

BIPEDAL HOPPING TIMED WITH A METRONOME TO DETECT IMPAIRMENTS IN
ANTICIPATORY MOTOR CONTROL IN PEOPLE WITH MILD MULTIPLE SCLEROSIS

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Abstract

Background: People with mild multiple sclerosis (MS) often report difficulty in balance and cognition but display no measurable deficits on many clinical assessments. We examined whether hopping to a metronome beat has the potential to detect anticipatory motor control deficits among people with mild MS (Expanded Disease Severity Score ≤ 3.5).

Methods: Participants with MS (n=13), matched controls (n=9), and elderly subjects (n=13) completed tests of cognition (Montreal Cognitive Assessment (MoCA)) and motor performance (Timed 25 Foot Walk Test (T25FWT)). Participants performed two bipedal hopping tasks: at 40 beats/minute (bpm) and 60-bpm in random order. Hop characteristics (length, symmetry, variability) and delay from the metronome beat were extracted from an instrumented walkway and compared between groups using a one-way ANOVA.

Results: The MS group became more delayed from the metronome beat over time whereas elderly subjects tended to hop closer to the beat during 40-bpm ($F=3.58$, $p=0.04$). Delay of the first hop during 60-bpm predicted cognition in people with MS ($R=0.55$, $\beta=4.64$ (SD 4.63), $F=4.85$, $p=0.05$) but not among control ($R=0.07$, $p=0.86$) or elderly subjects ($R=0.17$, $p=0.57$). In terms of hopping characteristics, people with MS performed similarly to the matched controls during 60-bpm, but shifted towards the elderly subjects' ability during 40-bpm.

Conclusions: This new timed hopping test may be able to detect both physical ability and feed-forward anticipatory control impairments in people with mild MS. Hopping at a frequency of 40-bpm seemed more challenging. Two aspects of anticipatory motor control can be measured: response time to the first metronome cue and the ability to adapt and anticipate the beat over time.

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List of Abbreviations

MS: Multiple Sclerosis

CNS: Central Nervous System

CIS: Clinically Isolated Syndrome

RRMS: Relapsing-Remitting Multiple Sclerosis

MRI: Magnetic Resonance Imaging

WML: White Matter Lesion

GML: Grey Matter Lesion

EDSS: Expanded Disability Status Scale

T25FWT: Timed Twenty-Five Foot Walk Test

BPM: Beats Per Minute

NHPT: Nine-Hole Peg Test

CoP: Center of Pressure

PD: Parkinson's Disease

RAS: Rhythmic Auditory Stimulation

CV: Coefficient of Variability

p: Calculated Probability

F: F-Statistic

SD: Standard Deviation

t: t-Statistic

R: Regression Coefficient

Chapter 1: Introduction and Literature Review

1.1 GENERAL INTRODUCTION

Multiple sclerosis (MS) is a demyelinating, neurodegenerative disease of the central nervous system (CNS) with an uncertain pattern of progression (National Multiple Sclerosis Society). Although a heterogeneous disease, a picture of a typical MS patients can be depicted as a female around 20-40 years old presenting with neurological symptoms such as vision loss, balance impairment, difficulties with walking and other sensory impairment; and these impairments are in conjunction with lesions to the CNS as viewed through Magnetic Resonance Imaging (MRI). During the 20 years following diagnosis, a typical patient will gradually lose the ability to walk independently, have difficulties with bowel and bladder control, will progressively think slower and struggle with cognitive impairment, and will experience high levels of fatigue. On average, the majority of these patients will use a walking aid 20 years after diagnosis.

Early in the disease course, prior to physical disability, there are often undetectable underlying inflammatory mechanisms occurring, causing lesions to the CNS and degeneration (Grigoriadis & van Pesch, 2015). Once a clinical symptom emerges, medications and therapy are prescribed in an attempt to slow or halt accumulating lesions and degeneration, however, eventually these physiological impairments accumulate to cause a wide range of disability (Fahrbach et al., 2013). Once physical impairment can be measured using clinical assessments, treatment efficacy is based on improvement or decline in physical functioning and reduction of disease relapses (Broadley et al., 2014). However, there remains a period, early in the disease,

where it is difficult to measure subtle changes in physical functioning, leaving physicians and researchers uncertain as to the efficacy of treatments.

The ability to expose deficits in individuals with MS early in the disease course could help play a pivotal role in targeting therapy and interventions for this group to halt or slow the progression of disability. Previous work has shown that bipedal hopping can detect motor deficits in individuals with MS in the low Expanded Disability Status Scale (EDSS) range ($EDSS \leq 3.5$) (Kirkland et al., 2016). However, not all individuals present with primary motor deficits; some have primarily sensory or cognitive deficits (DeLuca & Nocentini, 2011). Therefore, adding a sensory/cognitive domain to bipedal hopping may expose and measure both motor and mixed deficits. In this study, we added a metronome while hopping in order to determine whether individuals with MS would be able to synchronize hopping to a metronome to the same extent as a control group, and whether potential impairments in timing were suggestive of an early form of senescence by comparing performance among people with MS to an elderly control group.

This thesis is prepared in manuscript format with three chapters. Chapter One provides an overview of MS and associated impairments, followed by an explanation of bipedal hopping and the previous use of hopping in MS. The metronome task is explained, including neural pathways of motor entrainment, sensorimotor synchronization and the use of rhythmic auditory stimulation in MS. Chapter Two is a manuscript measuring metronome hopping in individuals with mild MS compared to control and elderly groups (age ≥ 70 years). This manuscript is written in the format for publication in *Clinical Biomechanics*. Lastly, Chapter Three concludes with an expanded discussion on potential mechanisms underlying impaired metronome timing in individuals with MS and why differences in hopping and metronome timing could be similar and different from

the effects of senescence, respectively. Chapter Three concludes with suggestions for future directions in developing metronome hopping as both an outcome measure and clinical assessment tool, and discusses limitations of this study.

1.2 OVERVIEW OF MULTIPLE SCLEROSIS

1.2.1 *Epidemiology*

MS is a demyelinating, neurodegenerative disease of the CNS that affects over 2.3 million people worldwide (National Multiple Sclerosis Society). Typically diagnosed during the early ages of adulthood (20-40 years old), many newly diagnosed individuals with MS are in the midst of starting careers and families (National Multiple Sclerosis Society). There is no known cause of MS, but many environmental and genetic factors have been proposed that increase susceptibility for this disease (Sadovnick & Ebers, 1993). The most prominent environmental factors associated with the risk of developing MS are low vitamin D levels (Bjørnevik et al., 2014; Cortese et al., 2015; Munger, Levin, Hollis, Howard, & Ascherio, 2006), Epstein-Barr virus exposure (Handel et al., 2010), early-life obesity (Hedström, Lima Bomfim, et al., 2014; Munger et al., 2013; Munger, Chitnis, & Ascherio, 2009) and smoking (Handel et al., 2011; Hawkes, 2007; Hedström, Alfredsson, et al., 2014; Hedström, Bäärnhielm, Olsson, & Alfredsson, 2009, 2011; Hedström, Ryner, et al., 2014; Heydarpour et al., 2014). Genetic factors also play a role in creating a ‘perfect storm’ for MS susceptibility. People with MS share some of the same genetic characteristics of people with other autoimmune diseases such as rheumatoid arthritis (Sadovnick, Dyment, & Ebers, 1997). These characteristics include genes involved in vitamin D binding, cytokine cascades and immune system regulation (Sawcer et al., 2011). Thus,

it is likely that a combination of both genetic predisposition and exposure to environmental factors can be attributed to susceptibility of developing MS.

1.2.2 Diagnosis and Disease Course

The disease course of MS varies from patient to patient and is highly unpredictable. Typically, the course of MS does not actually begin at diagnosis but much earlier, presenting as a single clinical episode. This is often first diagnosed as Clinically Isolated Syndrome (CIS; explained below) (Odenthal & Coulthard, 2015). Then, upon subsequent clinical episodes or radiological disease activity, the MS diagnosis is made (Katz Sand, 2015). Therefore, a significant period of disease activity and impairment accumulation occurs even before MS diagnosis (Miller et al., 2008). From diagnosis, there are three disease trajectories: benign (least common), relapsing-remitting (RRMS, most common) and progressive. Over time, almost all individuals with MS transition into a progressive course (Katz Sand, 2015). This heterogeneity between type and time of progression of impairment makes this disease very unpredictable, contributing to further psychological burden due to uncertainty about the future (Ghafari, Fallahi-Khoshknab, Nourozi, & Mohammadi, 2015).

Prior to MS diagnosis, 85% of individuals with MS present with a first episode of focal neurologic symptoms of CIS, such as sensory symptoms, blurred vision, ataxia and/or weakness (Compston & Coles, 2008). CIS is an acute episode of neurological dysfunction due to inflammatory demyelination (Miller et al., 2008). These attacks are indistinguishable from an MS relapse, except that they do not yet satisfy the MS diagnosis criteria of dissemination in both space and time (Brownlee & Miller, 2014). About two thirds of individuals with CIS will later be

diagnosed with MS as dissemination in space and time are both satisfied, usually with a second attack or further disease activity seen on MRI (Katz Sand, 2015). Dissemination in space is confirmed by at least two lesions in the CNS in different areas typically affected by MS. At least one of these lesions must be paraventricular, juxtacortical, infratentorial or in the spinal cord. Dissemination in time is satisfied if the MS lesions have developed over time, often confirmed by multiple attacks and the subsequent formation of new lesions over time (Katz Sand, 2015). There are three common syndromes in which CIS will first present itself: (a) spinal cord syndrome, (b) optic neuritis and (c) brainstem syndromes (Miller et al., 2008). Sensory symptoms caused by myelitis in a short segment of the spinal cord are the most common CIS syndrome (Eriksson, Andersen, & Runmarker, 2003). These sensory symptoms often start in one limb and ascend to a level involving the trunk or to the contralateral side (Eriksson et al., 2003). Mild sphincter disturbance is also a common symptom in spinal cord syndrome (Eriksson et al., 2003). Optic neuritis is the first symptom experienced by about 20% of individuals with MS and typically presents as blurring of vision in one eye and pain during eye movement (Balcer, 2001). Lastly, brainstem syndromes are experienced by about 25% of individuals with CIS and can present as double vision (most common), facial sensory loss, facial weakness, cerebellar ataxia, vertigo or paroxysmal symptoms referable to the brainstem (Brownlee & Miller, 2014; Miller et al., 2008). Importantly, although not yet meeting the MRI dissemination in time and space criteria to be diagnosed with MS, individuals with CIS experience lesions in the CNS and consequently develop associated impairment. Particularly, lesions affecting the brainstem and spinal cord, which are the most typical lesion sites in individuals with CIS, are associated with a higher risk of disability progression (Swanton et al., 2009; Tintore et al., 2010). There is no treatment or effective measures to prevent the development MS, therefore, the current objective

is to measure and monitor the abilities of individuals with CIS in the hopes that a second episode does not occur, leading to a diagnosis of MS.

