from subcortical areas (e.g., the brainstem) above the level of the motoneurons.

## Chapter 5: Modulation of the vestibulomotor response prior to complex movement onset

Chapter 2 (study 1) demonstrated that movement preparation processes can be altered by movement complexity. While unable to provide an answer as to whether these processes are cortically or segmentally mediated, chapter 3 (study 2) showed that movement complexity altered the excitability of the motor pathway. Chapter 4 (study 3) determined that these complexity-based increases in excitability were not cortically mediated, suggesting that subcortical areas may be responsible for integrating movement complexity into motor responses. Chapter 5 (study 4) probes this link.

### Background

The vestibular system encodes self-motion relating to the position of the head in space and provides essential information to the central nervous system (CNS) for movement and balance control via two important sources of information: angular acceleration from the semicircular canals and linear acceleration from the otoliths. Signals are transmitted via afferent fibres of the vestibulocochlear nerve (cranial nerve VIII) from the sensory end organs to the vestibular nuclei, which project to neural structures controlling eye movements, posture and balance (Cullen, 2012). This is accomplished through the central integration of sensorimotor cues involved in the conscious perception of postural orientation and functional transformation of balance control (Gurfinkel, Popov, Smetanin, & Shlykov, 1989; Massion, 1998; Popov, Smetanin, Gurfinkel, & Kudinova, 1987). These transformations can be investigated by inducing an isolated vestibular error during balance (Britton et al., 1993; Lund & Broberg, 1983; Nashner & Wolfson, 1974; Pastor et al., 1993) using electrical vestibular stimulation (EVS). Electrical vestibular stimulation evokes a virtual signal of head rotation (Day & Fitzpatrick, 2005; Peters et

al., 2016; Peters et al., 2015), interpreted by the CNS as an unexpected perturbation that elicits a whole-body response compensating for the balance disturbance (Fitzpatrick & Day, 2004).

A growing body of evidence suggests that the vestibulomotor system is also integral to arm control that may be independent of balance per se. This has been shown in a variety of upper limb movements, for example while participants reached towards either earth-fixed targets while seated (Bresciani, Blouin, Popov, Sarlegna, et al., 2002; Mars et al., 2003; Moreau-Debord et al., 2014; Smith & Reynolds, 2017) or standing (Bresciani, Blouin, Popov, Bourdin, et al., 2002). Importantly, while this implicates the vestibulomotor system in the *online* control of upper limb tasks, it is unclear if it is also involved in the *preparation* phase of a reaching movement. Furthermore, it is unknown if these preparatory processes are sensitive to the complexity requirements of a planned movement. Altered vestibular-evoked responses would not only confirm the vestibulomotor system's involvement in the online control of movement, but also that vestibular signals are likely incorporated into the preparation of a movement plan in a task-dependent manner.

Movement complexity has been shown to induce a task-dependent effect on movement preparation in simple RT paradigms. In their seminal experiment, Henry and Rogers (1960) demonstrated that simple RTs increased as the complexity of a task increased, via the addition of movement components. Crucially, the movement that is required is always known prior to an IS in a simple RT task, allowing participants to optimally prepare upcoming movement requirements. In addition to lengthened RTs, we have previously demonstrated that movement complexity delays anticipatory postural adjustment (APA) profiles in a task-dependent manner (Kennefick, Wright, Smirl, & van Donkelaar, 2018), but also increases motoneuron excitability (chapter 4, study 3). Since the motor pathway has been shown to be sensitive to complexity

manipulations, it is of interest as to whether vestibulomotor responses are modulated by complexity and hence, play a role in the preparation of complex reaching movements. Therefore, the purpose of the current study was to examine the modulation of the vestibulomyogenic response to EVS during the preparation of complex upper limb movements, in a simple RT paradigm similar to Henry and Rogers (1960). Reflective of the increased preparatory activity involved in complex movements, it was hypothesized that RTs would increase in parallel with movement complexity, which would be mirrored by increased vestibulomyogenic responses to EVS in both upper and lower limb musculature.

## Materials and Methods

### Participants

Twenty-one healthy participants (13 females; age range 18-38 years) with no history of neurological, sensory, or motor disorders participated in this study. Testing of each participant took place during a single session in a dimly lit room and required approximately 1.5 hours to complete. The study was conducted in accordance with ethical guidelines and was approved by the University of British Columbia's Clinical Research Ethics Board (CREB approval: H17-00796) and conformed to the guidelines of the Declaration of Helsinki, except for registration in a database.

### Experimental design

Participants stood shoeless without shoes on a force plate with feet together and parallel, head faced forward, and their right hand grasped the right manipulandum of a KINARM End-Point Lab (BKIN Technologies Ltd., Kingston, Canada) while the left arm was relaxed at their side. Arm movements were performed in the horizontal plane in response to targets presented on

an augmented reality display. The postural component of the arm reaching movement cannot be discounted as participants were unable to move in the vertical axis, only allowing for planar movements. Participants were informed that the upcoming task was a simple RT task consisting of a ballistic arm movement in one of three movement conditions. Prior to the IS, participants were informed which of the three movement conditions was to be performed. In the 1-target condition, movements were directed anteriorly (straight ahead) and terminated at the first target (A in Figure 1). In the 2-target condition, the participant reached the first target and performed a reversal in the posterior direction and to the right before terminating their movement at the second target (B in Figure 1). The 3-target condition involved a second reversal after reaching the second target, requiring an anterior (straight ahead) movement to reach the final target (C in Figure 1). Importantly, regardless of the final target position, the initial movement (i.e., home position to target one) was identical across all movement conditions, in line with Henry and Rogers' original experiment (Henry & Rogers, 1960). Each trial required the participant to first reach the home position, represented by a red dot that was positioned 19 cm in front of the participant's right arm. Following a random foreperiod (1000-3000 ms), the home position marker turned green, signaling the participant to initiate the movement. All targets were the same size (visual radius of 0.5 cm) and changed from white to green when reached successfully.

To familiarize the participants with the experimental protocol, they completed a practice block prior to testing that consisted of 10 trials for each movement complexity condition. Next, to examine the vestibular-evoked balance response in both the upper and lower limb, regardless of reaching task, participants stood quietly and were subjected to continuous EVS (details below) for 100 s while grasping the right handle of the KINARM system in the locked position. Because the handle was earth-fixed, an EVS-evoked response would indicate activation of a balance-

related reflex via the vestibulomotor pathway in both upper and lower limbs. Thus, these responses would then act as a control and confirmation of a vestibular-evoked myogenic response during the preparation phase of the reaching tasks. Testing trials were identical to those of the practice trials, with the exception that over the entire duration of each testing block (~6 min), participants received binaural, bipolar EVS. Participants performed 9 blocks consisting of 30 trials each for a total of 270 trials. As such, one block included 10 trials for each of the 1-, 2-, and 3-movement conditions that were presented in a pseudo-random order.

**Vestibular stimulation and data collection**

The EVS was delivered via carbon rubber electrodes (anode right; 9 $cm^2$) coated with Spectra 360 electrode gel (Parker Laboratories, Fairfield, NJ, USA), secured to the skin over the mastoid process with Durapore tape (3M Innovations, St. Paul, MN, USA) and an elastic headband. The electrical vestibular stimuli were generated in MATLAB (Forbes et al., 2014) and Spike2 software (version 8.10; Cambridge Electronic Design Ltd, Cambridge, UK) was used to send the signal to an isolated bipolar constant current stimulator (DS5; Digitimer Ltd, Welwyn Garden City, UK) via a 16-bit A/D converted (CED Power1401-3; Cambridge Electronic Design Ltd, Cambridge, UK). The EVS signal consisted of a filtered white noise scaled to a specific amplitude [i.e., stochastic vestibular stimulation (Dakin, Lee Son, Inglis, & Blouin, 2007; Forbes et al., 2014; Mian & Day, 2009)]. Participants were exposed to EVS with a bandwidth of 0-25 Hz and a peak to peak amplitude of ± 4.0 mA [root mean square (RMS) = 0.98 mA].

**Recording Equipment**

Surface EMG data were recorded via adhesive Ag-AgCl electrodes (10mm diameter, Cleartrace; ConMed, Utica, NY) with the active electrodes positioned over the muscle belly of four muscle groups of interest; the triceps and biceps brachii of the right arm, in addition to the

right and left medial gastrocnemii with reference electrodes placed over the corresponding distal tendons. A ground electrode was also placed on the humeral lateral epicondyle of the right arm. Surface EMG signals were sampled at 2041 Hz, amplified (×100) and bandpass filtered (30-1000 Hz) using a NeuroLog System (NL900D, Digitimer Ltd, Welwyn Garden City, UK).

**Data analysis**

For the control condition (i.e., KINARM in the locked position), the sampled EMG signals were time-locked to EVS onset and 88 continuous segments were analyzed per participant. These segments were concatenated for all subjects to create a pooled data set of 1704 segments (segment length: 1.003 s and resolution: 0.997 Hz) for the locked condition. For all reaching trials, the sampled EVS and EMG signals were time-locked to the IS. Segments of 1.003 s prior to the IS were created for each trial and all data records –regardless of reaching condition – were concatenated to create a pooled data set of 5400 segments (segment length: 1.003 s and resolution: 0.997 Hz). This pooled data record was used to determine whether a vestibulomyogenic response was present prior to reaching task. To evaluate the effect of complexity on reaching movements, the pooled data record was subdivided and pooled into the 3 movement complexity conditions, resulting in 1800 segments per condition.

The relationships between the EVS (input) and the EMG (output) signals were analyzed in the time domain using an archive of multivariate Fourier analyses in MATLAB (NeuroSpec 2.0: http://www.neurospec.org) (Halliday et al., 1995; Rosenberg, Amjad, Breeze, Brillinger, & Halliday, 1989). Pooled data from all participants were used for visualization of the cumulant density function and pooled individual subject data were used to determine mean values for EVS-EMG cumulant density peak-to-peak amplitudes for statistical analyses. Cumulant density is an associative measure between two signals (Dakin et al., 2007; Reynolds, 2010) that is

calculated by transforming the cross-spectra of the EVS signal (input) and the muscular responses (motor output) and normalizing the vector norms (Dakin, Luu, Doel, Inglis, & Blouin, 2010). Therefore, the cumulant density estimate values are bounded between -1 and +1. Uncorrelated signals have an expected value of 0, and values significantly deviating from 0 indicate a correlation between the two signals with a distinct time lag. Significance is determined based on 95% confidence intervals that are constructed from the total number of segments. The cumulant density function produces a biphasic motor response consisting of short and medium latencies – similar to traditional EVS (Ali, Rowen, & Iles, 2003; Britton et al., 1993; Dakin et al., 2007; Nashner & Wolfson, 1974; Welgampola & Colebatch, 2001) – which are generally considered to be of vestibular origin (Dakin et al., 2007; Mian, Dakin, Blouin, Fitzpatrick, & Day, 2010; Welgampola & Colebatch, 2002). The role of the short latency response is largely undefined; however, it appears to have a general balance function (Mian et al., 2010). The medium latency response represents whole-body corrective postural reactions to a vestibular error signal (Mian et al., 2010; Mian & Day, 2009, 2014). We evaluated the vestibular-evoked myogenic response using peak-to-peak amplitude (i.e., combined short and medium latency response) and values were considered significant when the peak-to-peak amplitude exceeded the 95% confidence intervals. It was first determined if vestibulomyogenic responses were elicited while participants both stood quietly grasping the locked robotic handle and while performing the required movements. Following this confirmation, the data segments were pooled by movement complexity condition to determine if the peak-to-peak amplitudes of the vestibular-evoked response were altered by movement complexity. Data from each participant were evaluated per complexity condition and were removed from further analysis if the peak-to-peak amplitudes did not surpass the 95% confidence intervals. This resulted in the removal of data

from 1 participant for the triceps brachii analysis, 2 participants for the biceps brachii analysis, and 2 for the LMG and RMG analyses.

Mean RT was calculated for each testing trial and was defined as the time between the IS and movement onset (i.e., when the participant leaves the home position). Dependent measures greater than 2 standard deviations from each individual's overall mean were removed from the analysis. Peak-to-peak response amplitudes, as well as RT measures were subjected to one-way repeated-measures (RM) analyses of variance (ANOVA). Unless otherwise stated, all one-way RM-ANOVAs were run using movement complexity as the within-subject variable. For all RM-ANOVAs, Greenhouse-Geiser Epsilon was used to adjust degrees of freedom for violations of sphericity, when necessary. Subsequent to the initial RM-ANOVA, post-hoc analyses were performed using 95% confidence intervals for the mean difference for each comparison and pairwise comparisons with a Holm-Bonferroni correction for multiple comparisons. All ANOVA analyses were conducted using SPSS version 23 (SPSS Inc., Chicago, IL, USA). Differences with a $p<0.05$ were considered significant. Data are presented as mean ± SD.