There are two types of MS that are typically diagnosed. The most common, RRMS, is defined as clinical stability with intermittent periods of acute exacerbation in the disease that either completely or almost completely recovers (Katz Sand, 2015). These exacerbations and associated findings on an MRI are the basis of diagnosis. As previously mentioned, diagnosis is confirmed if the MRI reveals dissemination in both space and time (Katz Sand, 2015). Following a relapsing remitting course, about 60-70% of individuals with MS will shift to a progressive disease course by 20 years following a first event (secondary-progressive MS) (Scalfari, Neuhaus, Daumer, Muraro, & Ebers, 2014). The second type of MS typically diagnosed is primary progressive MS, defined as progressive decline in neurological function from disease onset. To be diagnosed as primary progressive MS, individuals must present with clinical progression for at least one year following symptom onset as well as evidence of dissemination in space on an MRI image (Katz Sand, 2015). Therefore, dependent on the type of MS diagnosed, individuals will typically have either a course of acute episodes followed by remission, or a steady decline in functioning. However, there is vast heterogeneity among individuals who do not always follow a typical pattern, thus resulting in uncertainty following diagnosis (Ghafari et al., 2015). Regardless of diagnosis type, white and grey matter lesions as well as axonal degeneration begins at very early stages of the disease process, resulting in cognitive impairment and subtle sensorimotor changes (Biberacher et al., 2015; Kuceyeski et al., 2015; Nygaard et al., 2015; Pérez-Miralles et al., 2013; Rojas, Patrucco, Míguez, Besada, & Cristiano, 2015).

1.2.3 Lesions and Neurodegeneration

1.2.3.1 White Matter Lesions

In white matter lesions (WMLs), there is a profound disturbance of the blood brain barrier due to damage of tight junctions (Hochmeister et al., 2006; Kebir et al., 2007; Kirk, Plumb, Mirakhor, & McQuaid, 2003), and resulting perivascular infiltration of leukocytes leading to damaged myelin and axons (Booss, Esiri, Tourtellotte, & Mason, 1983; Disanto, Morahan, Barnett, Giovannoni, & Ramagopalan, 2012; Kaur, Trowsdale, & Fugger, 2013; Wucherpfennig et al., 1992). Various T cells may also play a role in MS lesions. Specifically, lesion formation is speculated to be initiated by CD4⁺ T cells and amplified by cytotoxic CD8⁺ T cells (McFarland & Martin, 2007; Prins et al., 2015; Sospedra & Martin, 2016). However, lesions are still able to form in the absence of T cells, suggesting that B cells may also play a crucial role in lesion formation (Prins et al., 2015). Two types of macrophages are expressed in MS WMLs: M1, which expresses pro-inflammatory and cytotoxic factors and therefore contributes to demyelination and axonal damage, and M2, which secretes anti-inflammatory and growth factors, creating a protective environment (Mosser & Edwards, 2008; Prins et al., 2015). Depending on the distribution of these macrophages, lesions can either be formed and maintained, or have the potential to be repaired and remyelinated with the presence of M2 macrophages. Unfortunately, in active WMLs, most macrophages display an M1 activation status (Vogel et al., 2013). In addition, astrocytes function as immunocompetent cells and secrete either neurotropic and/or neurotoxic factors, hence they too can help or hinder the formation of inflammatory lesions dependent on their activation status (Prins et al., 2015). Microglia and astrocyte activation happens even before infiltration of immune cells, and therefore may be

involved in signalling an immune response and subsequent migration of leukocytes to the lesion site (D'Amelio, Smith, & Eng, 1990; Morcos, Lee, & Levin, 2003; Ponomarev, Shriver, Maresz, & Dittel, 2005). Moreover, microglia tend to be found near the border of lesions, which is also the site where extensive oligodendrocyte damage occurs (Peterson, Bö, Mörk, Chang, & Trapp, 2001). Therefore, these cells may be the driving force behind the formation of new WMLs. However, glial cells also play a beneficial role as they are crucial for remyelination (Kotter, Zhao, van Rooijen, & Franklin, 2005; Miljković, Timotijević, & Mostarica Stojković, 2011; Rawji & Yong, 2013; Voss et al., 2012), demonstrating the dual role of glial cells in MS lesions (Prins et al., 2015). Importantly, these lesions arise in various areas of the CNS, creating heterogeneity in disability across the MS population (Faizy et al., 2016). In addition to WMLs, there is emerging evidence to indicate that lesions also occur in grey matter.

1.2.3.2 Grey Matter Lesions

MS was originally thought to be a disease of WMLs, and not until recently has it become evident that lesions also occur in grey matter (Bagnato et al., 2006; Bö, Geurts, van der Valk, Polman, & Barkhof, 2007; Calabrese et al., 2007; Calabrese, Rocca, et al., 2009; Filippi et al., 2013; Kutzelnigg et al., 2005; Lucchinetti et al., 2011; Sethi et al., 2012). Grey matter includes the cell bodies and dendrites within the CNS, whereas white matter consists of myelinated axons that transmit information originating in the grey matter (Filippi, Tortorella, & Bozzali, 1999). Grey matter lesions (GMLs) may occur in various regions of the brain, such as the cerebral cortex (Gilmore et al., 2009; Kutzelnigg et al., 2005; Vercellino et al., 2005), thalamus (Gilmore et al., 2009; Vercellino et al., 2005), hippocampus (Geurts et al., 2007; Papadopoulos et al., 2009), cerebellum (Geurts et al., 2007; Gilmore et al., 2009; Kutzelnigg et al., 2007; Kutzelnigg

et al., 2005; Papadopoulos et al., 2009; Vercellino et al., 2005) and the spinal cord grey matter (Gilmore et al., 2009; Prins et al., 2015). There are three pathological patterns for GMLs: type I are leukocortical lesions that include both subcortical white matter and cortex, type II are lesions in the cortex without extending to the surface of the brain or subcortical white matter, and type III lesions extend from the pial surface to the cortex and are considered subpial (Peterson et al., 2001; Prins et al., 2015). There is also an emerging 4th category, type IV, which describes lesions extending throughout the full width of the cerebral cortex without affecting the white matter (Bø, Vedeler, Nyland, Trapp, & Mørk, 2003). GMLs do not form in the same manner as WMLs. GMLs have far fewer infiltrated leukocytes than WMLs, and consequently display fewer T-cells, microglia and astrocytes (Peterson et al., 2001; Prins et al., 2015). The exact mechanism then of GMLs is unknown, but it has been proposed that a model of oxidative stress, mitochondrial damage and resulting state of hypoxia may be responsible for grey matter damage (Friese, Schattling, & Fugger, 2014; Lassmann & van Horssen, 2011; Trapp & Stys, 2009). GMLs have been associated with a vast number of impairments related to MS, and have helped to explain why many impairments cannot be explained by WMLs alone. Clinical features including cognitive impairment and memory loss have now been explained by GMLs in deep cortical structures such as the thalamus, hippocampus and amygdala (Calabrese, Agosta, et al., 2009). Furthermore, recognizing now that GMLs exist in the cerebellum provides a better explanation for impairments in motor learning and incoordination experienced by many individuals with MS (Geurts et al., 2007; Gilmore et al., 2009; Kincses et al., 2011; Kutzelnigg et al., 2007; Kutzelnigg et al., 2005; Papadopoulos et al., 2009; Vercellino et al., 2005). Importantly, GMLs can occur early in the disease process, and can precede the formation of WMLs (Calabrese et al., 2010; Calabrese et al., 2007). Although our understanding of GMLs is growing, detecting these

lesions on an MRI is extremely difficult compared to WMLs (van Munster, Jonkman, Weinstein, Uitdehaag, & Geurts, 2015) for a number of reasons: (a) due to the small amount of myelin in grey matter, the loss of this myelin elicits very little contrast (Newcombe et al., 1991), (b) grey matter lesions are typically small in size, and therefore cannot be detected on MRI unless there is sufficient spatial resolution (Pitt et al., 2010; Seewann et al., 2011) and (c) it can be hard to distinguish lesions from the surrounding normal tissue due to volume effects of nearby cerebrospinal fluid (Kidd et al., 1999). More advanced MRI techniques are being pioneered in attempt to better detect GMLs such as diffusion tensor imaging and proton magnetic resonance spectroscopy (Inglese, Oesingmann, Casaccia, & Fleysler, 2011). However, the expertise and high-grade equipment needed to perform these scans are impractical for use in clinical settings. Therefore, it would be more practical to develop simple clinical assessment tools to test for impairments known to be caused by GMLs, and draw clinical conclusions on the presence and progression of these lesions.

1.2.3.3 Axonal Degeneration

In addition to the accumulation of both white and grey matter lesions, axonal degeneration is also a hallmark of MS. MS was originally believed to be a purely inflammatory disease during the relapsing-remitting phase, and a purely axonal neurodegenerative disease upon transition to a progressive disease course (Steinman, 2001). However, we now know that degeneration occurs very early in the disease course, in conjunction with inflammation (De Stefano et al., 2002; Kuhlmann, Lingfeld, Bitsch, Schuchardt, & Brück, 2002). This axonal loss begins as early as CIS, but is counteracted by neuroprotection and is therefore clinically silent until a threshold level of axonal loss is achieved due to exhaustion of these compensatory

resources (Confavreux, Vukusic, Moreau, & Adeleine, 2000; Wujek et al., 2002). The exact mechanism of neurodegeneration is unclear, but it has been suggested that mitochondrial dysfunction and accumulating oxidative stress triggered by inflammatory mechanisms, are the causes of axonal loss (Grigoriadis & van Pesch, 2015; Lassmann, 2014). Axonal loss is highly correlated to disability, particularly loss of walking ability (Peterson & Fujinami, 2007). Therefore, early, accumulating axonal loss may contribute to disability progression over the disease course. One of the most common sites of axonal degeneration is in the corpus callosum (Evangelou et al., 2000). The anterior two thirds of the corpus callosum is critical for coordinating bilateral movement (Preilowski, 1972), such as walking, and thus it is plausible that degeneration in this area is related to loss of walking ability. However, this progressive decline in walking ability due to neurodegeneration can be slowed. Individuals with MS undergoing rehabilitation programs have been shown to maintain bilateral coordination abilities and preserve white matter integrity in the corpus callosum more effectively than those not receiving rehabilitation (Bonzano et al., 2014). Therefore, being able to detect accumulation of degeneration in the corpus callosum prior to loss of walking ability is critical for highlighting individuals in need of rehabilitation in order to slow the progression of this axonal loss and help individuals with MS maintain walking ability longer.

1.2.4 MS Similarities to Senescence

It has been demonstrated that individuals with MS have what appears to be premature aging of the neuroimmune system (Thewissen et al., 2005). Individuals with autoimmune disease (such as Rheumatoid Arthritis and MS) had decreased number of T-cell receptor excision circles and increased frequency of CD4+CD28 (null) T cells than control subjects matched for age

(Thewissen et al., 2005). These specialized T-cells play a role in infiltrating the blood-brain barrier and causing inflammatory WML's (described in page 6-7). Interestingly, elderly individuals display T-cell counts similar to younger individuals with T-cell autoimmune disease, indicating these changes may naturally occur with aging (Thewissen et al., 2005). Resultantly, there is a high prevalence of blood-brain barrier dysfunction and resulting WMLs in elderly individuals, and this prevalence increases with age (de Leeuw et al., 2001; Xiong & Mok, 2011). Blood-brain barrier dysfunction and WMLs are also characteristic of MS (described in page 6-7). Therefore, immune system regulation, specifically in regards to T-cells, naturally declines with age, but seems to occur prematurely in individuals with MS (Thewissen et al., 2005). It is therefore conceivable that MS-related impairments in sensorimotor function and cognition could resemble similar impairments in the elderly due to parallel patterns of inflammatory regulation and resultant WMLs. Thus, there is justification in comparing individuals with MS to elderly adults to determine whether impairments are a result of early senescence or are unique to MS. Similarities and differences between MS impairment and senescence are summarized in Table 1.1.

Table 1.1 Comparison of MS and senescence.

Characteristic	MS	Senescence
White Matter Lesions	Yes ¹	Yes ²
Grey Matter Lesions	Yes ³	Yes ⁴
Corticospinal Tract Degeneration	Yes ⁵	Yes ⁶
		Manifests around age 50
Neural Muscle Drive	Reduction ⁷	Reduction ⁶
Muscle Weakness	Yes ⁷	Yes ⁶
Type II Muscle Fibres	Atrophy ⁸	Atrophy ⁹
Balance Impairment	Yes ¹⁰	Yes ¹¹
	Likely due to somatosensory conduction	Multifactorial Causation (visual, somatosensory or vestibular)
Bilateral Coordination	Impaired ¹²	Enhanced ¹³
	Due to affected corpus callosum	Increased connectivity activation across hemispheres
Spasticity	Yes ¹⁴	No ¹⁵
Cerebellar Impairment	Yes ¹⁶	Yes ¹⁷
	Typical WML, degeneration of the superior peduncle tract and GML	Atrophy specifically in the cerebellar vermis

MS: Multiple Sclerosis; WML: White Matter Lesion; GML: Grey Matter Lesion; 1-(van Nierop et al., 2017); 2-(de Leeuw et al., 2001); 3-(Bagnato et al., 2006); 4-(Thewissen et al., 2005); 5-(De Stefano et al., 2002); 6-(Jang & Seo, 2015); 7-(Stevens, Goodman, Rough, & Kraft, 2013); 8-(Garner & Widrick, 2003); 9-(Nilwik et al., 2013); 10-(Martin et al., 2006); 11-(Lin & Bhattacharyya, 2012); 12-(Kern, Sarcona, Montag, Giesser, & Sicotte, 2011); 13-(Davis, Kragel, Madden, & Cabeza, 2012); 14-(Barnes, Kent, Semlyen, & McMullen, 2003); 15-(Barnes, 2001); 16-(Penhune & Doyon, 2005); 17-(Luft et al., 1999).

1.2.5 Lesion Location and Impairment

Lesions in the CNS (both WMLs and GMLs) viewed on an MRI contribute significantly to the diagnosis and monitoring of MS disease progression (Fazekas, Soelberg-Sorensen, Comi, & Filippi, 2007). However, lesion load does not directly correlate with clinical disability, termed the clinical-radiological paradox (Amato et al., 2004; Arnett et al., 1994; Calabrese, Agosta, et al., 2009; Comi et al., 1999; De Stefano et al., 2003; Deloire et al., 2005; Foong et al., 1997; Miki et al., 1999; Nijeholt et al., 1998; Portaccio et al., 2006; Rovaris et al., 1998; Schreiber et al., 2001; Summers et al., 2008; Swirsky-Sacchetti et al., 1992). What matters is not the total volume of lesions (lesion load), but the location of lesions in the CNS in critical areas. The EDSS is the most common clinical scale for tracking progression of physical disability through walking ability in MS (Kurtzke, 1983). This score is correlated with lesions in the periventricular white matter around the posterior horns and at the left frontal horn (Kincses et al., 2011). Therefore, lesions specifically in this area will likely contribute to overall physical disability clinically measured through the EDSS. Furthermore, when dividing the EDSS into its sub-categories, significant correlations were found between sensory symptoms and lesion location in the left thalamus (Kincses et al., 2011). Additionally, impairments in coordination of movement were correlated with lesion location in the right middle cerebellar peduncles. Pyramidal lesions were not correlated with a specific subsection of the EDSS (Kincses et al., 2011). Therefore, the EDSS prompts physicians to assign one score based on a variety of impairments with differing lesion locations. Specific clinical measures with the ability to differentiate between pyramidal, sensory and coordination symptoms would provide a more useful measure of progression relative to specific lesion locations, as each location may relate to a particular motor impairment. In addition to lesions and degeneration, there are many other mechanisms of injury documented in MS, such as atrophy of the thalamus and the brain overall, which can also lead to impaired

cognitive abilities (De Stefano et al., 2016). However, for the purposes of this discussion, lesions and degeneration are the primary focus because these mechanisms of injury often lead to physical impairment. Four relevant motor impairments that will be discussed in the following section are weakness, imbalance, incoordination and spasticity.

1.3 MOTOR IMPAIRMENT

1.3.1 Muscle Weakness

People with MS tend to have less force generation during a muscle contraction (muscle weakness) due to reduced central motor drive of the corticospinal tract and subsequent reduced muscle recruitment and muscle atrophy due to disuse (Stevens et al., 2013). The corticospinal tract is the main tract carrying motor information from the brain through the spinal cord and eventually to the muscle to elicit muscle contraction (Jang, 2014). Although MS lesions commonly occur in the subcortical white matter and corona radiata (higher centers of the corticospinal tract), damage to these areas are not associated with muscle weakness (Reich et al., 2008). Weakness has been shown to be strongly associated with abnormalities further down (more caudally) in the brainstem (Reich et al., 2008). Since relevant damage related to weakness is found in the brainstem and not the periventricular inflammatory lesions common in MS, neurodegeneration may be the driving factor, rather than primary inflammation (Reich et al., 2008). Similarly, in people without MS, the corticospinal tract degenerates continuously with age, particularly manifesting around age 50 (Jang & Seo, 2015). Therefore, elderly individuals exhibit some of the same reduction in neural muscle drive as individuals with MS, and consequently also experience muscle weakness (Jang & Seo, 2015). This reduced neural drive

often translates to non-use in the muscles, consequently causing changes in muscle fibre characteristics, further contributing to muscle weakness (Stevens et al., 2013).

There are two types of skeletal muscle fibres: (a) type I (slow twitch), which have slow contraction times and a high resistance to fatigue, enabling long-endurance activities and (b) type II (fast twitch), which contract quickly and fatigue faster, thus are used in powerful bursts of movement. Furthermore, type II fibres can be split into type IIa and type IIb; type IIb are characterized by high force and speed with low endurance, whereas type IIa have more endurance and oxidative capacity but not to the extent of type I fibres (Frontera & Ochala, 2015). Muscle fibres have filaments that bind together to form cross-bridges; the head of a myosin filament connects to an actin filament. This attachment allows the actin filament to slide past the myosin filament during a power stroke in order to create a muscle contraction (Frontera & Ochala, 2015; Herzog, Leonard, Joumaa, DuVall, & Panchangam, 2012; Koubassova & Tsaturyan, 2011). Changes in muscle fibre characteristics such as thinner filaments and decreased density of cross-bridges leading to a force deficit in the muscles of MS individuals are likely due to gross atrophy of type IIa fibres and the subsequent loss in number of potential cross-bridges (Garner & Widrick, 2003). Additionally, it appears that the density (related to isoform change) of cross-bridges is reduced consequently contributing to a decrease in average force per cross-bridge in type I fibres (Garner & Widrick, 2003). These changes in muscle fibre cross-bridge characteristics, both reduction in filament thickness and cross-bridge density, cause a loss in peak force capacity from the muscle. Similarly, type II muscle fibres naturally decline in size with increasing age (Nilwik et al., 2013). Therefore, elderly individuals may experience similar reductions in peak force capacity as a person with MS, due to similar changes in type II

muscle fibre characteristics. However, resistance training for individuals with MS has been shown to both promote neuromuscular adaptations, thereby improving motor unit activation by the corticospinal tract and promoting hypertrophy of type II muscle fibres, increasing the number of cross-bridges and subsequent strength of the muscle (Nilwik et al., 2013; Stevens et al., 2013). This form of strength training is achieved during rehabilitation and can help to maintain muscle strength longer in disease progression (Stevens et al., 2013). Identifying MS individuals with muscle weakness is critical in order to refer them for these strength training rehabilitation programs in a timely manner. Therefore, clinical assessments to measure muscle strength would be beneficial for measuring and detecting weakness in individuals with MS.