## Results

### Reaction time

To determine if the complexity manipulation led to differences in RT, one-way RM-ANOVA was performed. There was an increase in RT (Figure 17) with complexity between the 1- and 2- movement conditions ($M$ = -25.8 ms, 95% CI [-39.9, -11.7], $p < 0.001$), and the 1- and 3- movement conditions ($M$ = -35.6 ms, 95% CI [-55.1, -16.2], $p < 0.001$), but no detectable difference between the 2- and 3-movement conditions ($M$ = -9.84 ms, 95% CI [-21.8, -2.16], $p$ = 0.134).

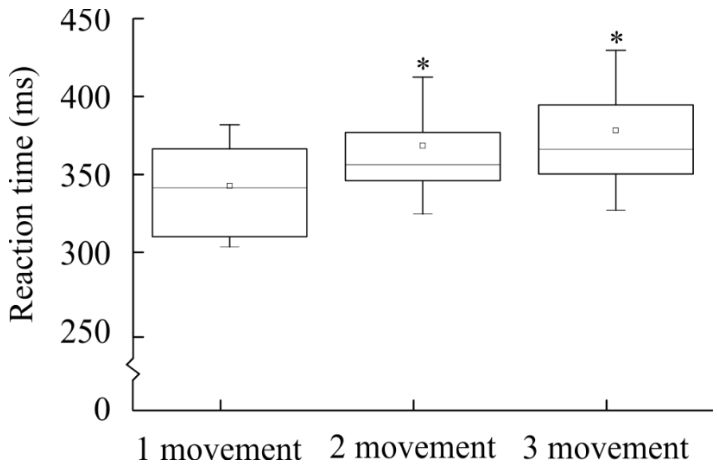


**Figure 17.** Boxplot of the mean premotor RT across the 3 complexity levels. Box boundaries represent the 25$^{th}$ and 75$^{th}$ percentiles, solid horizontal lines represent medians, the small squares within the box represent means, and error bars represent the standard deviation. The asterisk (*) denotes a significantly slower RT compared to the 1-movement condition.

**Cumulant density – control condition**

To confirm the timing and presence of a vestibular-evoked balance response in all muscles, the peak-to-peak amplitude of the EVS-EMG cumulant density function was analyzed. Each muscle exhibited a significant vestibular-evoked response, as short- and medium-latency peak amplitude values surpassed the 95% confidence limits (Figure 18a-d). The timing of the short- and medium-latency peaks in the triceps brachii were ~37 ms and ~72 ms respectively. The short-latency peak timing is inline with the timing of ~35 ms found by Britton and colleagues (1993). The novel finding from this study was the characterization of the time points for the short- and medium-latency peaks in the biceps brachii. These were ~38 ms and ~72 ms respectively, nearly identical to the peaks in the triceps brachii. Interestingly, despite being antagonistic pairs, the peaks in the triceps and biceps brachii had the same polarities.

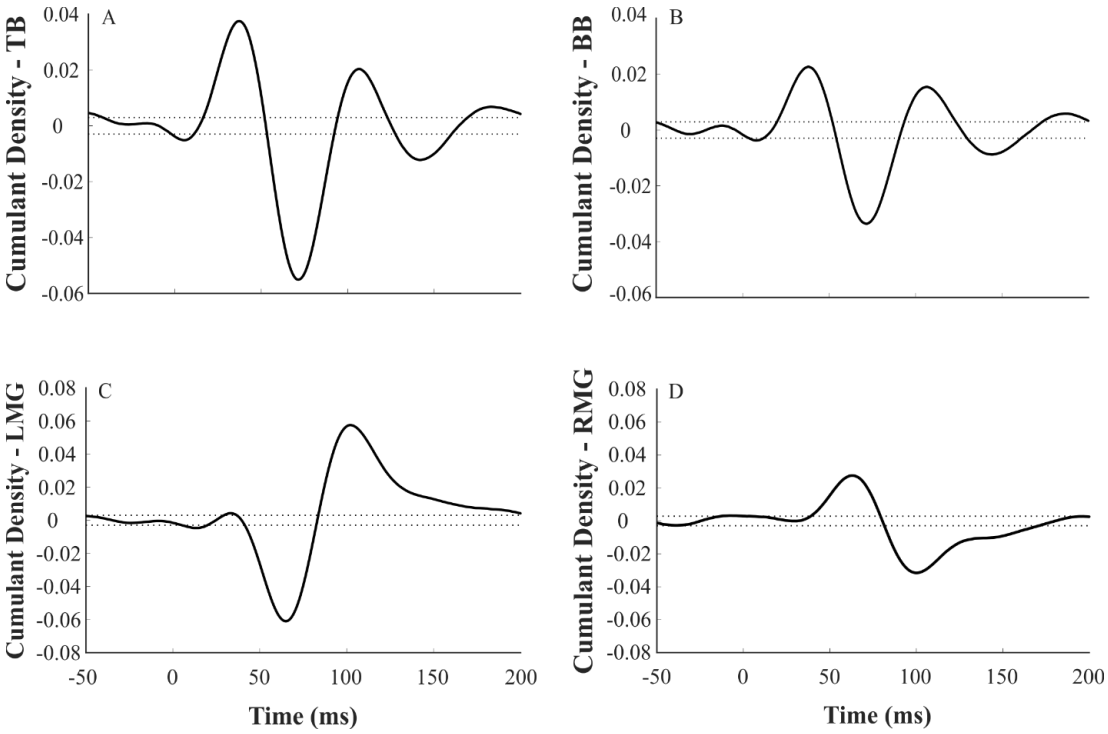


**Figure 18.** Cumulant density estimates for the four sampled muscles during 90 s of standing and grasping of an immovable handle (A- triceps brachii; B – biceps brachii; C- left gastrocnemius; D- right gastrocnemius) displayed vestibular-evoked biphasic responses that exceeded the 95% confidence limits (gray horizontal dashed lines). All values are in arbitrary units.

### Cumulant density of pooled participant data

The mean values for the EVS-EMG cumulant density function peak-to-peak amplitudes from the upper and lower limbs are summarized in Table 3. To determine whether a generalized vestibular-evoked response was present during the preparation of reaching movements while standing, the peak-to-peak cumulant density functions for each muscle, collapsed across all movement conditions was estimated. All muscles demonstrated a significant vestibular-evoked response, as both short- and medium-latency peak amplitudes exceeded the 95% confidence limits (Figure 19a-d).

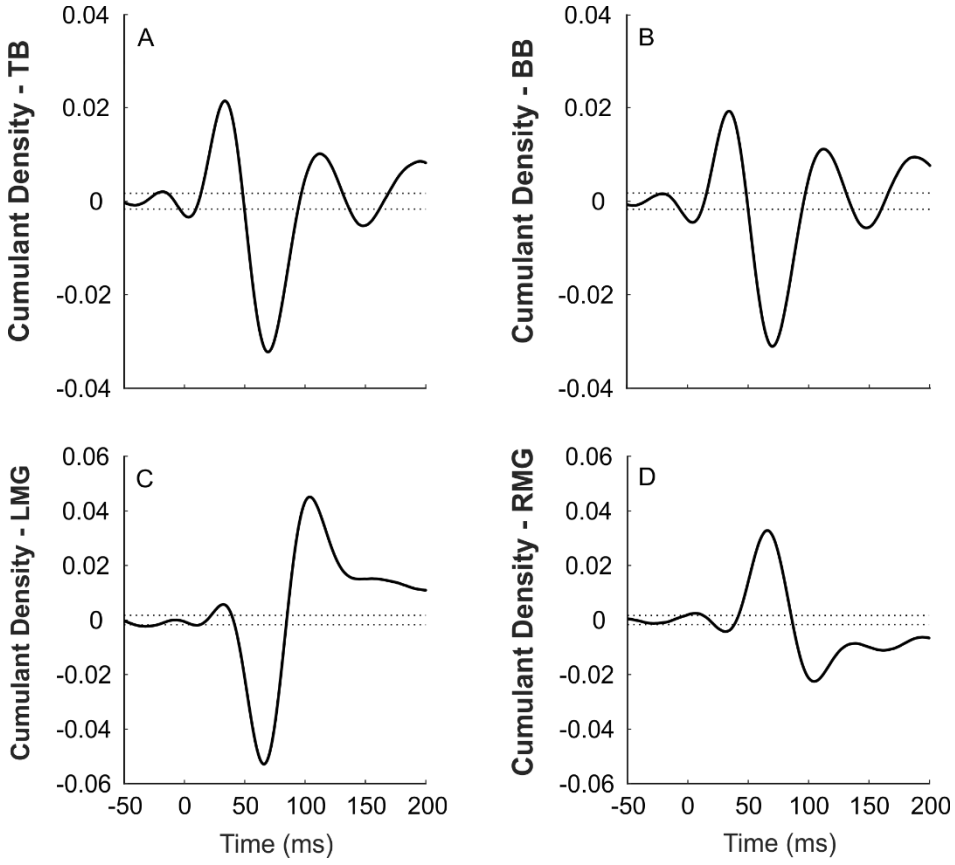


**Figure 19.** Pooled cumulant density estimates for the four sampled muscles (A- triceps brachii; B – biceps brachii; C- left gastrocnemius; D- right gastrocnemius) displayed vestibular-evoked biphasic responses that crossed the 95% confidence limits (gray horizontal dashed lines). All values are in arbitrary units.

### Cumulant density of pooled participant data subdivided by complexity

To determine if the vestibulomotor response during the preparatory phase of a reaching task (i.e., prior to the IS) is altered with movement task, the EVS-EMG cumulant density peak-to-peak amplitudes were analyzed across the three movement complexities. The analysis of the triceps brachii data (Figure 18a) indicated no differences in the vestibulomotor response between movement conditions (all *p*-values >0.296) amplitudes. In the biceps brachii (Figure 20b), there was a larger response between the 1- and 3- movement conditions ($M$ = 0.005, 95% CI [0.001, 0.009], $p$ = 0.008).

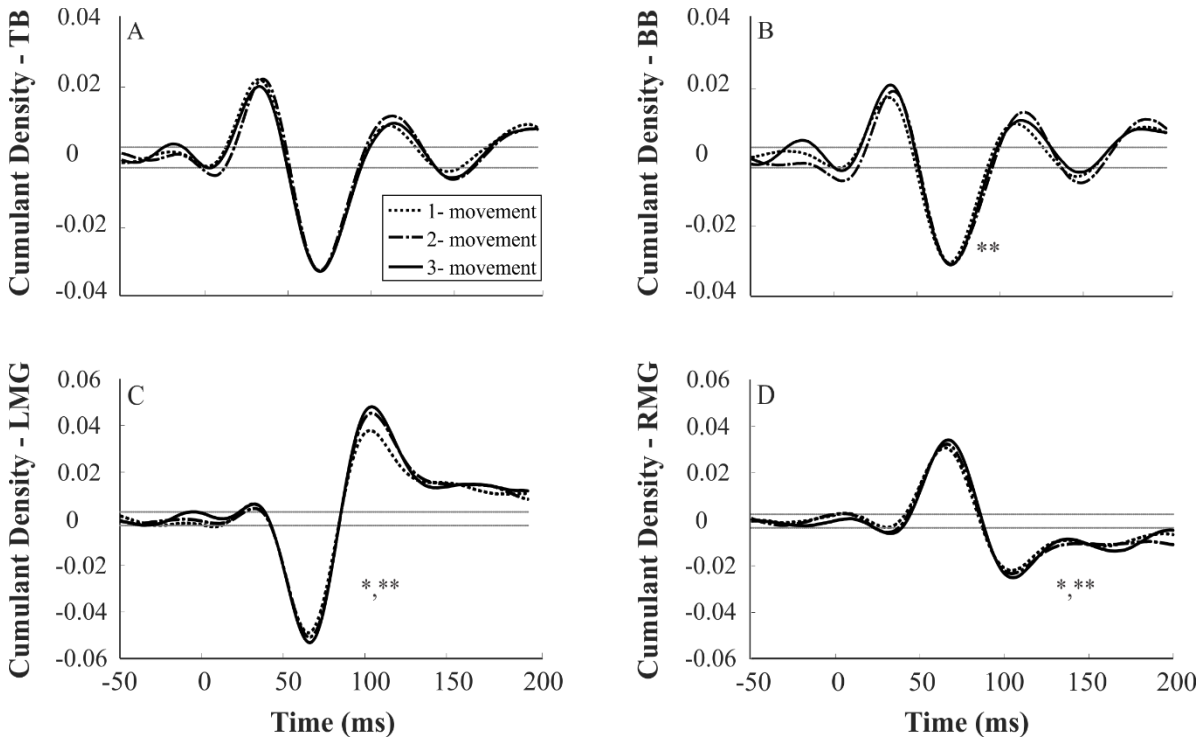


**Figure 20.** Pooled cumulant density estimates by movement complexity for the four measured muscles (A- triceps brachii; B – biceps brachii; C- left gastrocnemius; D- right gastrocnemius) displayed biphasic responses. Dashed lines represent 95% confidence limits. Single dagger (*) represent a significant difference in the peak-to-peak response between the 1- and 2- movement conditions. Double daggers (**) represent a significant difference in the peak-to-peak response between the 1- and 3- movement conditions. All values are in arbitrary units.

In the lower limbs, there was also a larger response in the left gastrocnemius, between the 1- and 2- movement ($M$ = 0.011, 95% CI [0.004, 0.017], $p$ = 0.003), and 1- and 3- movement ($M$ = 0.009, 95% CI [0.005, 0.033], $p$ < 0.009) conditions (Figure 20c). Furthermore, there was a larger response in the right gastrocnemius between the 1- and 2- movement conditions ($M$ = 0.007, 95% CI [0.000,0.013]) and between the 1- and 3- movement conditions ($M$ = 0.006, 95% CI [0.000,0.012]); however, neither survived the Holm-Bonferroni correction, with respective $p$-values of 0.036 and 0.042 (Figure 18d).

**Table 3.** Mean vestibular-evoked response peak-to-peak amplitude data for all muscles across the 3 complexity levels. All values are expressed in arbitrary units and values in parentheses indicate standard deviations.

| | **Movement** | | |
|---|---|---|---|
| | One movement | Two movement | Three movement |
| Right triceps brachii | **0.0599** (0.0265) | **0.0631** (0.0256) | **0.0626** (0.0214) |
| Right biceps brachii | **0.0526** (0.0227) | **0.0543** (0.0216) | **0.0576** (0.0227) * |
| Left medial gastrocnemius | **0.106** (0.0383) | **0.117** (0.0453) * | **0.125** (0.0571) * |
| Right medial gastrocnemius | **0.0613** (0.0230) | **0.0681** (0.0216) * | **0.0676** (0.0249) * |

* denotes a significantly different peak-to-peak amplitude from the 1-movement condition.

## Discussion

The purpose of this study was to examine the modulation of the vestibular-evoked myogenic response during the preparation of complex reaching movements. The major finding was that this response was not only present in all four muscles involved in this task, but that it also increased with movement complexity. This demonstrates that vestibulomotor reflexes are modulated by complexity, and hence, vestibulomotor cues are likely used by the CNS in the preparation of complex reaching movements.

We first sought to determine if the vestibular error signal in the current behavioural paradigm induced an evoked muscular response in the upper limbs. Britton and colleagues (1993) have previously demonstrated this evoked response can be elicited in the triceps brachii at ~35 ms, which was confirmed in the current study. In addition, the current study determined the timing of the medium-latency peak in the triceps brachii was ~70 ms. While the timing of the evoked response in triceps brachii had previously been described in the literature, it was

unknown if the same response existed in the biceps brachii. Indeed, we found the timing of both the short- and medium-latency responses were nearly identical at ~38 ms and ~72 ms respectively. Curiously, the peaks in the triceps and biceps brachii had the same polarities. This indicated that despite being antagonistic pairs, these muscles had similar balance goals during the preparation phase of movement. The same peaks have latencies of ~60 ms and ~110 ms have previously been established in the lower limbs (Britton et al., 1993; Fitzpatrick, Burke, & Gandevia, 1994; McGeehan, Woollacott, & Dalton, 2017; Nashner & Wolfson, 1974; Wallace, Rasman, & Dalton, 2018; Welgampola & Colebatch, 2002). The timing of the lower limb responses were in line with the current literature at ~64 ms and ~103 ms. Importantly, these responses were opposite in polarity, indicating different underlying purposes.

The timing of the response can be used to determine whether similar vestibulomotor processes were present when participants were actively engaged in a balancing task (control session; figure 18) and when participants were preparing for complex movements, with the hand free to move in the horizontal plane (figure 19). A visual analysis of the timing of the short and medium latency peak responses between the control and reaching conditions revealed similar onset times (Figures 18 and 19), which indicates similar vestibulomotor pathways were likely engaged in both the active balancing control task and during the preparation phase of movement. Furthermore, the cumulant density function can be used to assess the magnitude of the vestibular-evoked response (Forbes et al., 2016). A visual comparison of the peak-to-peak amplitudes between the control and reaching data also revealed larger responses during the control session, while the participants were actively engaged in balance. The vestibulomotor system computes self-motion via the integration of sensorimotor signals that are important for eye movements, posture, and balance (Cullen, 2012). However, the current results demonstrate

that while EVS elicited a myogenic response in the control condition when participants were only required to maintain upright balance, similar myogenic response was found prior to the reaching task. This indicates the vestibulomotor pathway is also involved in the planning of movement, as the vestibular-evoked response was present during the preparation phase of movement, when the movement requirements of task are visible and the hand is moving freely, limiting its involvement in balance control.

In contrast to the current study which sought to describe the vestibular contribution to preparatory processes, previous reports have demonstrated the vestibulomotor system is an integral component for online control of arm movements in both seated (Bresciani, Blouin, Popov, Sarlegna, et al., 2002; Mars et al., 2003; Moreau-Debord et al., 2014; Smith et al., 2017; Smith & Reynolds, 2017) and standing (Bresciani, Blouin, Popov, Bourdin, et al., 2002) positions. For example, Smith and Reynolds (2017) asked participants to either point their arm to a memorized 30-degree angle (earth-fixed condition) or straight ahead (0-degree angle; body-fixed condition). The authors found that when participants attempted to continuously point to an earth-fixed location while being rotated in a chair, arm movements were modified by the vestibular error signal. Yet, there was no effect of EVS on the arm in the body-fixed condition. Importantly, this not only suggests the vestibular system was engaged when the arm was active in the task, but also that the vestibulomotor response was task-dependent. Indeed, the results of our study support the task-dependency of the vestibular-evoked response and extend these findings to the preparation phase of voluntary upper limb movements as the vestibulomotor responses increased with increasing movement complexity for the biceps brachii (figure 20b), and both gastrocnemii (figure 20c-d). Thus, greater complexity enhances the vestibular-evoked

myogenic response during movement planning, indicating a heightened sensitivity of the vestibulomotor pathway prior to a more difficult movement.

The current study was heavily influenced by the seminal experiment by Henry and Rogers (1960), in which they demonstrated that RT increased with the number of movement components. In a previous study by Maslovat and colleagues (2014), the authors demonstrated that in a 3-button (component) press, non-isochronous movements, the length of the first interval (i.e., between key-press one and two) had a profound effect on overall RT. For example, when the length of the first interval was long (450 ms), overall RT was quicker than when the first interval was short (150 ms). The authors suggested that some participants may have only prepared the first movement component (first button press) in advance, with the remaining components completed online. In this button press task, the agonist muscle was performing the same fine movement, with an additional timing requirement. With this degree of specificity, the role of the agonist muscle was clear. The role of the muscle used for the initial gross elbow extension movement in the current study (i.e., triceps brachii) alternated between agonist and antagonist as participants moved through the three targets. Interestingly, the current RT data (figure 17) indicate that while both the 2- and 3-movement conditions were slower than the simple 1-movement condition, the 2- and 3-movement conditions had the same RTs. This indicates that participants may have only preplanned certain aspects of the entire movement sequence. In other words, participants may have only preplanned the first movement reversal (between target 1 and target 2), while completing the second reversal in an online manner. As depicted in all cumulant density estimates (figures 18, 19, and 20), both the triceps and biceps brachii demonstrate the same short and medium latency polarities, indicating similar movement goals during the preparation phase. However, since the first movement reversal in the current

study required an arm flexion movement, the biceps brachii would thus become the *de facto* prime mover. This is supported by the biceps brachii (figure 20b) having a larger peak-to-peak response in the 3-movement compared to the 1-movement condition.

Prior to the current study, movement complexity had been shown to elicit robust alterations in corticospinal and motoneuronal excitability (chapters 3/4, study 2/3). For example, we applied transcranial magnetic stimulation (TMS) over the motor cortex during the same arm movement protocol (while seated) and reported the 3-movement condition elicits a larger MEP in the triceps brachii. The MEP is an index of corticospinal excitability (Rothwell, 1997) resulting from a series of descending corticospinal tract volleys. Importantly, the corticospinal tract is part of the pyramidal tract, and is essential for the control of voluntary movement (Rea, 2015). However, the control of movement is also mediated by extrapyramidal tracts, further subdivided into tectospinal, rubrospinal, reticulospinal and vestibulospinal descending tracts (Waldman, 2009), which TMS cannot probe. While all extrapyramidal tracts contribute to movement, the vestibulospinal tract functions to maintain equilibratory reflexes from the input of the vestibular apparatus (Rea, 2015). Multimodal information processing in the vestibular system does not occur in one single cortical area. Input to the vestibular nuclei can originate from cortical, cerebellar, and other brainstem areas (Cullen, 2016). Based on extensive reciprocal connections between the reticular formation, vestibular nuclei and vestibulo-cerebellum (Wilson & Peterson, 1981), the reticular formation has been implicated in EVS-evoked reflexes (Britton et al., 1993; Welgampola & Colebatch, 2002). Importantly, the reticular formation has also been shown to influence a range of muscles in the upper limbs of non-human primates via the reticulospinal tract (Riddle, Edgley, & Baker, 2009). Thus, the results of the current study

suggest that subcortically mediated processes are also important in the successful integration of movement parameters into global motor plans.

Interestingly, we demonstrated the vestibulomotor pathway is likely integral to the preparation of arm movements. Our study established the CNS incorporates movement complexity into the transformation of vestibular-evoked myogenic responses prior to the onset of goal-directed upper limb movements. These results suggest that movement complexity-based modulations are possibly influenced by subcortical areas projecting down extrapyramidal pathways.

## Chapter 6: Conclusion

### Overview

The global motivation underlying my doctoral research was born out of a curiosity developed over the course of my Master's research. The results of that research did not align with the literature, nor did it align with the hypotheses (c.f. Kennefick et al., 2016). Upon reflection, I realized the movement task I had used was fundamentally different than the seminal study on which it was based. The original study by Henry and Rogers (1960) was a very simple design, as was common at a time that had limited technology. However, their study elicited very strong effects. Simply put, the addition of movement components, independent of any other experimental manipulations, resulted in the lengthening of RTs. The central issue with the methodology in my Master's research was that in addition to increasing the number of movement components, a timing structure similar to that of Morse code was also imposed on the participants. Inadvertently, this confound affected the manner in which participants prepared for the upcoming task. Thus, instead of research based solely on Henry and Rogers' work, it was blended with Stuart Klapp's complexity work (Klapp, 1995, 2003; Klapp et al., 1974). My experimental manipulation resulted in a depression of CE, which was speculated to be the result of a strict timing requirement imposed on the participants, and of increased inhibition in the motor system to prevent the premature release of prepared movements. This was still a significant finding; however, as I transitioned into my doctoral research, I stepped back and decided to simplify the methodology in an attempt to describe how the motor pathway is affected solely by the addition of movement components. Now, nearly 60 years following Henry and Rogers' original work, technological advancements have allowed me to incorporate the essence of their methodology into a more controlled environment using the KINARM End-Point Lab.

Therefore, all four studies contained within this thesis use the same behavioural task described below:

> *"Arm movements were performed in the horizontal plane in response to targets presented on an augmented reality display. Participants were informed the upcoming task was a simple RT task consisting of a ballistic arm movement for one of three movement conditions. Prior to the IS, the visual display indicated which of the three movement conditions was to be performed. In the 1-target condition, movement was directed anteriorly (straight ahead) and terminated at the first target. In the 2-target condition, the participant reached the first target and performed a reversal in the posterior direction and to the right before terminating their movement at the second target. The 3-target condition involved a second reversal after reaching the second target, requiring an anterior (straight ahead) movement to reach the final target. Importantly, regardless of the final target position, the initial movement (i.e., home position to target one) was identical across all movement conditions, in line with Henry and Rogers' original experiment (Henry & Rogers, 1960). Each trial required the participant to first reach the home position, represented by a red dot that was positioned 19 cm in front of the participant's right arm. Following a random foreperiod (1000-3000 ms), the home position marker turned green (imperative stimulus), signaling the participant to initiate the movement. All targets were the same size (visual radius of 0.5 cm) and changed from white to green when reached successfully".*

Normalizing the behavioural task in such a way allowed me to use different stimulation techniques (e.g., TMS, transmastoid stimulation, EVS) to indirectly assess how this task affected the way humans prepare for, and execute complex movements. Specifically, the combination of these techniques allowed me to isolate various regions of the motor pathway and determine their excitability prior to movements of varying complexity.

The first study (chapter 2) sought to describe how movement complexity affected whole-body APAs. In this study, all hypotheses were confirmed. It was first showed that primary effector RT increased as movement complexity increased, confirming the manipulation for this behavioural task increased in complexity. Secondly, the complexity modulation lengthened APA onset times before the IS. Prior to this study, various researchers had demonstrated that APAs could be modified in a task-dependent manner (Aruin & Latash, 1995; Friedli et al., 1988; Horak

et al., 1989; Lowrey et al., 2017; Weerdesteyn et al., 2008); however, this study was the first to establish that movement complexity could be integrated into a global motor plan meant to counteract the internal and external constraints that disturb posture and balance (Massion, 1992).