1.3.2 Balance

In addition to muscle strength deficits, people with MS often have difficulties balancing. Balance is mediated by the central integration of three sensory systems to produce coordinated movement: visual, somatosensory and vestibular (Stevens et al., 2013). The visual system provides information about the environment, including locating obstacles to avoid. The somatosensory system is important for detecting the location of the body in space and the movement and force production of the extremities. Lastly, the vestibular system coordinates eye and head movements, providing body information relative to gravity and angular/linear velocity (Stevens et al., 2013). Inability to integrate these three systems as well as muscle weakness often results in balance impairment, which is displayed as decreased ability to maintain position, limited and slow movement towards limits of stability and delayed responses to postural displacements or perturbations. In terms of position, people with MS have greater standing postural sway than control subjects, with postural sway typically increasing with increasing

disability (EDSS score)(Martin et al., 2006). Also, during gait initiation, people with MS have smaller excursions of their center of pressure (CoP), move slower, and have more difficulty achieving stability boundaries than control subjects (Martin et al., 2006). Lastly, people with MS display delayed automatic postural responses to postural perturbations (Martin et al., 2006). These balance deficits have been related to slowed spinal somatosensory conduction and central integration deficits in people with MS, which are unlike imbalance in cerebellar disorders (Martin et al., 2006). These deficits have been detected in the early stages of disease progression, even in the absence of clinical disability (Martin et al., 2006), and likely contribute to the increased incidence of falls in people with MS (Cameron and Lord, 2010). Therefore, early identification of imbalance is critical in order to direct rehabilitation interventions to focus on sensory facilitation and dual-task training, which are both effective in improving balance control (Cameron & Lord, 2010). Elderly individuals also experience difficulties in balance. It is estimated that one in every five individuals over the age of 65 report difficulties with their balance (Lin & Bhattacharyya, 2012). Currently, it is not known which specific sensory system (visual, somatosensory or visual) is impaired causing imbalance in the elderly, but is likely to vary between individuals based on associated factors such as muscle weakness, prescription medications and comorbid conditions (e.g. hypertension, depression, etc.).

1.3.3 Coordination

Bilateral coordination of motor movement is a critical skill for many gross motor movements imperative to daily living, such as walking. The basis for bilateral coordination is communication between brain hemispheres to appropriately time both sides of the body relative to the other. This inter-hemispheric communication typically occurs via the corpus callosum, but

other areas of the brain also contribute to bimanual movements including: the cerebellum, supplementary motor area, cingulate motor cortex and premotor cortex (Fling, Bernard, Bo, & Langan, 2008). Performance on the Nine-Hole Peg Test (a test of manual dexterity using one hand; NHPT), for example, was related to the integrity of the transcallosal hand motor fibres in individuals with MS (Kern et al., 2011). Therefore, callosal involvement in MS may contribute to bimanual motor impairment. In relapsing-remitting MS, the corpus callosum is often affected very early in the disease course with early presence of macroscopic lesions on an MRI (Ozturk et al., 2010). However, prior to lesion appearance on an MRI, individuals with EDSS 0-2.0 already have atrophy in callosal motor fibres and reduced short-interval interhemispheric inhibition measured using transcranial magnetic stimulation (Wahl et al., 2011). Although many manual dexterity tasks exist that could expose early callosal involvement, gross bilateral tasks of the lower limb are often excluded. Walking is one of the most challenging bilateral motor tasks currently assessed in individuals with MS. However, walking involves many cortical regions and is also subcortically controlled by the central pattern generator in the spinal cord to coordinate movement (Marder & Bucher, 2001) providing compensation for any slight callosal impairment (Hamacher, Herold, Wiegel, & Schega, 2015). Therefore, a more challenging, less automated bilateral motor movement of the lower limb such as hopping may provide earlier indications of corpus callosum tract damage prior to visual inspection of a lesion on an MRI.

1.3.4 Spasticity

Spasticity refers to a condition in which certain muscles are continuously contracted, causing stiffness or tightness in the muscle (Stevens et al., 2013). Spasticity is common among the MS population, with 47% of individuals with MS reporting clinically significant spasticity in

at least one leg (Barnes et al., 2003). Most commonly, spasticity in individuals with MS is reported in the lower limbs (Barnes et al., 2003). Specifically, there are four muscle groups that are commonly spastic: (a) plantarflexors, which cause the toe to point downwards and makes toe clearance difficult during gait; (b) hamstrings, which cause difficulty achieving full extension of the knee and often results in decreased swing duration and consequent shortened stride length during gait; (c) quadriceps, which makes bending the knee difficult, thereby causing problems in advancing the leg during gait and; (d) hip adductors, which decrease efficiency of gait and decrease stride length, resulting in a scissoring gait (extreme adduction resulting in the knees or thighs crossing while walking) (Stevens et al., 2013). Additionally, spasticity in antagonist muscles causes co-contraction, which results in negative biomechanical work as the antagonist muscle is working against the primary muscle. Since these muscles are working in opposition, more effort is needed for the primary muscle to overcome the antagonist muscle to perform the task and contributes to inefficiencies during gait and resultant increased energy consumption. Spasticity is a manifestation of pyramidal tract involvement, and although easily quantified, it can be hard to manage clinically. Various oral medications (such as benzodiazepines) and injections (such as botulinum toxin) are often prescribed in an attempt to alleviate and manage spasticity (Heinzlef & Monteil-Roch, 2012). Also, rehabilitation therapy focused on stretching and increasing passive range of motion can be useful in reducing spasticity (Cameron & Lord, 2010). This is important, as co-contraction of the antagonist muscle during a gross motor movement largely interferes with the performance of that movement. Therefore, when the impairment is identified, rehabilitation can help to alleviate spasticity, as well as improve balance and coordination, and maintain muscle strength.

1.4 REHABILITATION AND MEASUREMENT

1.4.1 Rehabilitation Goals and Importance of Measurement Tools

Rehabilitation is critical in the field of MS to slow progression of motor deficits by maintaining physical functioning (Campbell et al., 2016; Kalron et al., 2015). However, unlike other rehabilitation areas such as stroke, the primary goal of MS rehabilitation is preservation of physical functioning rather than improvement of physical functioning (Dalgas, 2011; Peresedova, Chernikova, & Zavalishin, 2013). This is because MS is overall a progressive disease throughout the lifespan. Therefore, maintenance of physical functioning, particularly ambulation, for longer periods of time is considered successful rehabilitation. For instance, physiotherapy has been shown to be effective in slowing decline in functioning in people with progressive MS (Campbell et al., 2016) and Kalron et al. (2015) found that walking ability can be preserved for longer periods with rehabilitation (Kalron et al., 2015). However, due to the heterogeneity of MS, generic rehabilitation programs (for example exercise provided in groups) are not as effective as programs that are personalized to the individual patient (Rannisto et al., 2015). Thus, clinical outcome measurements are imperative to highlight the type of impairment, thus directing the type of rehabilitation program to use and determining whether these programs are effective by accurately tracking progression over time. For instance, rehabilitation for muscle weakness would involve more strength training, whereas coordination impairment would involve more balance training and task-specific fine-motor activities (Cameron & Wagner, 2011). Accurate clinical measurement can improve assessment of recovery/decline and improve clinical decision-making capabilities (Bowden et al., 2012). One problem in MS rehabilitation is that current standardized outcome measures may not be capturing meaningful outcomes for the individual patient (Rannisto et al., 2015). Many of the measurements are not useful for detecting

clinically relevant change following physical rehabilitation, particularly in those with EDSS scores < 4.5 (mild to moderate impairment) (van Winsen, Kragt, Hoogervorst, Polman, & Uitdehaag, 2010).

1.4.2 Expanded Disability Status Scale

The EDSS scale was developed in the 1980's to measure disease progression, and is still popular among neurologists for use in clinical settings (Bevan & Cree, 2014; Kurtzke, 1983). The scale ranges from 0-10 in increments of 0.5, with 0-3.5 indicating good functional status with no assistance required, 4.0-5.5 indicating decreased walking ability and 6.0-9.5 indicating increased need of assistance for daily living (Kurtzke, 1983). The EDSS focuses largely on ambulation ability, and does not often consider other functional capacities (such as cognition and manual dexterity). Although ambulation is a primary target for assessment, many individuals with MS do not experience any walking impairments until EDSS reaches 4.0 (Bethoux & Bennett, 2011). Therefore, the EDSS has greater relevance at higher disability when walking impairment is evident, but has limited ability to distinguish between individuals in the mild stages of disability (EDSS 0-3.5) (Hobart, Freeman, & Thompson, 2000). A change of one unit (not 0.5) on this scale is required to signify a reliable measurement of change in disability (Noseworthy, Vandervoort, Wong, & Ebers, 1990). Since the EDSS typically changes slowly over time, this measure has limited sensitivity in detecting treatment related changes in disability or minor disability progression over time (Rabadi & Vincent, 2013; Zhang, Waubant, Cutter, Wolinsky, & Glanzman, 2013). Thus, the EDSS scale has poor psychometric properties, with low sensitivity, poor reliability and low responsiveness to change (Hobart et al., 2000; Sharrack, Hughes, Soudain, & Dunn, 1999). Therefore, although widely used in clinical settings, EDSS

may not be the best indication of small changes in functioning, particularly in individuals with MS with mild disability (EDSS 0-3.5).