Importantly, APAs occur prior to movement initiation (Belen'kii et al., 1967; Massion, 1992) and thus the whole-body modifications that ensue due to the complexity manipulation are specifically tied to movement preparation strategies. In a simple RT paradigm such as the one used in all four studies contained in this thesis, there is a single stimulus requiring a single response. Therefore, this response can be fully prepared, or preprogrammed, prior to the IS. In a choice RT paradigm however, the response to be made is indicated by the stimulus, meaning the response cannot be preprogrammed, and must be selected and programmed during the RT interval. This has been corroborated by Carlsen and colleagues (2004) when they demonstrated a SAS can reduce premotor RT by ~70 ms when the control IS (84 dB) was replaced with a 124 dB startle tone in a simple RT paradigm, but not in a choice RT paradigm. Reductions in RT due to a SAS are termed the "StartReact" effect (Valls-Sole, Kumru, & Kofler, 2008). Valls-Solé and colleagues (1999) argued that normal cortical initiation processes must be bypassed for voluntary responses to be elicited at short latencies (in some cases less than 65 ms). This interpretation was based on cortically-initiated processes requiring 35 ms for the IS to reach the auditory cortex (Erwin & Buchwald, 1986) and 20-30 ms to account for nerve conduction time from the motor cortex to the limbs (Rothwell, 1997). However, based on the observed RTs by Valls-Solé and colleagues (1999), there would be almost no time left for the generation of an efferent volley. In the years following, two dominant models have emerged. The first postulated that, due to the low latencies elicited by the SAS, sufficient detail about the response to be made is stored in brainstem structures, such as the reticular formation (Carlsen et al., 2004; Valls-Solé et al.,

1999). The second is that a cortically-stored response is triggered by a SAS via an alternate fast conducting pathway, such as the reticulo-thalamo-cortical pathway (Alibiglou & MacKinnon, 2012; Carlsen, Maslovat, & Franks, 2012). Importantly, both models rely on activity in the reticular formation acting to trigger the prepared response at the short latency (Carlsen, 2015). In the context of APAs, both Valls-Solé and colleagues (1999) and MacKinnon and colleagues (2007) have shown that a SAS can trigger the APA sequence at a shorter latency. Thus, as evidenced by the lengthening of the primary effector RT, as delayed APA profiles due to the complexity of the movement seen in chapter 2 (study 1), it appears that subcortical structures, namely the reticular formation, could be responsible for the integration of movement complexity into motor responses.

Indeed, the combined results of chapters 3 and 4 (studies 2 and 3) lend further support to the idea. In chapter 3 (study 2), TMS was used to demonstrate that MEPs increased as a consequence of movement complexity. This increase in CE was mirrored by an increase in RTs, which confirmed the hypotheses. Given that MEPs are influenced by cortical, spinal, and peripheral excitability, this study could not speak to spinal influences. However, to address this limitation, chapter 4 (study 3) used a combination of TMS and transmastoid stimulation to determine if motoneuron excitability contributed to the increases in CE seen in chapter 3 (study 2). It was hypothesized that both cortical and motoneuron excitability would increase prior to movement onset, as well as in response to movement complexity. These hypotheses were confirmed as both MEP and CMEP amplitudes increased as movement onset approached. When normalized to the CMEP, there was no increase in MEP amplitude, suggestive of minimal influence of cortical excitability to the previously observed increases in CE with movement complexity in chapter 3 (study 2). It was also found that motoneuron excitability increases at

least 50% earlier than previously described in the literature. This is an important finding because independent of movement complexity, the time course of spinal excitability had never been measured. Thus, this adds to the existing literature describing the time course of corticospinal excitability, providing a more complete picture of preparatory processes. The results of this study further point to the contribution of subcortical areas (e.g., the brainstem) above the level of the motoneurons in the mediation of complex movements.

As stated in chapter 1, the control of movement is also mediated by extrapyramidal tracts, which can be further divided into tectospinal, rubrospinal, reticulospinal and vestibulospinal descending tracts (Waldman, 2009). Transcranial magnetic stimulation cannot probe these pathways, but it has been hypothesized that transmastoid stimulation can stimulate descending motor pathways other than the corticospinal tract, such as the reticulospinal or vestibulospinal tracts (Nielsen & Petersen, 1994). While TMS and transmastoid stimulation allow for cortical versus spinal comparisons, they do not allow researchers to probe activity in extrapyramidal tracts. The vestibulospinal tract functions to maintain equilibratory reflexes from the input of the vestibular apparatus (Rea, 2015), which provides the CNS with information required for effective standing balance (Fitzpatrick & Day, 2004). As EVS evokes a virtual signal of head rotation (Day & Fitzpatrick, 2005; Peters et al., 2016; Peters et al., 2015), interpreted by the CNS as an unexpected perturbation that elicits a whole-body response compensating for the disturbance to balance (Dakin, Héroux, Luu, Inglis, & Blouin, 2016), this type of stimulation allows researchers to isolate extrapyramidal contributions to movement. There has been growing evidence which suggests that, in addition to its vital role in balance, the vestibulomotor system is also integral to arm control. This has been shown in a variety of upper limb movements; e.g., when participants reached towards either earth-fixed targets while seated (Bresciani, Blouin,

Popov, Sarlegna, et al., 2002; Mars et al., 2003; Moreau-Debord et al., 2014; Smith et al., 2017) or standing (Bresciani, Blouin, Popov, Bourdin, et al., 2002), or reached to body-fixed targets while seated (Smith & Reynolds, 2017). In particular, the seated conditions demonstrate that arm control responses can be dissociated from postural or balance constraints. In chapter 5 (study 4), an isolated vestibular error (EVS) was used to examine if the vestibulomotor system was altered during the preparation phase of complex reaching movements. It was hypothesized that there would be a task-dependent increase in the vestibular-evoked response in both the upper and lower limb musculature, which would be mirrored by an increase in primary effector RT. The results demonstrated that in addition to postural (lower limb) contributions, the vestibulomotor system was also involved in arm (upper limb) control processes. Most importantly however, this study also showed an increase in the vestibulomotor response between the simplest movement and the two more complex movements in the LMG and RMG. Additionally, there was also an increase in the vestibulomotor response between the simplest and most complex movement in the biceps brachii. The hypotheses were confirmed, and this was the first study to show that both lower and upper limb responses were tuned to movement complexity. Furthermore, this study substantiated the speculation in the conclusion of chapter 4 that subcortical structures above the level of the motoneurons influence complexity-based changes in CE.

The vestibulospinal reflex coordinates head and neck movements with the trunk and body to maintain the upright position of the head. This reflex is mediated by vestibular afferents to the vestibular nuclei, which in turn project to motoneurons. More specifically, afferent fibres of the vestibulocochlear nerve carry signals from receptors cells of the sensory organs to the vestibular nuclei, which project to neural structures controlling eyes movements, posture, and balance, as well as neural structures involved in the computation of self-motion (Cullen, 2012). There are

four vestibular nuclei; superior, lateral, medial and inferior, on each side of the brainstem. Via commissural fibres, they accept input from 4 sources: the vestibular afferents (via the vestibulocochlear nerve), the vestibular cerebellum, the reticular formation and the contralateral vestibular afferents (Ruckenstein, 2004). Based on extensive reciprocal connections between the reticular formation, vestibular nuclei and vestibulo-cerebellum (Wilson & Peterson, 1981), the reticular formation has been implicated in electrically-evoked vestibulomotor reflexes (Britton et al., 1993). Therefore, not only is the reticular formation involved in electrically-evoked responses, but as the reticular formation has been linked to every neural stimulation-based study in this thesis, it is proposed the reticular formation is fundamental to the integration of complexity into voluntary movement.

One final piece of evidence supports this proposal. In their 2014 study, Maslovat and colleagues varied the complexity of a key-press movement by having participants perform either single element or multiple element key-press sequences with varying isochronous or non-isochronous timing structures. Furthermore, they used a SAS to trigger prepared movements and to probe which movements were preprogrammed. This study contained four movement sequences which included: (a) a single key-press [1-press]; (b) a three-key sequence with an isochronous timing pattern of 300 ms between the end of each movement element and the beginning of the next [3-press iso]; (c) a three key-press sequence with a non-isochronous short interval of 150 ms between the end of the first element and the start of the second element, and a long interval of 450 ms between the end of the second element of the start of the third element [3-press SL]; (d) a three key-press sequence with a non-isochronous long interval of 450 ms between the end of the first element and the second element and a short interval of 150 ms between the end of the second element and the start of the third element [3-press LS]. All key-

press durations were 150 ms and the total movement time for the 3 complex movements was 1050 ms. The results demonstrated that complexity was properly manipulated as RT increased between the 3-press iso condition and the 3-press non-isochronous movements. Furthermore, there was a main effect of stimulus type (SAS vs. normal IS), indicating the prepared responses could be triggered at a shorter latency via the proposed reticular formation-mediated pathway. Therefore, this thesis has demonstrated that subcortical structures integrate movement complexity parameters into a global motor plan that is finally mediated by the spinal cord. Furthermore, this thesis presents evidence implicating the reticular formation in this integration.

A second finding from the Maslovat and colleagues (2014) paper was that in addition to the complexity of the movements increasing RT, the authors also found the 3-press LS movement was performed at a shorter latency compared to the 3-press SL movement in both non-SAS and SAS conditions. They demonstrated that in non-isochronous movements, the length of the first interval (i.e., between key-press one and two) had a profound effect on overall RT. For example, when the length of the first interval was long (450 ms), overall RT was quicker than when the first interval was short (150 ms). The authors suggested that some participants may have only prepared the first movement component (first button press) in advance, with the remaining components prepared online. Participants were separated into two groups, those with the slowest RTs (N=6) and those with the fastest RTs (N=6). Participants with the slowest RTs had near identical RTs for the 3-press LS versus SL movements, whereas the participants with the fastest RTs had significantly faster LS compared to SL movements. This was presumed to be because they were able to prepare the LS movement online. This demonstrated that even though the overall goal for all participants was to produce their movement as “fast and accurately as possible”, participants adopted different strategies for the preparation of complex movements.

The curious finding from this thesis is that different RT patterns were found between chapters 2/3 (studies 1/2) and chapters 4/5 (studies 3/4). In chapters 2/3 (studies 1/2), there were differences in RT between the 1- and 2-movement, the 1- and 3-movement, *and* the 2- and 3-movement conditions, whereas in chapters 4/5 (studies 3/4) there was no increase in RT between the 2- and 3-movement conditions. This indicated that some participants may have only preplanned certain aspects of the entire movement sequence. In other words, some participants may have only preplanned the first movement reversal (between target 1 and target 2), while completing the second reversal in an online manner. As an exploratory analysis, participants were separated in chapter 4 (study 3) in a similar manner to Maslovat and colleagues (2014) to probe whether the motoneuron response was different between those who exhibited clear RT differences between the 2- and 3-movement conditions, and those who did not. This resulted in 2 groups (N=4 each), the first group with a mean difference of 25 ms between the 2-and 3-movement conditions, and the second group with a mean difference of 4 ms. The remaining participants were excluded from this analysis because they either had negative RT differences between the 2- and 3-movement conditions (N=7) or had mean RT differences between the 2- and 3- movement conditions of 11 ms (range 10-12 ms; N=3) and thus could not be included in either group. A t-test determined this difference was significant ($p$ =0.007). When further analyzed via a 3-way RM ANOVA, there was a significant interaction between the motoneuron response in the two groups over time. As depicted in figure 21 (appendix 1), it appears that those participants that preprogrammed the entire movement ahead of time (i.e. those who showed differences in RT between the 2- and 3-movement conditions) had a very flat motoneuron excitability profile over the RT interval. In contrast, those who presumably only prepared the 1$^{st}$ reversal prior to the IS had steep increases in motoneuron excitability. Perhaps this preparation

strategy allowed participants to gradually raise motoneuron excitability to a level just below the activation threshold for movement, so as not to prematurely release the movement prior to the IS.

Importantly, in chapter 4 (study 3), intensities for transmastoid stimulation and TMS were set to achieve the desired evoked response sizes in triceps brachii, which was equivalent across all participants. Responses in biceps brachii had no such control across participants so could not be considered for analysis. However, as no such procedures were used in chapter 5 (study 4), the biceps brachii response to EVS can be further investigated. As a reminder, this study showed an incrementally striated response of the vestibulomotor system between the simplest movement and the two more complex movements in the LMG and RMG. Interestingly, there was also an increase in the vestibulomotor response between the simplest and most complex movement in the biceps brachii. Similar to chapter 4 (study 3), the group RT was not different between the 2- and 3-movement conditions. Even though the triceps brachii was the primary muscle for the initiation of the entire movement, perhaps this indicated that participants again only preplanned to the first movement reversal. By virtue of this interpretation, the only complexity-related activity the vestibulomotor system had to prepare prior to the IS was that of the biceps brachii response, making that muscle the *de facto* prime mover in this study, as the first reversal required participants to transition from elbow extension to elbow flexion. The results from chapter 5 (study 4) support this interpretation as the biceps brachii response (figure 20b) was the only upper limb muscle that was shown to be sensitive to movement complexity planning mediated by the vestibulomotor system.