1.4.3 Timed 25-Foot Walk Test

In addition to the EDSS, the Timed 25-Foot Walk Test (T25FWT) is widely used among clinicians and researchers. The T25FWT is a test of walking ability, recording the time it takes for a patient to transverse a 25-foot walkway. This test has shown excellent psychometric properties and is a more practical assessment tool than the EDSS as a trained observer is not needed to administer the test and it takes much less time (Bethoux & Bennett, 2011). Further, the time to complete this test shows a high correlation with the EDSS (Rudick, Cutter, & Reingold, 2002), particularly at higher disability levels (Kalkers et al., 2000). This is logical as the EDSS is primarily an assessment of walking ability, particularly at higher disability levels. The T25FWT also has high reliability in the greater disability range (EDSS 5.0-6.5) (Learmonth, Paul, McFadyen, Mattison, & Miller, 2012). Tests of walking speed over a short distance, such as the T25FWT, are recommended as an outcome measure for both people with neurological conditions and the elderly (Goldman et al., 2013). However, a major limitation of the T25FWT is a floor effect, rendering this test to be less sensitive for detecting differences among individuals with MS with very mild disability (Bethoux & Bennett, 2011). Individuals with MS must take six seconds or longer to complete the test to be considered as having walking disability and large changes of 20% in score are needed to be clinically meaningful (Goldman et al., 2013). Many individuals with MS with EDSS < 4.0 often can perform the T25FWT in under six seconds, and are therefore classified as having no disability. Therefore, although more practical than the EDSS, the T25FWT may only be useful in individuals with walking disability (EDSS 4.0-6.5)

and may not be able to distinguish impairment in individuals with mild disability. There is no commonly used assessment tool available to measure motor disability in individuals with EDSS < 4.0.

1.4.4 Need for Challenging Motor Assessment

Currently, there are limited tools to assess motor impairment in people with MS, particularly with low levels of disability. Both the T25FWT and EDSS are useful for providing an indication of motor ability, but only in certain ranges of impairment (EDSS>3.5). There are no commonly used measurement tools to test motor ability in people with mild disability who have surpassed the floor effect in the T25FWT (can walk the distance in under six seconds). As previously stated, clinicians rely on the use of measurement tools to distinguish the type of motor impairment in order to prescribe individualized rehabilitation programs and to monitor the progress of these impairments. Measurement tools are important to guide and optimize the individualized rehabilitation program. Therefore, there is a need in the field of rehabilitation for a more complex, challenging motor task to expose subtle deficits and detect change in motor functioning in people with MS with mild disability.

1.5 BIPEDAL HOPPING

1.5.1 Neuromuscular Control of Hopping

Bipedal hopping is a forward jump in which both feet leave the ground simultaneously, with forward displacement between take-off and landing locations. This form of hopping is a challenging motor task that requires immense power, coordination, balance and ability to reduce muscular co-contraction to efficiently perform the task (Smith, 2014). Power refers to the ability

to exhibit strength over a shorter time (Kockum & Heijne, 2015). Therefore, muscle strength and contraction speed largely contribute to the ability to produce power for a hop. The stretch-shortening cycle of skeletal muscles is a key component in generating power for a hop (Lloyd, Oliver, Hughes, & Williams, 2012). Secondly, coordination refers to accurate firing of appropriate muscles in a coordinated fashion with precise timing. Coordination of motor movement is driven by the cerebellum (Koziol et al., 2014). Balance is also critical for hopping, since hopping involves complete displacement of both feet from the ground resulting in a challenging landing phase. Lastly, co-contraction, when the force-producing muscle is congruently contracted with its antagonist pair, reduces the efficiency of the work produced. Both muscles are simultaneously producing force in the opposite direction, thus requiring greater energy by the primary muscle in order to overcome this opposing force. This ability to accurately relax the antagonist muscle can be hindered by spasticity (Smith, 2014). Thus, the four domains often affected by MS as well as by aging that were discussed previously (pg. 13-18): muscle strength, coordinating motor movement, imbalance and spasticity are also the four main predictors of hopping performance (power, coordination, balance and reducing co-contraction).

1.5.2 Biomechanical Phases of Hopping

Bipedal hopping involves five stages of movement: eccentric, isometric, concentric, airborne and landing phases (Lamontagne & Kennedy, 2013). During the first stage (eccentric) loading of the muscles takes place. The hips, knees and ankles bend, lengthening muscles while they contract, lowering the center of gravity towards the ground. During the forward bend, the gluteal muscles control the flexion of the hip. The muscles and connective tissue in the quadriceps and calves stretch and store elastic energy. This stretch activates muscle spindles, the

reflex response of which moves the hop into the next phase. The isometric phase of hopping is the shortest phase, but also the most important for predicting the power of the hop (Kubo, Yata, Kanehisa, & Fukunaga, 2006). The isometric phase is at the bottom of the loading phase, during the shift from an eccentric to a concentric contraction where no muscle length change occurs during the contraction. Muscle spindles, previously stretched, reflexively send signals to the spinal cord to contract the muscle and relieve the stretch, transitioning into the concentric phase. The concentric phase involves the shortening of muscles during contraction and execution of the hop, which is largely driven by the power source of the quadriceps (Lamontagne & Kennedy, 2013). As the force is transmitted from the quadriceps through the ground, the triceps surae and achilles tendon act as force transmitters and amplifiers. The strength and elasticity of the achilles tendon is responsible for approximately 73% of force transmission (Farcy et al., 2014). The amount of power generated is directly proportional to the amount of stored elastic energy through the stretch-shortening cycle. However, this pause between loading and contraction (isometric phase) must be quick in order to achieve maximal power. Long time periods in the stretch phase causes the stored elastic energy to be lost and allows muscle spindles to accommodate to the stretch and reduce the strength of the reflex. Once both feet leave the ground is considered the airborne phase. The hips knees and ankles extend and forward displacement is achieved. The final stage is considered as soon as one foot reaches the ground. Balance must briefly be achieved by maintaining the CoP of the foot within the bounds of stability, and then the eccentric phase begins again to prepare for the next hop. These phases are depicted in Figure 1.1.

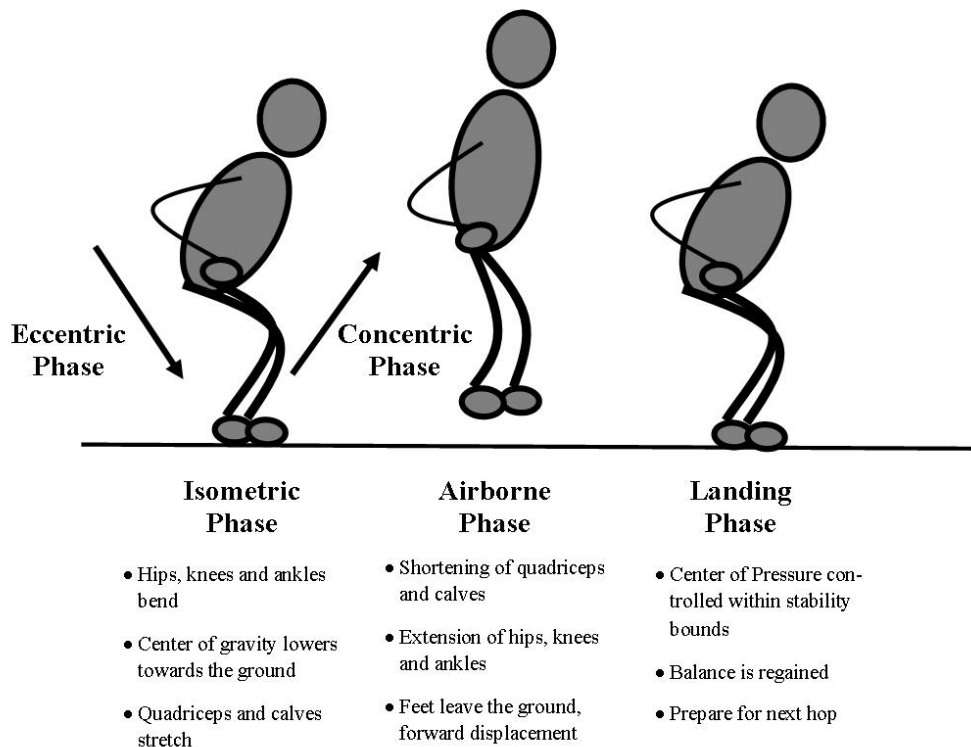


Figure 1.1: Biomechanical Phases of Hopping

1.5.3 Hopping as an Assessment Tool

Hopping is a complex task that has been used clinically to detect deficits in other rehabilitation domains. In children, hopping is a fundamental movement skill that must be acquired during development. Many types of hopping, such as one-foot hopping or a horizontal jump, are included in this skill. Therefore, impairments in hopping ability can highlight developmental delays (Morgan et al., 2013). For instance, in children with cerebral palsy, one of the primary assessment tools (Gross Motor Function Measure) utilizes jumping (Park, 2016). These children are required to jump forward 30 cm, on both feet simultaneously. Being able to

perform this task indicates the highest level of physical functioning achievable on this measure (Park, 2016). Similarly, the most advanced task on both the Chedoke-McMaster Stroke Assessment and Rivermead Motor Assessment for individuals with prior stroke involves a hopping task, performing one-foot hopping on the hemiplegic side (Gowland et al., 1993; Park & Kim, 2016). Lastly, return to play after an anterior cruciate ligament (ACL) reconstruction requires the ability to perform a symmetrical hop to indicate optimal symmetrical functioning of the lower limbs (Zwolski, Schmitt, Thomas, Hewett, & Paterno, 2016). Therefore, hopping is a measure that has been used to determine peak functioning of these lower body functional measures and has multiple implications for applicability across a wide range of rehabilitation fields.