Overall, this thesis demonstrates a complex interaction of multiple motor systems in the execution of movement. Based on the tools that were used, it can be surmised that movement complexity-based increases in CE are not principally mediated at a cortical level but may rather

involve the direct influence of subcortical areas (e.g., the reticular formation) on motoneuron excitability. Furthermore, it showed that participants were able to either fully or partially preplan their movements prior to the IS. Participants that partially preplanned their movements appeared to use their biceps as the prime mover for task, indicating they preplanned up to the first movement reversal and completed the 2$^{nd}$ reversal in an online manner. Finally, there is also evidence to suggest that this strategy allowed participants to gradually raise motoneuron excitability to a level just below the activation threshold for movement, so as not to prematurely release the movement prior to the IS.

**Strengths and limitations**

The major strength of this thesis was that every study used the same behavioural task. As previously mentioned, this normalization allowed for a discussion of how the various regions of the motor pathway may contribute to the same complex movement. A further strength of this thesis is the behavioural tasks were all performed on the KINARM End-Point Lab, which restricted movement to 2 dimensions. This ensures that movements do not extend into a third dimension, which would have increased the degrees of freedom of the movements and made the interpretation of the results more difficult. Another advantage of using the KINARM system is that it allows user to create fully customizable behavioural tasks, or research protocols, via MATLAB, Simulink and Stateflow.

The behavioural task used in this thesis was specifically designed to manipulate the complexity of the task by adding movement components. As demonstrated in chapters 2 (study 1) and 3 (study 2), RTs became statistically slower from one another as the task become more complex. However, in chapters 4 (study 3) and 5 (study 4), RTs in the 2- and 3- movement conditions were slower than the 1-movement condition but were not different from one another.

This indicates the task may have been too difficult to fully preplan, requiring some participants to adopt online correction strategies. While this was a limitation, it also allowed for a greater discussion of movement preparation strategies.

**Potential applications of the research findings.**

Due to the mechanistic nature of this thesis, the potential applications of the findings are limited. However, chapters 2 (study 1) and 5 (study 4) use tasks and tools that disrupt balance and posture. Over the past 30 years, fall prevention within the home has been identified by the Centre for Disease Control as major research topic of interest (Sleet, Moffett, & Stevens, 2008). It is estimated that 30% of adults over the age of 65 fall at least once per year (Logan et al., 2010), due to a combination of physical, functional, and cognitive impairments (McKay & Anderson, 2010). Kanekar and Aruin (2014) have shown that aging delays anticipatory muscle activity and elicit larger compensatory muscular responses, resulting in older adults being more unstable. Furthermore, older adults require greater corticospinal excitability to stand compared to younger adults (Baudry, Penzer, & Duchateau, 2014), which produces increased plantar flexion and co-activation of antagonist dorsiflexors (Baudry, Lecoeuvre, & Duchateau, 2012; Baudry et al., 2014; Benjuya, Melzer, & Kaplanski, 2004; Laughton et al., 2003) due to potential age-related alterations in the vestibular, proprioceptive and visual systems (Lord, Clark, & Webster, 1991; Lord & Menz, 2000; Shaffer & Harrison, 2007). Indeed, Dalton and colleagues (2014) have demonstrated smaller short and larger medium latency peak forces in older adults, presumably related to lower operational frequencies of the vestibulomotor pathway, which may reflect greater instability in older adults. Importantly, as no studies prior to those presented in this thesis have investigated how movement complexity alters the vestibulomotor pathway or APAs, the outcomes of chapters 2 (study 1) and 5 (study 4), provide insights into how complex

movements affect posture and balance. From an educational perspective, this could be translated into increased awareness of the risk that complex movements pose to older adults.

**Potential future directions**

There are two major potential future directions from this thesis. The first is the to use a SAS in the same behavioural paradigm used throughout this thesis. This would allow for a greater understanding of the movement preparation strategies involved in the execution of the 3-movement condition. Participants could once again be divided into groups based on their RTs in the 2- and 3-movement conditions. If control and startled RTs were found to be similar between the 2- and 3-movement conditions, this would indicate that participants were only preparing up to the first reversal prior to the IS. Furthermore, as APAs have been shown to be triggerable by a SAS, a further study could use an SAS to determine if the APAs associated with the different movement conditions could be triggered at faster latencies compared to control conditions (non-startling IS). This would add further evidence implicating the reticular formation in the integration of movement complexity into a motor response.

The second direction is the further exploration of the task dependent increase of the vestibulomotor response in the biceps brachii. I have presented an argument to consider the biceps brachii as the *de facto* prime mover in chapter 5 (study 4), based on the first reversal requiring participants to transition from an elbow extension to elbow flexion movement. A further study could invert the current behavioural task making the first reversal movement an elbow extension, as opposed to an elbow flexion movement. This would now make the biceps brachii the primary initiator of the motor response and the triceps brachii the primary effector. If the vestibulomotor system truly programmed the biceps brachii as the prime mover in chapter 5

(study 4), this manipulation should result in a vestibular evoked response in triceps brachii sensitive to movement complexity, which would not be mirrored in the biceps brachii.

**References**


Abbruzzese, G., Trompetto, C., & Schieppati, M. (1996). The excitability of the human motor cortex increases during execution and mental imagination of sequential but not repetitive finger movements. *Experimental Brain Research, 111*(3), 465-472.

Adrian, E. D., & Yamagiwa, K. (1935). The origin of the berger rhythm. *Brain, 58*, 317-+.

Ali, A. S., Rowen, K. A., & Iles, J. F. (2003). Vestibular actions on back and lower limb muscles during postural tasks in man. *Journal of Physiology, 546*(Pt 2), 615-624.

Alibiglou, L., & MacKinnon, C. D. (2012). The early release of planned movement by acoustic startle can be delayed by transcranial magnetic stimulation over the motor cortex. *Journal of Physiology, 590*(4), 919-936. doi:10.1113/jphysiol.2011.219592

Arbib, M. A. (1981). Perceptual structures and distributed motor control. In V. B. Brooks (Ed.), *Handbook of Physiology, Section 1, The Nervous System* (Vol. 2, pp. 1449-1480). Bethesda: American Physiological Society.

Aruin, A. S., & Latash, M. L. (1995). Directional specificity of postural muscles in feed-forward postural reactions during fast voluntary arm movements. *Experimental Brain Research, 103*(2), 323-332. doi:10.1007/bf00231718

Barker, A. T., Freeston, I. L., Jalinous, R., & Jarratt, J. A. (1987). Magnetic stimulation of the human-brain and peripheral nervous-system - an introduction and the results of an initial clinical evaluation. *Neurosurgery, 20*(1), 100-109.

Barker, A. T., Freeston, I. L., Jalinous, R., Merton, P. A., & Morton, H. B. (1985). Magnetic stimulation of the human brain. *Journal of Physiology-London, 369*(DEC), P3-P3.

Barker, A. T., & Jalinous, R. (1985). Non-invasive magnetic stimulation of the human motor cortex. *Lancet, 1*(8437), 1106-1107.

Baudry, S., Lecoeuvre, G., & Duchateau, J. (2012). Age-related changes in the behavior of the muscle-tendon unit of the gastrocnemius medialis during upright stance. *J Appl Physiol (1985), 112*(2), 296-304. doi:10.1152/japplphysiol.00913.2011

Baudry, S., Penzer, F., & Duchateau, J. (2014). Input–output characteristics of soleus homonymous Ia afferents and corticospinal pathways during upright standing differ between young and elderly adults. *Acta Physiologica, 210*(3), 667-677. doi:10.1111/apha.12233

Belen'kii, V. E., Gurfinkel, V. S., & Pal'tsev, E. I. (1967). [Control elements of voluntary movements]. *Biofizika, 12*(1), 135-141.

Benjuya, N., Melzer, I., & Kaplanski, J. (2004). Aging-induced shifts from a reliance on sensory input to muscle cocontraction during balanced standing. *Journals of Gerontology. Series A: Biological Sciences and Medical Sciences, 59*(2), 166-171.

Bent, L. R., Bolton, P. S., & Macefield, V. G. (2006). Modulation of muscle sympathetic bursts by sinusoidal galvanic vestibular stimulation in human subjects. *Experimental Brain Research, 174*(4), 701-711. doi:10.1007/s00221-006-0515-6

Benvenuti, F., Stanhope, S. J., Thomas, S. L., Panzer, V. P., & Hallett, M. (1997). Flexibility of anticipatory postural adjustments revealed by self-paced and reaction-time arm movements. *Brain Research, 761*(1), 59-70.

Berrigan, F., Simoneau, M., Martin, O., & Teasdale, N. (2006). Coordination between posture and movement: interaction between postural and accuracy constraints. *Experimental Brain Research, 170*(2), 255-264. doi:10.1007/s00221-005-0210-z

Bestmann, S., & Krakauer, J. W. (2015). The uses and interpretations of the motor-evoked potential for understanding behaviour. *Experimental Brain Research, 233*(3), 679-689. doi:10.1007/s00221-014-4183-7

Bockisch, C. J., & Haslwanter, T. (2007). Vestibular contribution to the planning of reach trajectories. *Experimental Brain Research, 182*(3), 387-397. doi:10.1007/s00221-007-0997-x

Bresciani, J.-P., Blouin, J., Popov, K., Bourdin, C., Sarlegna, F., Vercher, J. L., & Gauthier, G. M. (2002). Galvanic vestibular stimulation in humans produces online arm movement deviations when reaching towards memorized visual targets. *Neuroscience Letters, 318*(1), 34-38.

Bresciani, J.-P., Blouin, J., Popov, K., Sarlegna, F., Bourdin, C., Vercher, J.-L., & Gauthier, G. M. (2002). Vestibular signals contribute to the online control of goal-directed arm movements. *Current Psychology of Cognition, 21*(2/3), 263-280.

Britton, T. C., Day, B. L., Brown, P., & Rothwell, J. C. (1993). Postural electromyographic responses in the arm and leg following galvanic vestibular stimulation in man. *Experimental Brain Research, 94*(1), 143-151.

Carlsen, A. N. (2015). A broadband acoustic stimulus is more likely than a pure tone to elicit a startle reflex and prepared movements. *Physiol Rep, 3*(8). doi:10.14814/phy2.12509

Carlsen, A. N., Chua, R., Inglis, J. T., Sanderson, D. J., & Franks, I. M. (2004). Can prepared responses be stored subcortically? *Experimental Brain Research, 159*(3), 301-309. doi:10.1007/s00221-004-1924-z

Carlsen, A. N., Maslovat, D., & Franks, I. M. (2012). Preparation for voluntary movement in healthy and clinical populations: Evidence from startle. *Clinical Neurophysiology, 123*(1), 21-33.

Carpenter, R. H. S., & Williams, M. L. L. (1995). Neural computation of log likelihood in control of saccadic eye-movements. *Nature, 377*(6544), 59-62. doi:10.1038/377059a0

Chen, R., Yaseen, Z., Cohen, L. G., & Hallett, M. (1998). Time course of corticospinal excitability in reaction time and self-paced movements. *Annals of Neurology, 44*(3), 317-325. doi:10.1002/ana.410440306

Churchland, M. M., Yu, B. M., Ryu, S. I., Santhanam, G., & Shenoy, K. V. (2006). Neural variability in premotor cortex provides a signature of motor preparation. *Journal of Neuroscience, 26*(14), 3697-3712. doi:10.1523/jneurosci.3762-05.2006

Cisek, P., & Kalaska, J. F. (2005). Neural Correlates of Reaching Decisions in Dorsal Premotor Cortex: Specification of Multiple Direction Choices and Final Selection of Action. *Neuron, 45*(5), 801-814. doi:https://doi.org/10.1016/j.neuron.2005.01.027

Cohen, B., Suzuki, J.-I., & Bender, M. B. (1965). Nystagmus Induced by Electric Stimulation of Ampullary Nerves. *Acta Oto-Laryngologica, 60*(1-6), 422-436. doi:10.3109/00016486509127026

Cohen, B., Yakushin, S. B., & Holstein, G. R. (2011). What does galvanic vestibular stimulation actually activate? *Frontiers in Neurology, 2*, 90. doi:10.3389/fneur.2011.00090

Courjon, J. H., Precht, W., & Sirkin, D. W. (1987). Vestibular nerve and nuclei unit responses and eye movement responses to repetitive galvanic stimulation of the labyrinth in the rat. *Experimental Brain Research, 66*(1), 41-48.

Crone, C., & Nielsen, J. (1989). Methodological implications of the post activation depression of the soleus H-reflex in man. *Experimental Brain Research, 78*(1), 28-32.

Cullen, K. E. (2012). The vestibular system: multimodal integration and encoding of self-motion for motor control. *Trends in Neurosciences, 35*(3), 185-196. doi:10.1016/j.tins.2011.12.001

Cullen, K. E. (2016). Physiology of central pathways. *Handbook of Clinical Neurology, 137*, 17.

Cullen, K. E., Huterer, M., Braidwood, D. A., & Sylvestre, P. A. (2004). Time course of vestibuloocular reflex suppression during gaze shifts. *Journal of Neurophysiology, 92*(6), 3408-3422. doi:10.1152/jn.01156.2003

Dakin, C. J., Héroux, M. E., Luu, B. L., Inglis, J. T., & Blouin, J.-S. (2016). Vestibular contribution to balance control in the medial gastrocnemius and soleus. *Journal of Neurophysiology, 115*(3), 1289-1297. doi:10.1152/jn.00512.2015

Dakin, C. J., Lee Son, G. M., Inglis, J. T., & Blouin, J.-S. (2007). Frequency response of human vestibular reflexes characterized by stochastic stimuli. *The Journal of Physiology, 583*(Pt 3), 1117-1127. doi:10.1113/jphysiol.2007.133264

Dakin, C. J., Luu, B. L., Doel, K. v. d., Inglis, J. T., & Blouin, J.-S. (2010). Frequency-Specific Modulation of Vestibular-Evoked Sway Responses in Humans. *Journal of Neurophysiology, 103*(2), 1048-1056. doi:10.1152/jn.00881.2009

Dalton, B. H., Blouin, J. S., Allen, M. D., Rice, C. L., & Inglis, J. T. (2014). The altered vestibular-evoked myogenic and whole-body postural responses in old men during standing. *Experimental Gerontology, 60*, 120-128. doi:10.1016/j.exger.2014.09.020

Davranche, K., Temesi, J., Verges, S., & Hasbroucq, T. (2015). Transcranial magnetic stimulation probes the excitability of the primary motor cortex: A framework to account for the facilitating effects of acute whole-body exercise on motor processes. *Journal of Sport and Health Science, 4*(1), 24-29. doi:https://doi.org/10.1016/j.jshs.2014.09.001

Day, B. L., Dressler, D., Maertens de Noordhout, A., Marsden, C. D., Nakashima, K., Rothwell, J. C., & Thompson, P. D. (1989). Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. *Journal of Physiology, 412*, 449-473.

Day, B. L., & Fitzpatrick, R. C. (2005). Virtual head rotation reveals a process of route reconstruction from human vestibular signals. *The Journal of Physiology, 567*(Pt 2), 591-597. doi:10.1113/jphysiol.2005.092544

Day, B. L., & Reynolds, R. F. (2005). Vestibular reafference shapes voluntary movement. *Current Biology, 15*(15), 1390-1394. doi:10.1016/j.cub.2005.06.036

Day, B. L., Rothwell, J. C., & Marsden, C. D. (1983). Transmission in the spinal reciprocal Ia inhibitory pathway preceding willed movements of the human wrist. *Neuroscience Letters, 37*(3), 245-250.

Day, B. L., Rothwell, J. C., Thompson, P. D., Dick, J. P., Cowan, J. M., Berardelli, A., & Marsden, C. D. (1987). Motor cortex stimulation in intact man. 2. Multiple descending volleys. *Brain, 110 ( Pt 5)*, 1191-1209.

Deecke, L. (1996). Planning, preparation, execution, and imagery of volitional action. *Cognitive Brain Research, 3*(2), 59-64. doi:10.1016/0926-6410(95)00046-1

Dum, R. P., & Strick, P. L. (2002). Motor areas in the frontal lobe of the primate. *Physiology and Behavior, 77*(4), 677-682. doi:10.1016/S0031-9384(02)00929-0

Erwin, R. J., & Buchwald, J. S. (1986). Midlatency auditory evoked responses: Differential recovery cycle characteristics. *Electroencephalography and Clinical Neurophysiology, 64*(5), 417-423. doi:https://doi.org/10.1016/0013-4694(86)90075-1

Ezure, K., Cohen, M. S., & Wilson, V. J. (1983). Response of cat semicircular canal afferents to sinusoidal polarizing currents: implications for input-output properties of second-order neurons. *Journal of Neurophysiology, 49*(3), 639-648. doi:10.1152/jn.1983.49.3.639

Fitts, P. M. (1954). The information capacity of the human motor system in controlling the amplitude of movement. *Journal of Experimental Psychology, 47*(6), 381-391.

Fitzpatrick, R. C., Burke, D., & Gandevia, S. C. (1994). Task-dependent reflex responses and movement illusions evoked by galvanic vestibular stimulation in standing humans. *The Journal of Physiology, 478*(Pt 2), 363-372. doi:10.1113/jphysiol.1994.sp020257

Fitzpatrick, R. C., & Day, B. L. (2004). Probing the human vestibular system with galvanic stimulation. *Journal of Applied Physiology, 96*(6), 2301-2316. doi:10.1152/japplphysiol.00008.2004

Flament, D., Goldsmith, P., Buckley, C. J., & Lemon, R. N. (1993). Task dependence of responses in 1st dorsal interosseusmuscle to magnetic brain-stimulation in man. *Journal of Physiology, 464*, 361-378.

Forbes, P. A., Dakin, C. J., Geers, A. M., Vlaar, M. P., Happee, R., Siegmund, G. P., . . . Blouin, J. S. (2014). Electrical vestibular stimuli to enhance vestibulo-motor output and improve subject comfort. *PloS One, 9*(1), e84385. doi:10.1371/journal.pone.0084385

Forbes, P. A., Luu, B. L., Van der Loos, H. F. M., Croft, E. A., Inglis, J. T., & Blouin, J.-S. (2016). Transformation of Vestibular Signals for the Control of Standing in Humans. *The Journal of Neuroscience, 36*(45), 11510-11520. doi:10.1523/jneurosci.1902-16.2016

Franks, I. M., Nagelkerke, P., Ketelaars, M., & Van Donkelaar, P. (1998). Response preparation and control of movement sequences. *Canadian Journal of Experimental Psychology/Revue canadienne de psychologie expérimentale, 52*(2), 93.

Friedli, W. G., Cohen, L., Hallett, M., Stanhope, S., & Simon, S. R. (1988). Postural adjustments associated with rapid voluntary arm movements. II. Biomechanical analysis. *Journal of Neurology, Neurosurgery, and Psychiatry, 51*(2), 232-243.

Fuhr, P., Agostino, R., & Hallett, M. (1991). Spinal motor-neuron excitability during the silent period after cortical stimulation. *Electroencephalography and Clinical Neurophysiology, 81*(4), 257-262. doi:10.1016/0168-5597(91)90011-l

Gandevia, S. C., Petersen, N., Butler, J. E., & Taylor, J. L. (1999). Impaired response of human motoneurones to corticospinal stimulation after voluntary exercise. *The Journal of Physiology, 521*(Pt 3), 749-759. doi:10.1111/j.1469-7793.1999.00749.x

Gottlieb, G. L., Agarwal, G. C., & Stark, L. (1970). Interactions between voluntary and postural mechanisms of thehuman motor system. *Journal of Neurophysiology, 33*(3), 365-381.

Greene, P. (1972). Problems of organization of motor systems. In R. Rosen & F. Snell (Eds.), *Progress in Theoretical Biology* (Vol. 2, pp. 304-338). New York: Academic Press.

Greenhouse, I., Saks, D., Hoang, T., & Ivry, R. B. (2015). Inhibition during response preparation is sensitive to response complexity. *Journal of Neurophysiology, 113*(7), 2792-2800. doi:10.1152/jn.00999.2014

Groppa, S., Oliviero, A., Eisen, A., Quartarone, A., Cohen, L. G., Mall, V., . . . Siebner, H. R. (2012). A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee. *Clinical Neurophysiology, 123*(5), 858-882. doi:10.1016/j.clinph.2012.01.010

Groppa, S., Oliviero, A., Eisen, A., Quartarone, A., Cohen, L. G., Mall, V., . . . Siebner, H. R. (2012). A practical guide to diagnostic transcranial magnetic stimulation: Report of an

IFCN committee. *Clinical Neurophysiology*, *123*(5), 858-882. doi:10.1016/j.clinph.2012.01.010

Groppa, S., Schlaak, B. H., Munchau, A., Werner-Petroll, N., Dunnweber, J., Baumer, T., . . . Siebner, H. R. (2012). The human dorsal premotor cortex facilitates the excitability of ipsilateral primary motor cortex via a short latency cortico-cortical route. *Human Brain Mapping*, *33*(2), 419-430. doi:10.1002/hbm.21221

Guedry, F. E. (1974). Psychophysics of vestibular sensation. In H. H. Kornhuber (Ed.), *Handbook of Sensory Physiology* (pp. 3-154). Berlin, Heidelberg, New York: Springer Verlag.

Gurfinkel, V. S., Popov, K. E., Smetanin, B. N., & Shlykov, V. Y. (1989). Changes in the direction of vestibulomotor response in the course of adaptation to protracted static head turning in man. *Neurophysiology (New York)*, *21*(2), 159-164. doi:10.1007/BF01056975

Hadar, A. A., Rowe, P., Di Costa, S., Jones, A., & Yarrow, K. (2016). Motor-evoked potentials reveal a motor-cortical readout of evidence accumulation for sensorimotor decisions. *Psychophysiology*, *53*(11), 1721-1731. doi:10.1111/psyp.12737

Halliday, D. M., Rosenberg, J. R., Amjad, A. M., Breeze, P., Conway, B. A., & Farmer, S. F. (1995). A framework for the analysis of mixed time series/point process data--theory and application to the study of physiological tremor, single motor unit discharges and electromyograms. *Progress in Biophysics and Molecular Biology*, *64*(2-3), 237-278.

Hanes, D. P., & Schall, J. D. (1996). Neural control of voluntary movement initiation. *Science*, *274*(5286), 427-430. doi:10.1126/science.274.5286.427

Hannah, R., Cavanagh, S. E., Tremblay, S., Simeoni, S., & Rothwell, J. C. (2018). Selective Suppression of Local Interneuron Circuits in Human Motor Cortex Contributes to Movement Preparation. *Journal of Neuroscience*, *38*(5), 1264-1276. doi:10.1523/jneurosci.2869-17.2017

Hasbroucq, T., Kaneko, H., Akamatsu, M., & Possamai, C. A. (1997). Preparatory inhibition of cortico-spinal excitability: A transcranial magnetic stimulation study in man. *Cognitive Brain Research*, *5*(3), 185-192. doi:10.1016/s0926-6410(96)00069-9

Hasegawa, M., Majima, K., Itokazu, T., Maki, T., Albrecht, U. R., Castner, N., . . . Sato, T. R. (2017). Selective Suppression of Local Circuits during Movement Preparation in the Mouse Motor Cortex. *Cell Reports*, *18*(11), 2676-2686. doi:10.1016/j.celrep.2017.02.043

Henry, F. M., & Rogers, D. E. (1960). Increased response latency for complicated movements and a memory drum theory of neuromotor reaction. *Research Quarterly*, *31*(3), 448-458.

Hess, C. W., Mills, K. R., & Murray, N. M. (1987). Responses in small hand muscles from magnetic stimulation of the human brain. *Journal of Physiology*, *388*, 397-419.

Horak, F. B., Diener, H. C., & Nashner, L. M. (1989). Influence of central set on human postural responses. *Journal of Neurophysiology*, *62*(4), 841-853.

Hoshiyama, M., Kitamura, Y., Koyama, S., Watanabe, S., Shimojo, M., & Kakigi, R. (1996). Reciprocal change of motor evoked potentials preceding voluntary movement in humans. *Muscle and Nerve*, *19*(2), 125-131. doi:10.1002/(sici)1097-4598(199602)19:2<125::aid-mus1>3.0.co;2-g

Hultborn, H., Meunier, S., Pierrot-Deseilligny, E., & Shindo, M. (1987). Changes in presynaptic inhibition of Ia fibres at the onset of voluntary contraction in man. *Journal of Physiology*, *389*, 757-772.

Huterer, M., & Cullen, K. E. (2002). Vestibuloocular reflex dynamics during high-frequency and high-acceleration rotations of the head on body in rhesus monkey. *Journal of Neurophysiology, 88*(1), 13-28. doi:10.1152/jn.2002.88.1.13

Inghilleri, M., Berardelli, A., Cruccu, G., & Manfredi, M. (1993). Silent period evoked by transcranial stimulation of the human cortex and cervicomedullary junction. *Journal of Physiology, 466*, 521-534.

Jackson, A., Baker, S. N., & Fetz, E. E. (2006). Tests for presynaptic modulation of corticospinal terminals from peripheral afferents and pyramidal tract in the macaque. *Journal of Physiology, 573*(Pt 1), 107-120. doi:10.1113/jphysiol.2005.100537

Jeka, J. J., & Lackner, J. R. (1995). The role of haptic cues from rough and slippery surfaces in human postural control. *Experimental Brain Research, 103*(2), 267-276.

Kandel, E., Schwartz, J., & Jessell, T. (2000). *Principles of Neural Science, Fourth Edition*: McGraw-Hill Companies,Incorporated.