1.5.4 Effect of Age on Hopping

The effects of aging on the body, particularly the musculoskeletal system, include, but are not limited to: muscle fibre atrophy, fewer mitochondria within skeletal muscles and increased co-contraction of opposing muscles (Häkkinen, Kraemer, & Newton, 1997; Hoffrén, Ishikawa, Rantalainen, Avela, & Komi, 2011). These changes largely affect motor tasks, especially during a challenging gross motor movement such as hopping. There have been multiple studies examining the changes in hopping ability that occur with aging. For example, elderly individuals have a decline in muscle cross-sectional area, and this atrophy is particularly evident in fast-twitch muscle fibres (Häkkinen et al., 1997). This results in a decrease in strength with age, which is demonstrated as decreasing explosive force while hopping (Häkkinen et al., 1997). In terms of muscle activation, during the landing phase of hopping, elderly participants had lower agonist activity than young adults (Hoffrén et al., 2011). Also, elderly individuals showed an

increase in antagonist co-activation during dynamic explosive movements (Häkkinen et al., 1997). Therefore, not only is there atrophy in the fast-twitch muscle fibres required for optimal hopping performance, but the muscle fibres are not activating to their full extent, and may also be counteracted by antagonist muscle activity. Another predictor of hopping performance is the ability of the muscles to shorten and tendons to stretch and shorten, particularly the gastrocnemius muscle and achilles tendon. It was found that elderly individuals have less muscle shortening than young adults, but no difference in the tendons' ability to shorten (Hoffrén, Ishikawa, Avela, & Komi, 2012). Therefore, age-related changes in stretch shortening cycle can be attributed to a decrease in muscle shortening, with no age-related decline in tendon functioning. However, training through physical activity can improve hopping ability in the elderly by enhancing the ability of the gastrocnemius medialis muscle to shorten, thereby improving tendon utilization to create more elastic energy for the stretch-shortening cycle (Hoffrén-Mikkola, Ishikawa, Rantalainen, Avela, & Komi, 2015). These changes in hopping ability that occur naturally with increasing age are similar to motor impairments in individuals with MS, and therefore hopping ability in people with MS may be similarly affected.

1.5.5 Hopping in MS

There has been one study that has measured hopping ability in people with mild MS. This study reported that people with MS display hopping abilities characteristic of an older individual, demonstrating potential early senescence of the neuromuscular system (Kirkland et al., 2016). In this particular study, MS subjects with mild disability as well as age and gender matched controls and elderly subjects performed a two-foot, forward hop at their self-selected pace. In many of the variables, participants with MS performed at a level between the two groups (elderly and age and

gender matched controls). For instance, the control group hopped the furthest distance, and the elderly group the shortest. Participants with MS exhibited hopping distance somewhere between these two groups, creating a staircase effect. Typically, participants with MS would be expected to perform similarly to participants their own age (control group), however, their performance shifted towards the elderly group, demonstrating characteristics similar to older adults. Bipedal hopping seemed to expose deficits in this group of mildly affected individuals with MS. Importantly, the study also confirmed a floor effect in the T25FWT, showing that people with MS could easily perform this test in under six seconds (clinical cut-off). Therefore, while the T25FWT was not sensitive enough to detect subtle motor impairment, hopping was able to expose these motor deficits in the same group of individuals. Hopping variables were also predictive of EDSS score ($r^2 = 0.38$, $p = 0.02$) (Kirkland et al., 2016). These findings suggest that bipedal hopping may be useful in exposing underlying motor impairment in individuals with low disability scores (Kirkland et al., 2016). Therefore, in the present study, we utilized bipedal hopping as the motor task for the measure we developed. However, individuals with MS are not limited to motor impairment. Since patients can present with sensorimotor impairment even in the absence of motor deficits, an even more complex method of hopping was developed.

1.6 SENSORIMOTOR SYSTEM

1.6.1 Role of Cerebellum in the Sensorimotor System

The sensorimotor system involves sensory, motor and central integration involved in maintaining joint homeostasis during movement. The cerebellum plays a large role in coordinating motor control by planning and modification of movement initiation (Riemann & Lephart, 2002). The cerebellum collects sensory information from the central and peripheral

sensory areas as well as information of the motor command from the motor control areas to integrate this information into meaningful corrections to motor movement commands. Specifically, the spinocerebellar division of the cerebellum is responsible for movement correction. Information is received from the four spinocerebellar tracts as well as the vestibular labyrinth, visual and auditory organs and an efferent copy of the motor command arriving at the ventral roots of the spinal cord. After integration of information, movement adjustment commands are sent through the thalamus to the motor cortex. In this way, the cerebellum plays a role in motor learning (Riemann & Lephart, 2002).

1.6.2 Cerebellar Impairment in MS

Cerebellar impairment is extremely common in individuals with MS, particularly early in the disease progression. There is often neurodegeneration in the cerebellum even in the earlier days of symptom onset (Penhune & Doyon, 2005). This generation often occurs in the dentate nucleus as well as the middle and superior peduncles (Albert et al., 2016; Preziosa et al., 2014; Sbardella et al., 2017), which results in disintegration of regional processing in the cerebellum and a disruption of input into the cerebellum (Dogonowski et al., 2014). Without the appropriate information and the ability to integrate this information, the cerebellum cannot accurately update movement, which has serious implications for movement correction and thus motor learning. These degenerative effects are often subtle in the early stages, and are not detected on an MRI until substantial progression has occurred and clinical symptoms are present (Weier et al., 2015). In fact, early signs of cerebellar impairment predict individuals with MS who are more likely to have a rapid, progressive disease course (Jacobs & Kasser, 2012). Therefore, being able to detect

and measure cerebellar impairment early has the potential to highlight those in need of pre-rehabilitation to slow disability progression.

1.6.3 Role of the Basal Ganglia in the Sensorimotor System

The basal ganglia are a group of five subcortical nuclei that are located deep within the cerebral hemispheres. While the cerebellum has multiple input and output connections with all three levels of motor control, the basal ganglia are limited to only connections with the cerebral cortex. However, the basal ganglia receive input from the entire cerebral cortex and are not limited to only sensory and motor functions as is the cerebellum. Therefore, the basal ganglia play a role in higher-order cognitive aspects of motor control with regards to the sensorimotor system (Riemann & Lephart, 2002).

1.6.4 Basal Ganglia are Affected by MS

There is emerging evidence about how the basal ganglia are affected in individuals with MS. Specifically, primary links to symptoms of fatigue, walking ability and non-motor symptoms have been identified (Finke et al., 2015; Horowski, Zettl, Benecke, & Walter, 2011; Motl et al., 2015). Recently, it was found that individuals with RRMS had alterations in basal ganglia volumes and functional connectivity compared to control subjects and specific types of functional connectivity were associated with fatigue. Importantly, greater functional connectivity between the caudate nucleus and motor cortex was associated with more severe fatigue (Finke et al., 2015). Therefore, impaired functioning of the basal ganglia has strong implications for fatigue in people with MS, which is one of the most debilitating symptoms reported by MS individuals (Akaishi, Nakashima, Misu, Fujihara, & Aoki, 2015). Walking ability has also been

linked to basal ganglia dysfunction in MS. It was found that time to complete the T25FWT was significantly associated with volume of the thalamus, caudate, pallidum and putamen (Motl et al., 2015). Lastly, neurodegenerative lesions due to an accumulation of iron in the substantia nigra have been linked to non-motor symptoms in MS, specifically cognitive dysfunction, cognitive fatigue and urinary incontinence (Horowski et al., 2011). Thus, there is emerging evidence to show that the basal ganglia can be affected by MS, typically resulting in greater fatigue, declines in walking ability and cognitive impairment. However, it is not known how early these deficits occur in the MS disease course or whether impairments can be detected prior to the manifestation of impairments.

1.6.5 Need for Early Measurement of Sensory-Motor Impairment

Measuring subtle cerebellar impairment is difficult, and is currently being assessed in individuals with MS using the NHPT or eye-tracking. The NHPT measures the ability to place nine specifically shaped pegs into their appropriate hole on a board, which is an indication of finger dexterity (Moroso et al., 2017). Although correlated with cerebellar function, the NHPT is not specific for cerebellar symptoms, as motor deficits and spasticity can also play a role in performance. Eye-tracking can differentiate between individuals with MS with and without the cerebellar deficits more effectively than the NHPT (Moroso et al., 2017). However, eye-tracking impairments are characteristic of ataxic symptoms, which is a different function of the cerebellum from motor learning. Therefore, although individuals with MS may experience ataxia, many experience impairment in motor learning without the presence of ataxic symptoms (Tacchino et al., 2014). Thus, a task that involves the cerebellum for motor learning may be also able to distinguish those with cerebellar dysfunction due to ataxia from those related to motor

learning. In terms of measuring basal ganglia degeneration, the only method currently available involves imaging (Motl et al., 2015). Many of the symptoms of basal ganglia involvement (fatigue, uncoordinated walking, decrease in cognitive ability) can be attributed to multiple regions of the brain and therefore the basal ganglia alone cannot be specified as the root cause. Performance of a task that relies primarily on the basal ganglia would involve the addition of a rhythmic timing element.

1.7 METRONOME

1.7.1 *Rhythmic Timing*

Rhythmic timing theory states that motor movements rely on temporal information to optimize movement (Thaut, 2015). For instance, velocity of walking is a time derived rhythmic motor movement, which involves inter-limb coordination dependent on timing. In order to optimize gait, precise timing to a rhythm must be adhered to in order to achieve smooth, rhythmic gait. Therefore, temporal information is integrated within mechanisms of motor control (Thaut, 2015). There are two types of temporal information in which motor movements can be based on: internally triggered and externally triggered timing.

1.7.1.1 *Internally Triggered Timing*

Internally triggered temporal information refers to a person's internal clock or pacemaker, which monitors movements that are based on a time-structured rhythm, such as walking (Avanzino et al., 2016). A rhythm similar to a metronome beat must be created and maintained within the brain. The internal clock involves the sensorimotor circuit of the basal ganglia, including the supplementary motor area, putamen and ventrolateral thalamus. Several

integrated loops link the basal ganglia, specifically substantia nigra, to distinct cortical areas; motor, associative and limbic networks (Avanzino et al., 2016). The pathway in which internal rhythm is generated is depicted in Figure 1.2. Since the substantia nigra is critical for temporal prediction ability, people with Parkinson's Disease (PD) tend to have difficulties with internally generated movements (Avanzino et al., 2016). The underlying pathology of PD is a decline in dopamine, which is the primary neurotransmitter of basal ganglia circuitry (Brotchie & Fitzner-Attas, 2009). Therefore, insufficient amounts of dopamine impair the connectivity of the basal ganglia, which is important for movement initiation and internal timing. Characteristic of PD is bradykinesia, which is slowness of movement initiation and execution (Daneault, Carignan, Sadikot, & Duval, 2013). Particularly, this is evident during gait, as bradykinesia can present as slow shuffling stride, accelerating gait or highly variable and random stride times (Daneault et al., 2013). These manifestations of bradykinesia are also internally generated sequential movements and could therefore be the result of dysfunction of an internal clock that is modulated by dopamine. Consequently, many individuals with PD activate an alternative timing network that relies on more cerebellar activation, characteristic of external triggered timing (Avanzino et al., 2016). Although individuals with MS tend to have atrophy and disruption in functional connectivity of basal ganglia circuitry, it is currently unknown how this impairment affects timing abilities. However, it may be speculated that impairments in internal timing mechanisms in the basal ganglia circuitry explains why people with MS tend to have more variable gait patterns than controls. This is particularly evident as MS disability increases as individuals with MS are not able to maintain a consistent time derivative during gait performance. (Kalron, 2016).

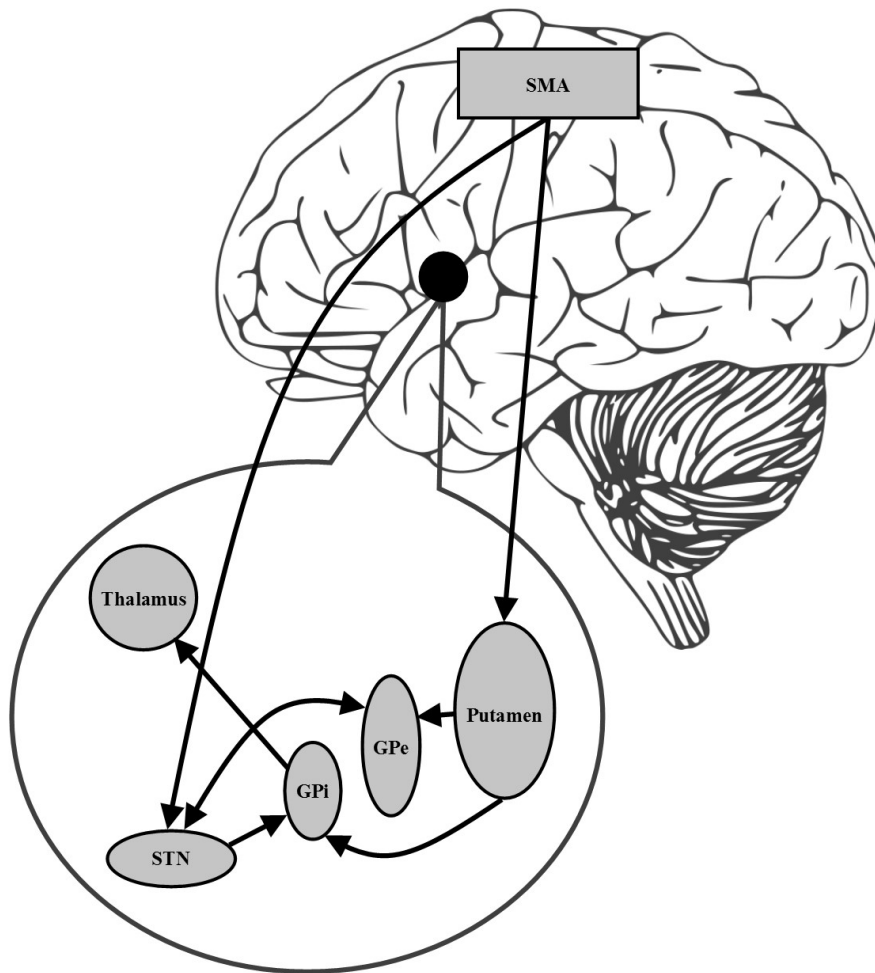


Figure 1.2: Intrinsic clock circuitry

Circuitry for intrinsic timing used for rhythmic derived movement (such as gait). This circuitry relies largely on interconnections between the basal ganglia and thalamus. The thalamus is then responsible for initiating the pathway for motor movement. The arrows indicate the process of generating internal timing. SMA: Supplementary Motor Area; STN: SubThalamic Nucleus; GPi: Globus Pallidus internal; GPe: Globus Pallidus external.

1.7.1.2 Externally Triggered Timing

Externally triggered temporal information requires matching motor movement to an external stimulus, such as the tone from a metronome. Rhythm provides precise anticipatory cues

and therefore provides the brain with a time constraint and fixes the duration of the movement. The brain is constantly deriving velocity and acceleration from time to optimize movement. Therefore, an external timing mechanism gives the brain constant reminders of a fixed time interval, allowing for optimization of motor planning (Thaut, 2015). External timing also encompasses the concept of motor entrainment, which is the theory that one system's frequency entrains the frequency of another system; in this case, the auditory system is entraining the frequency of the motor system. There are many richly distributed connections between the auditory and motor system (Thaut, 2015). These interactions between rhythm processing and auditory motor system take place in widely distributed, hierarchically organized neural networks, extending from the brainstem and spinal levels to cerebellar, basal ganglia and cortical loops. The auditory system primes the motor system for movement through reticulospinal pathways, which all occurs below levels of conscious perception (Thaut, 2015). In other words, it is not only the conscious perception of hearing a signal and creating a conscious effort to drive a motor movement, but there are subconscious interconnections between these two systems that prime the movement. The motor system is already prepared to respond to an auditory cue even before conscious perception of the signal. This subconscious connection and priming is the basis for the theory of externally triggered rhythmic timing. There are three stages to externally triggered timing: (a) beat perception, (b) rhythmic timing and (c) timing optimization.

1.7.2 Perceiving an Externally Triggered Beat

Beat perception has three processes: detecting the beat interval, creating and maintaining predictions of beat intervals and updating predictions of future beat intervals based on evidence from sensory feedback (Merchant & de Lafuente, 2014). In considering the detection of rhythm,

the auditory system turns physical information (sound) into action potentials in the sensory receptors. It then projects this information through thalamic nuclei to the primary sensory areas of the cerebral cortex and then this stimulus is processed in cortical and subcortical circuits. Lastly, high order sensory processing is used to direct perception, learning, memory and voluntary motor action (Merchant & de Lafuente, 2014). This is the point in which a person consciously perceives a rhythmic beat. However, this system takes time. By the time the beat is consciously perceived, there has been a time delay and the motor response is therefore delayed from the beat. Motor entrainment shortens this time. The auditory system has a privileged capacity for time quantification, and therefore, temporal information of the sound is extracted early in the chain of processing (Merchant & de Lafuente, 2014). This information is sent to complex networks of core timing mechanisms in the parietal, temporal and frontal lobes as well as the basal ganglia and cerebellum (Merchant & de Lafuente, 2014). Thus, the temporal information (rhythmic beat) of sound is extracted and processed prior to conscious perception of the entire sound. Therefore, information about this rhythmic beat can prime the motor system before conscious perception can create a motor command. Upon beat perception, the motor system is primed by inducing a greater connectivity between the putamen and the supplementary motor area as well as between the putamen and the premotor cortex. This “shortcut” in sound perception helps reduce the delay between the external stimulus and motor response (Merchant & de Lafuente, 2014).

1.7.3 Rhythmic Timing

The mechanism of timing delay from the beat is intrinsic to the basal ganglia networks. As previously mentioned, upon beat perception the motor system is primed by greater

connectivity between the putamen and the supplementary motor area as well as between the putamen and the premotor cortex. The putamen is the beginning of the basal ganglia circuitry responsible for eliciting a motor response to the externally triggered beat. The putamen then connects through the globus pallidus external to the sub-thalamic nucleus then to globus pallidus internal which connects through the thalamus to the premotor areas and motor cortex. The motor cortex sends motor information through the corticospinal tract to elicit the appropriate motor movement. This circuitry is depicted in Figure 1.3 (Avanzino et al., 2016; Thaut, 2015).

The ability to time motor movement to an external rhythm is quantified based on timing error, the amount of time between the rhythmic stimulus and motor movement initiation. The relative timing error can be negative, which means the person anticipated the beat and moved slightly before the stimulus, or positive, which means the person reacted by moving after the stimulus. Negative error is typical, as anticipation is the natural timing mechanism (Repp & Su, 2013). This seems counterintuitive, as motor movement must come after the stimulus since the stimulus must be processed first. However, repetitive external stimulus allows for motor learning and consequent feed-forward control in the cerebellum.

1.7.4 Timing Optimization

The cerebellum can mediate a feedforward process of motor commands capable of anticipating the sensory input. However, this can only be achieved if the sensory target is predictable: a stable rhythm (Molinari, Leggio, & Thaut, 2007). The cerebellum can detect error between the cue event and motor response, then feeds this information forward to the thalamus to correct the following motor response. Areas of the cerebellum important for this timing

correction are the anterior and posterior cerebellar lobes. Specifically, the posterior cerebellar hemisphere is important for responding to changes in rhythm (Molinari et al., 2007). Larger disparity between the rhythmic stimuli and motor movement will cause greater synchronization error, thus increasing activation of the cerebellum to make a larger motor correction (Molinari et al., 2007). The cerebellum achieves this by entraining the firing rates of different neural populations to improve their temporal code coincidence and facilitate efficient network formation. However, although critical for error correction to improve timing, the cerebellum is only an optimization system and is not directly involved in rhythm perception (Molinari et al., 2007). Cerri et al. (2005) found that individuals with MS with cerebellar lesions were still able to time each individual rhythmic beat as this process happens within basal ganglia circuitry (as described on page 30-32). However, participants were not able to respond to changes in rhythm or alter their motor movement to improve their synchronization error over time (Cerri, Esposti, Locatelli, & Cavallari, 2005). Thus, the cerebellum is responsible for optimization of rhythmic timing, not rhythmic timing itself. Optimization functions involve fine-tuning and adequate modulation of sensory acquisition and integration processes underlying the perceptual, cognitive and motor functions. Where the ability to retain error feedback and the use of feed-forward control to adjust timing is attributed to the cerebellum, the process of perceiving the rhythm and eliciting a motor movement timed to this stimulus happens in the basal ganglia circuitry. The process of externally triggered timing, including beat perception, rhythmic timing and timing optimization are depicted in Figure 1.3.