Kanekar, N., & Aruin, A. S. (2014). The effect of aging on anticipatory postural control. *Experimental Brain Research, 232*(4), 1127-1136. doi:10.1007/s00221-014-3822-3

Kaufman, M. T., Seely, J. S., Sussillo, D., Ryu, S. I., Shenoy, K. V., & Churchland, M. M. (2016). The Largest Response Component in the Motor Cortex Reflects Movement Timing but Not Movement Type. *eNeuro, 3*(4). doi:10.1523/eneuro.0085-16.2016

Kennefick, M., Maslovat, D., Chua, R., & Carlsen, A. N. (2016). Corticospinal excitability is reduced in a simple reaction time task requiring complex timing. *Brain Research, 1642*, 319-326. doi:http://dx.doi.org/10.1016/j.brainres.2016.04.006

Kennefick, M., Wright, A. D., Smirl, J. D., & van Donkelaar, P. (2018). Anticipatory postural adjustments as a function of response complexity in simple reaction time tasks. *Neuroscience Letters, 684*, 1-5. doi:https://doi.org/10.1016/j.neulet.2018.06.058

Klapp, S. T. (1995). Motor response programming during simple and choice-reaction time -the role of practice. *Journal of Experimental Psychology: Human Perception and Performance, 21*(5), 1015-1027. doi:10.1037//0096-1523.21.5.1015

Klapp, S. T. (2003). Reaction time analysis of two types of motor preparation for speech articulation: action as a sequence of chunks. *J Mot Behav, 35*(2), 135-150. doi:10.1080/00222890309602129

Klapp, S. T., Wyatt, E. P., & Lingo, W. M. (1974). Response programming in simeple and choice reactions. *Journal of Motor Behavior, 6*(4), 263-271.

Klein-Flugge, M. C., Nobbs, D., Pitcher, J. B., & Bestmann, S. (2013). Variability of human corticospinal excitability tracks the state of action preparation. *Journal of Neuroscience, 33*(13), 5564-5572. doi:10.1523/jneurosci.2448-12.2013

Kobayashi, M., & Pascual-Leone, A. (2003). Transcranial magnetic stimulation in neurology. *Lancet Neurology, 2*(3), 145-156. doi:https://doi.org/10.1016/S1474-4422(03)00321-1

Kuypers, H. G. J. M. (1981). Anatomy of the descending pathways. In B. J.M. & M. V.B. (Eds.), *Handbook of Physiology, The Nervous System, Motor Control* (pp. 597-666). Baltimore, Maryland: Williams and Wilkins.

Kuypers, H. G. J. M., & Brinkman, J. (1970). Precentral projections to different parts of the spinal intermediate zone in the rhesus monkey. *Brain Research, 24*(1), 29-48. doi:https://doi.org/10.1016/0006-8993(70)90272-6

Laughton, C. A., Slavin, M., Katdare, K., Nolan, L., Bean, J. F., Kerrigan, D. C., . . . Collins, J. J. (2003). Aging, muscle activity, and balance control: physiologic changes associated with balance impairment. *Gait and Posture, 18*(2), 101-108.

Lawrence, D. G., & Kuypers, H. G. (1968). The functional organization of the motor system in the monkey. II. The effects of lesions of the descending brain-stem pathways. *Brain, 91*(1), 15-36.

Lee, W. A., Buchanan, T. S., & Rogers, M. W. (1987). Effects of arm acceleration and behavioral conditions on the organization of postural adjustments during arm flexion. *Experimental Brain Research, 66*(2), 257-270.

Lemon, R. N. (2008). Descending pathways in motor control. *Annual Review of Neuroscience, 31*, 195-218. doi:10.1146/annurev.neuro.31.060407.125547

Lemon, R. N., & Griffiths, J. (2005). Comparing the function of the corticospinal system in different species: organizational differences for motor specialization? *Muscle and Nerve, 32*(3), 261-279. doi:10.1002/mus.20333

Logan, P. A., Coupland, C. A., Gladman, J. R., Sahota, O., Stoner-Hobbs, V., Robertson, K., . . . Avery, A. J. (2010). Community falls prevention for people who call an emergency ambulance after a fall: randomised controlled trial. *BMJ, 340*, c2102. doi:10.1136/bmj.c2102

Lord, S. R., Clark, R. D., & Webster, I. W. (1991). Postural stability and associated physiological factors in a population of aged persons. *Journal of Gerontology, 46*(3), M69-76.

Lord, S. R., & Menz, H. B. (2000). Visual contributions to postural stability in older adults. *Gerontology, 46*(6), 306-310. doi:10.1159/000022182

Lowrey, C. R., Nashed, J. Y., & Scott, S. H. (2017). Rapid and flexible whole body postural responses are evoked from perturbations to the upper limb during goal-directed reaching. *Journal of Neurophysiology, 117*(3), 1070-1083. doi:10.1152/jn.01004.2015

Lund, S., & Broberg, C. (1983). Effects of different head positions on postural sway in man induced by a reproducible vestibular error signal. *Acta Physiologica Scandinavica, 117*(2), 307-309. doi:10.1111/j.1748-1716.1983.tb07212.x

MacDougall, H. G., Brizuela, A. E., Burgess, A. M., Curthoys, I. S., & Halmagyi, G. M. (2005). Patient and normal three-dimensional eye-movement responses to maintained (DC) surface galvanic vestibular stimulation. *Otology & Neurotology, 26*(3), 500-511.

MacKinnon, C. D., Bissig, D., Chiusano, J., Miller, E., Rudnick, L., Jager, C., . . . Rogers, M. W. (2007). Preparation of Anticipatory Postural Adjustments Prior to Stepping. *Journal of Neurophysiology, 97*(6), 4368-4379. doi:10.1152/jn.01136.2006

Magladery, J. W., & McDougal, D., Jr. (1950). Electrophysiological studies of nerve and reflex activity in normal man. I. Identification of certain reflexes in the electromyogram and the conduction velocity of peripheral nerve fibers. *Bull Johns Hopkins Hosp, 86*(5), 265-290.

Marchand-Pauvert, V., Nicolas, G., Burke, D., & Pierrot-Deseilligny, E. (2002). Suppression of the H reflex in humans by disynaptic autogenetic inhibitory pathways activated by the test volley. *The Journal of Physiology, 542*(Pt 3), 963-976. doi:10.1113/jphysiol.2002.021683

Mars, F., Archambault, P. S., & Feldman, A. G. (2003). Vestibular contribution to combined arm and trunk motion. *Experimental Brain Research, 150*(4), 515-519. doi:10.1007/s00221-003-1485-6

Martin, P. G., Butler, J. E., Gandevia, S. C., & Taylor, J. L. (2008). Noninvasive stimulation of human corticospinal axons innervating leg muscles. *Journal of Neurophysiology, 100*(2), 1080-1086. doi:10.1152/jn.90380.2008

Martin, P. G., Gandevia, S. C., & Taylor, J. L. (2006). Output of human motoneuron pools to corticospinal inputs during voluntary contractions. *Journal of Neurophysiology, 95*(6), 3512-3518. doi:10.1152/jn.01230.2005

Maslovat, D., Klapp, S. T., Jagacinski, R. J., & Franks, I. M. (2014). Control of Response Timing Occurs During the Simple Reaction Time Interval but On-Line for Choice Reaction Time. *Journal of Experimental Psychology-Human Perception and Performance*. doi:http://dx.doi.org/10.1037/a0037522

Massion, J. (1992). Movement, posture and equilibrium: interaction and coordination. *Progress in Neurobiology, 38*(1), 35-56.

Massion, J. (1998). Postural Control Systems in Developmental Perspective. *Neuroscience and Biobehavioral Reviews, 22*(4), 465-472. doi:https://doi.org/10.1016/S0149-7634(97)00031-6

Massion, J., Alexandrov, A., & Frolov, A. (2004). Why and how are posture and movement coordinated? *Progress in Brain Research, 143*, 13-27. doi:10.1016/s0079-6123(03)43002-1

McConnell, K. A., Nahas, Z., Shastri, A., Lorberbaum, J. P., Kozel, F. A., Bohning, D. E., & George, M. S. (2001). The transcranial magnetic stimulation motor threshold depends on the distance from coil to underlying cortex: A replication in healthy adults comparing two methods of assessing the distance to cortex. *Biological Psychiatry, 49*(5), 454-459. doi:10.1016/s0006-3223(00)01039-8

McGeehan, M. A., Woollacott, M. H., & Dalton, B. H. (2017). Vestibular control of standing balance is enhanced with increased cognitive load. *Experimental Brain Research, 235*(4), 1031-1040. doi:10.1007/s00221-016-4858-3

McKay, C., & Anderson, K. E. (2010). How to manage falls in community dwelling older adults: a review of the evidence. *Postgraduate Medical Journal, 86*(1015), 299-306. doi:10.1136/pgmj.2009.093468

McNeil, C. J., Butler, J. E., Taylor, J. L., & Gandevia, S. C. (2013). Testing the excitability of human motoneurons. *Frontiers in Human Neuroscience, 7*, 152. doi:10.3389/fnhum.2013.00152

McNeil, C. J., Giesebrecht, S., Gandevia, S. C., & Taylor, J. L. (2011). Behaviour of the motoneurone pool in a fatiguing submaximal contraction. *Journal of Physiology, 589*(14), 3533-3544. doi:10.1113/jphysiol.2011.207191

McNeil, C. J., Martin, P. G., Gandevia, S. C., & Taylor, J. L. (2009). The response to paired motor cortical stimuli is abolished at a spinal level during human muscle fatigue. *Journal of Physiology, 587*(Pt 23), 5601-5612. doi:10.1113/jphysiol.2009.180968

Merton, P. A., & Morton, H. B. (1980). Stimulation of the cerebral-crotex in the intact human subject. *Nature, 285*(5762), 227-227. doi:10.1038/285227a0

Mian, O. S., Dakin, C. J., Blouin, J. S., Fitzpatrick, R. C., & Day, B. L. (2010). Lack of otolith involvement in balance responses evoked by mastoid electrical stimulation. *The Journal of Physiology, 588*(22), 4441-4451. doi:10.1113/jphysiol.2010.195222

Mian, O. S., & Day, B. L. (2009). Determining the direction of vestibular-evoked balance responses using stochastic vestibular stimulation. *The Journal of Physiology, 587*(Pt 12), 2869-2873. doi:10.1113/jphysiol.2009.171256

Mian, O. S., & Day, B. L. (2014). Violation of the Craniocentricity Principle for Vestibularly Evoked Balance Responses under Conditions of Anisotropic Stability. *The Journal of Neuroscience, 34*(22), 7696-7703. doi:10.1523/jneurosci.0733-14.2014

Moreau-Debord, I., Martin, C. Z., Landry, M., & Green, A. M. (2014). Evidence for a reference frame transformation of vestibular signal contributions to voluntary reaching. *Journal of Neurophysiology, 111*(9), 1903-1919. doi:10.1152/jn.00419.2013

Nashner, L. M., & Wolfson, P. (1974). Influence of head position and proprioceptive cues on short latency postural reflexes evoked by galvanic stimulation of the human labyrinth. *Brain Research, 67*(2), 255-268.

Nazir, T. A., & Jacobs, A. M. (1991). The effects of target discriminability and retinal eccentricity on saccade latencies - an analysis in terms of variable-criterion theory. *Psychological Research, 53*(4), 281-289. doi:10.1007/bf00920481

Nielsen, J., & Petersen, N. (1994). Is presynaptic inhibition distributed to corticospinal fibres in man? *Journal of Physiology, 477*(Pt 1), 47-58.

Nudo, R. J., & Masterton, R. B. (1990). Descending pathways to the spinal cord, III: Sites of origin of the corticospinal tract. *Journal of Comparative Neurology, 296*(4), 559-583. doi:10.1002/cne.902960405

Pascual-Leone, A., Brasil-Neto, J. P., Valls-Solé, J., Cohen, L. G., & Hallett, M. (1992). Simple reaction time to focal transcranial magnetic stimulation. Comparison with reaction time to acoustic, visual and somatosensory stimuli. *Brain, 115 Pt 1,* 109-122.

Pascual-Leone, A., Valls-Solé, J., Wassermann, E. M., Brasil-Neto, J., Cohen, L. G., & Hallett, M. (1992). Effects of focal transcranial magnetic stimulation on simple reaction time to acoustic, visual and somatosensory stimuli. *Brain, 115 ( Pt 4),* 1045-1059.

Pastor, M. A., Day, B. L., & Marsden, C. D. (1993). Vestibular induced postural responses in Parkinson's disease. *Brain (London, England : 1878), 116*(5), 1177-1190. doi:10.1093/brain/116.5.1177

Patton, H. D., & Amassian, V. E. (1954). Single-unit and multiple-unit analysis of cortical stage of pyramidal tract activation. *Journal of Neurophysiology, 17*(4), 345-363.

Peters, R. M., Blouin, J.-S., Dalton, B. H., & Inglis, J. T. (2016). Older adults demonstrate superior vestibular perception for virtual rotations. *Experimental Gerontology, 82,* 50-57. doi:10.1016/j.exger.2016.05.014

Peters, R. M., Rasman, B. G., Inglis, J. T., & Blouin, J.-S. (2015). Gain and phase of perceived virtual rotation evoked by electrical vestibular stimuli. *Journal of Neurophysiology, 114*(1), 264-273. doi:10.1152/jn.00114.2015

Peterson, B. W., Fukushima, K., Hirai, N., Schor, R. H., & Wilson, V. J. (1980). Responses of vestibulospinal and reticulospinal neurons to sinusoidal vestibular stimulation. *Journal of Neurophysiology, 43*(5), 1236-1250. doi:10.1152/jn.1980.43.5.1236

Phillips, C., & Porter, R. (1977). *Corticospinal neurones: their role in movement*. London: Academic press.

Pierrot-Deseilligny, E., Lacert, P., & Cathala, H. P. (1971). Amplitude et variabilité des réflexes monosynaptiques avant un mouvement volontaire. *Physiology and Behavior, 7*(4), 495-508. doi:http://dx.doi.org/10.1016/0031-9384(71)90100-4

Polson, M. J. R., Barker, A. T., & Freeston, I. L. (1982). Stimulation of nerve trunks with time-varying magnetic-fields. *Medical and Biological Engineering and Computing, 20*(2), 243-244. doi:10.1007/bf02441362

Popov, K. E., Smetanin, B. N., Gurfinkel, V. S., & Kudinova, M. P. (1987). Spatial perception and vestibulomotor responses in man. *Neurophysiology (New York), 18*(6), 548-554. doi:10.1007/BF01057795

Prut, Y., & Fetz, E. E. (1999). Primate spinal interneurons show pre-movement instructed delay activity. *Nature, 401*(6753), 590-594. doi:10.1038/44145

Rea, P. (2015). Chapter 9 - Spinal Tracts – Descending/Motor Pathways. In *Essential Clinical Anatomy of the Nervous System* (pp. 161-176). San Diego: Academic Press.

Reynolds, R. F. (2010). The effect of voluntary sway control on the early and late components of the vestibular-evoked postural response. *Experimental Brain Research, 201*(2), 133-139. doi:10.1007/s00221-009-2017-9

Riddle, C. N., Edgley, S. A., & Baker, S. N. (2009). Direct and Indirect Connections with Upper Limb Motoneurons from the Primate Reticulospinal Tract. *The Journal of neuroscience : the official journal of the Society for Neuroscience, 29*(15), 4993-4999. doi:10.1523/JNEUROSCI.3720-08.2009

Roosink, M., & Zijdewind, I. (2010). Corticospinal excitability during observation and imagery of simple and complex hand tasks: Implications for motor rehabilitation. *Behavioural Brain Research, 213*(1), 35-41. doi:10.1016/j.bbr.2010.04.027

Rosenberg, J. R., Amjad, A. M., Breeze, P., Brillinger, D. R., & Halliday, D. M. (1989). The Fourier approach to the identification of functional coupling between neuronal spike trains. *Progress in Biophysics and Molecular Biology, 53*(1), 1-31.

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., & Safety, T. M. S. C. G. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology, 120*(12), 2008-2039. doi:10.1016/j.clinph.2009.08.016

Rossini, P. M., Barker, A. T., Berardelli, A., Caramia, M. D., Caruso, G., Cracco, R. Q., . . . Tomberg, C. (1994). Noninvasive electrical and magnetic stimulation of the brain, spinal-cord and roots - basic principle and procedures for routine clinical-application-report of an IFCN committee. *Electroencephalography and Clinical Neurophysiology, 91*(2), 79-92. doi:10.1016/0013-4694(94)90029-9

Rothwell, J. C. (1997). Techniques and mechanisms of action of transcranial stimulation of the human motor cortex. *Journal of Neuroscience Methods, 74*(2), 113-122. doi:10.1016/s0165-0270(97)02242-5

Rothwell, J. C., Thompson, P. D., Day, B. L., Boyd, S., & Marsden, C. D. (1991). Stimulation of the human motor cortex through the scalp. *Experimental Physiology, 76*(2), 159-200.

Ruckenstein, M. J. (2004). *Comprehensive review of otolaryngology (1st edition)*. New York: Saunders.

Schmidt, R. A. (1982). *Motor Control and Learning: A Behavioural Emphasis* Champaign, IL: Human Kinetics.

Schmidt, R. A., & Lee, T. D. (2011). *Motor Control and Learning: a behavioral emphasis* (5th ed.). Champaign, IL: Human Kinetics.

Scott, S. H. (2003). The role of primary motor cortex in goal-directed movements: insights from neurophysiological studies on non-human primates. *Current Opinion in Neurobiology, 13*(6), 671-677. doi:https://doi.org/10.1016/j.conb.2003.10.012

Séverac Cauquil, A., Faldon, M., Popov, K., Day, B. L., & Bronstein, A. M. (2003). Short-latency eye movements evoked by near-threshold galvanic vestibular stimulation. *Experimental Brain Research, 148*(3), 414-418. doi:10.1007/s00221-002-1326-z

Shaffer, S. W., & Harrison, A. L. (2007). Aging of the somatosensory system: a translational perspective. *Physical Therapy, 87*(2), 193-207. doi:10.2522/ptj.20060083

Sleet, D. A., Moffett, D. B., & Stevens, J. (2008). CDC's research portfolio in older adult fall prevention: a review of progress, 1985-2005, and future research directions. *J Safety Res, 39*(3), 259-267. doi:10.1016/j.jsr.2008.05.003

Slijper, H., Latash, M. L., & Mordkoff, J. T. (2002). Anticipatory postural adjustments under simple and choice reaction time conditions. *Brain Research, 924*(2), 184-197.

Smith, C. P., Allsop, J. E., Mistry, M., & Reynolds, R. F. (2017). Co-ordination of the upper and lower limbs for vestibular control of balance. *The Journal of Physiology, 595*(21), 6771-6782. doi:doi:10.1113/JP274272

Smith, C. P., & Reynolds, R. F. (2017). Vestibular feedback maintains reaching accuracy during body movement. *The Journal of Physiology, 595*(4), 1339-1349. doi:10.1113/JP273125

Stefan, K., Kunesch, E., Cohen, L. G., Benecke, R., & Classen, J. (2000). Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain, 123*(3), 572-584. doi:10.1093/brain/123.3.572

Stinear, C. M., Coxon, J. P., & Byblow, W. D. (2009). Primary motor cortex and movement prevention: Where Stop meets Go. *Neuroscience and Biobehavioral Reviews, 33*(5), 662-673. doi:10.1016/j.neubiorev.2008.08.013

Tanji, J., & Evarts, E. V. (1976). Anticipatory activity of motor cortex neurons in relation to direction of an intended movement. *Journal of Neurophysiology, 39*(5), 1062-1068.

Tarkka, I. M., McKay, W. B., Sherwood, A. M., & Dimitrijevic, M. R. (1995). Early and late motor evoked potentials reflect preset agonist-antagonist organization in lower limb muscles. *Muscle and Nerve, 18*(3), 276-282. doi:10.1002/mus.880180303

Taylor, J. L. (2006). Stimulation at the cervicomedullary junction in human subjects. *Journal of Electromyography and Kinesiology, 16*(3), 215-223. doi:10.1016/j.jelekin.2005.07.001

Taylor, J. L., Butler, J. E., & Gandevia, S. C. (1999). Altered responses of human elbow flexors to peripheral-nerve and cortical stimulation during a sustained maximal voluntary contraction. *Experimental Brain Research, 127*(1), 108-115. doi:10.1007/s002210050779

Taylor, J. L., & Gandevia, S. C. (2004). Noninvasive stimulation of the human corticospinal tract. *J Appl Physiol (1985), 96*(4), 1496-1503. doi:10.1152/japplphysiol.01116.2003

Taylor, J. L., Petersen, N. T., Butler, J. E., & Gandevia, S. C. (2002). Interaction of transcranial magnetic stimulation and electrical transmastoid stimulation in human subjects. *The Journal of Physiology, 541*(Pt 3), 949-958. doi:10.1113/jphysiol.2002.016782

Tomberg, C., & Caramia, M. D. (1991). Prime mover muscle in finger lift or finger flexion reaction times: identification with transcranial magnetic stimulation. *Electroencephalography and Clinical Neurophysiology, 81*(4), 319-322.

Touge, T., Taylor, J. L., & Rothwell, J. C. (1998). Reduced excitability of the cortico-spinal system during the warning period of a reaction time task. *Electroencephalography and Clinical Neurophysiology, 109*(6), 489-495.

Ugawa, Y., Rothwell, J. C., Day, B. L., Thompson, P. D., & Marsden, C. D. (1991). Percutaneous electrical stimulation of corticospinal pathways at the level of the pyramidal decussation in humans. *Annals of Neurology, 29*(4), 418-427. doi:10.1002/ana.410290413

Valls-Sole, J., Kumru, H., & Kofler, M. (2008). Interaction between startle and voluntary reactions in humans. *Experimental Brain Research, 187*(4), 497-507. doi:10.1007/s00221-008-1402-0

Valls-Solé, J., Rothwell, J. C., Goulart, F., Cossu, G., & Muñoz, E. (1999). Patterned ballistic movements triggered by a startle in healthy humans. *The Journal of Physiology, 516*(Pt 3), 931-938. doi:10.1111/j.1469-7793.1999.0931u.x

van Donkelaar, P., & Franks, I. M. (1991). The effects of changing movement velocity and complexity on response preparation: evidence from latency, kinematic, and EMG measures. *Experimental Brain Research, 83*(3), 618-632. doi:10.1007/bf00229840

Waldman, S. D. (2009). CHAPTER 104 - The Extrapyramidal System. In *Pain Review* (pp. 179-181). Philadelphia: W.B. Saunders.

Wallace, J. W., Rasman, B. G., & Dalton, B. H. (2018). Vestibular-Evoked Responses Indicate a Functional Role for Intrinsic Foot Muscles During Standing Balance. *Neuroscience, 377*, 150-160. doi:10.1016/j.neuroscience.2018.02.036

Watson, S. R. D., Brizuela, A. E., Curthoys, I. S., Colebatch, J. G., MacDougall, H. G., & Halmagyi, G. M. (1998). Maintained ocular torsion produced by bilateral and unilateral galvanic (DC) vestibular stimulation in humans. *Experimental Brain Research, 122*(4), 453-458. doi:10.1007/s002210050533

Weerdesteyn, V., Laing, A. C., & Robinovitch, S. N. (2008). Automated postural responses are modified in a functional manner by instruction. *Experimental Brain Research. Experimentelle Hirnforschung. Experimentation Cerebrale, 186*(4), 571-580. doi:10.1007/s00221-007-1260-1

Welgampola, M. S., & Colebatch, J. G. (2001). Vestibulospinal reflexes: quantitative effects of sensory feedback and postural task. *Experimental Brain Research, 139*(3), 345-353.

Welgampola, M. S., & Colebatch, J. G. (2002). Selective effects of ageing on vestibular-dependent lower limb responses following galvanic stimulation. *Clinical Neurophysiology, 113*(4), 528-534. doi:10.1016/S1388-2457(02)00020-2

Welniarz, Q., Dusart, I., & Roze, E. (2017). The corticospinal tract: Evolution, development, and human disorders. *Developmental Neurobiology, 77*(7), 810-829. doi:10.1002/dneu.22455

Wickens, J., Hyland, B., & Anson, G. (1994). Cortical cell assemblies: a possible mechanism for motor programs. *Journal of Motor Behavior, 26*(2), 66-82. doi:10.1080/00222895.1994.9941663

Wilson, V. J., & Peterson, B. W. (1981). Vestibulosponal and reticulospinal system. In V. B. Brooks (Ed.), *Handbook of Physiology, section 1, The Nervous System, vol II, Motor Control, part 1* (pp. 667-702). Bethesda, MD: American Physiological Society.

Wilson, V. J., Peterson, B. W., Fukushima, K., Hirai, N., & Uchino, Y. (1979). Analysis of vestibulocollic reflexes by sinusoidal polarization of vestibular afferent fibers. *Journal of Neurophysiology, 42*(2), 331-346. doi:10.1152/jn.1979.42.2.331

Yacyshyn, A. F., Woo, E. J., Price, M. C., & McNeil, C. J. (2016). Motoneuron responsiveness to corticospinal tract stimulation during the silent period induced by transcranial magnetic stimulation. *Experimental Brain Research, 234*(12), 3457-3463. doi:10.1007/s00221-016-4742-1

Ziemann, U., & Hallett, M. (2000). Basic neurophysiological studies with TMS. In M. S. B. Gerorge, R.M. (Ed.), *Transcranial Magnetic Stimulation in Neuropsychiatry*. Washington: American Psychiatric Press.

Zink, R., Steddin, S., Weiss, A., Brandt, T., & Dieterich, M. (1997). Galvanic vestibular stimulation in humans: effects on otolith function in roll. *Neuroscience Letters, 232*(3), 171-174. doi:10.1016/s0304-3940(97)00610-1

## Appendices

**Appendix A.** Interaction of motoneuron excitability over time between two groups of participants. The first demonstrated no RT differences between the 2- and 3- movement conditions (straight black line) and the second demonstrated RT differences between the 2- and 3-movement conditions (dotted black line).