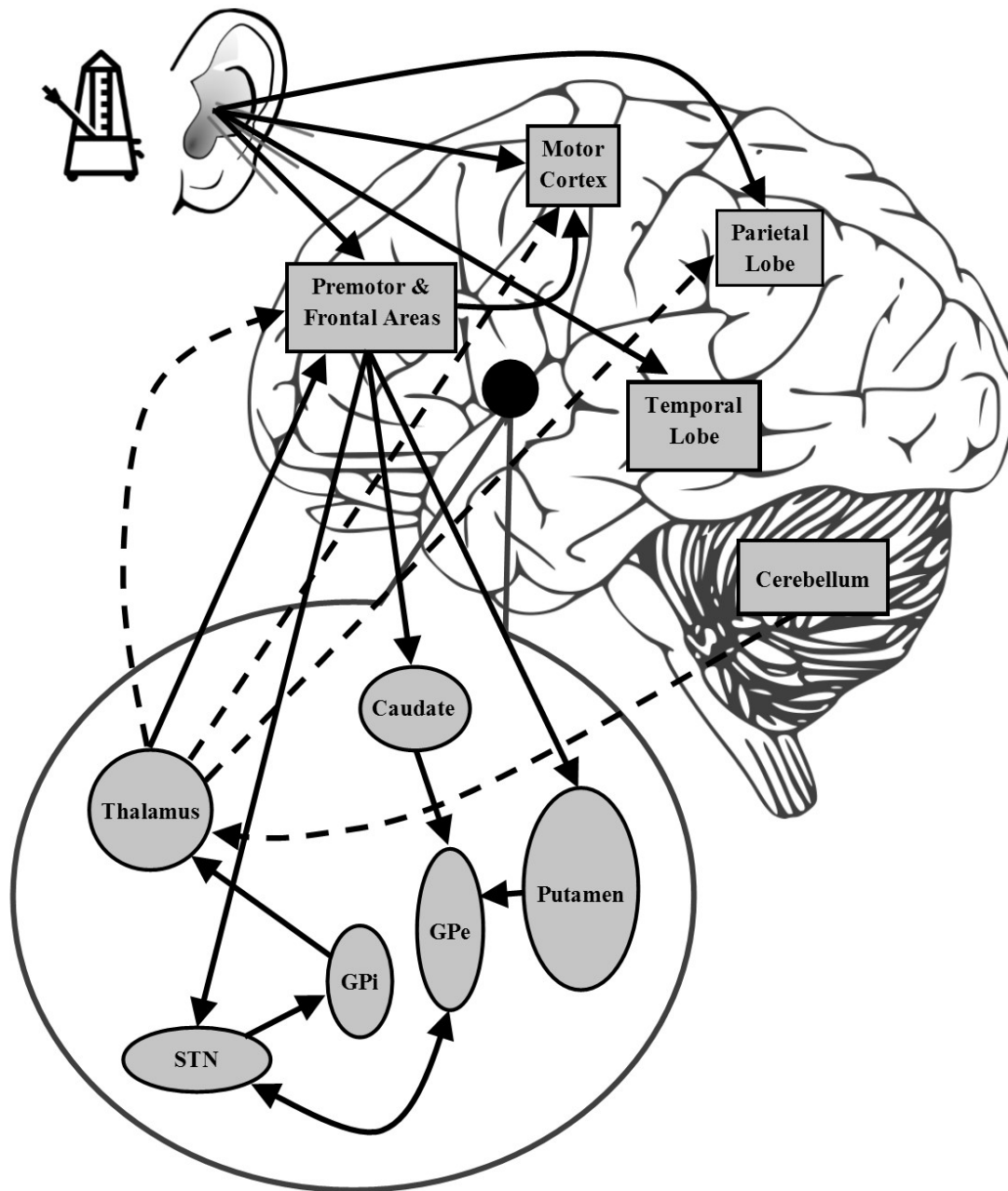


Figure 1.3: External Timing Circuitry

Circuitry for externally triggered timing used for matching a motor movement to an external time signal (such as a metronome beat). This circuitry relies on beat perception and response within the interconnections of basal ganglia circuitry (solid lines) and feedforward error detection and response through interconnections of cerebellar circuitry (dashed lines). STN: Subthalamic Nuclei; GPi: Globus Pallidus internal; GPe: Globus Pallidus external.

1.7.5 Does Rhythm Frequency Matter?

The frequency of a rhythm will determine the relative activation of basal ganglia circuitry versus the cerebellar circuitry. As previously mentioned, the brain through the basal ganglia circuit has an internally triggered temporal rhythm that guides gait and other rhythmic movements. This rhythm tends to be constant (Avanzino et al., 2016). The mechanism of internally triggered timing is very similar to how the basal ganglia networks responds to externally triggered timing. If the externally triggered rhythm is close to the natural internal rhythm, then internal rhythmic mechanisms (basal ganglia network) will be extremely active and precise as this is a recognized frequency (Avanzino et al., 2016). Therefore, less synchronization errors will occur, taking a large burden off cerebellar circuitry (Merchant & de Lafuente, 2014). However, if the frequency differs from the natural internal frequency, then the basal ganglia circuit will create more errors in timing, thus increasing the demand on cerebellar circuitry (Merchant & de Lafuente, 2014). Therefore, rhythm matters to determine which circuitry (timing vs. optimization) is more active.

1.7.6 Effect of Injury on Timing

Utilizing the neural circuitry described above and their interconnections are the ideal mechanisms to time and adapt motor movement to a rhythmic stimulus. However, there are changes to this system that occur due to injuries to the brain. The injured brain can still access rhythmic entrainment mechanisms often by compensating for lost networks by relying on alternate pathways (Thaut, McIntosh, & Hoemberg, 2014). For example, as previously mentioned, individuals with PD have impaired basal ganglia circuitry, which impairs internally

driven rhythmic movements. Externally driven rhythmic stimuli also require basal ganglia circuitry to elicit a motor response to this stimulus. However, individuals with PD can bypass the basal ganglia involvement for externally timed stimulus because the cerebellum is constantly working to optimize the rhythmic timing. So, although the basal ganglia are unable to accurately perceive and time movement, the cerebellar circuits are correcting these mistakes, thus compensating for basal ganglia impairments. There is a shift to demand more activation from the cerebellum to compensate for other areas of the brain (Avanzino et al., 2016; Thaut, 2015). Thus, in PD rehabilitation, many therapists will induce an external rhythm (metronome) during walking training to bypass the internally generated rhythm by the basal ganglia and rely more on cerebellar circuitry. This technique is called rhythmic auditory stimulation (RAS) (Thaut, 2015). Although RAS is used as a treatment intervention in this context, it is still a relevant topic to discuss when considering metronome as a measurement tool, as ability to synchronize a motor movement to a metronome and how this ability changes over time is indicative of changes in sensorimotor system impairment. However, there is a paucity of evidence regarding RAS in MS.

1.7.7 Rhythmic Auditory Stimulation

RAS is an emerging field in neurological rehabilitation. Specifically, RAS improves gait parameters in people with PD and previous stroke. RAS is also being used in a vast array of fields, including but not limited to epilepsy, coma patients, speech impediments and Huntington's disease (Wittwer, Webster, & Hill, 2013). The concept of motor entrainment of the auditory system on the motor system to increase cortico-motor excitability and thus plasticity is the underlying basis of RAS in rehabilitation. There are four proposed mechanisms by which the effects of RAS occur (a) accelerated motor learning, (b) qualitatively different motor learning,

(c) acquiring temporal skills and (d) motivation (Galińska, 2015; Schaefer, 2014). The theory of accelerated motor learning is that, due to metronome synchronicity, repetitive movements are performed more similarly every time, possibly resulting in more specific learning and increased plasticity. Pattern repetition globally facilitates many instances of identical movements, which translates to the core principles of experience-dependent plasticity (Galińska, 2015; Schaefer, 2014). Thus, precise repetitions leads to faster learning as there is little variability in the practised movements (Galińska, 2015; Schaefer, 2014). However, not only does RAS promote ubiquitous learning, but stimulates qualitatively different motor learning. RAS stimulates brain connectivity between the auditory and motor areas, thereby allowing compensatory movement through alternative transmission routes. Therefore, using RAS stimulates a different pathway for the motor movement, thus creating a different pathway in the brain and increasing plasticity in this alternate pathway (Galińska, 2015; Schaefer, 2014). This mechanism is likely the reason such profound effects of RAS are seen in PD. Therapists use RAS for individuals with PD to promote plasticity of the direct connection between auditory and motor areas, thereby bypassing the basal ganglia for movement initiation (Avanzino et al., 2016). The third mechanism of RAS is acquiring temporal skills. RAS provides a rhythmic structure as a basis for motor movement in time-derived tasks. Therefore, providing a template for pace in movement improves the predictive value of the movement. This is evident as RAS has been shown to increase connectivity in areas of the brain related to predictive processing (cortico-striatal connectivity) (Galińska, 2015; Schaefer, 2014). Lastly, RAS could work through a basic mechanism of motivation. Rehabilitation may feel less effortful by improving emotional engagement and providing a positive experience. More motivation tends to lead to increased practice, which is the best mechanism for promoting plasticity and recovery in the brain (Frühholz, Trost, &

Grandjean, 2014). However, this mechanism of motivation is most robust in music therapy studies as there is a well-documented link between music and emotion (Frühholz et al., 2014). There is likely less of a motivation effect when considering simple metronome timing tasks (Galińska, 2015; Schaefer, 2014). Since different people with varying neurological injury or diseases will react differently to RAS, the mechanism of action is likely related to the type of neural damage. Therefore, results from various neurological conditions cannot be directly generalized to all neurological conditions, and there is a paucity of evidence revolving MS in this field.

1.7.8 Rhythmic Auditory Stimulation in MS

Although proven efficacious in PD and other neurological disorders, very little evidence exists for using RAS in MS. One study utilized sequential finger touching to a metronome as one of the conditions of a larger study investigating manual dexterity in individuals with MS. The authors found that touch duration between fingers increased with metronome timing in comparison to control subjects, thereby indicating that individuals with MS needed more time to evaluate finger contact (Bonzano et al., 2013). This was one of the first pieces of evidence to suggest that there could be impairment in sensorimotor integration in MS. A review was conducted in 2013 to evaluate how RAS can improve walking in various neurological conditions (Wittwer et al., 2013). Well documented in other conditions (such as stroke and Huntington's Disease), only one study at this point investigated the effect of RAS in MS (Wittwer et al., 2013). In this randomized control trial (RCT), investigators found that two weeks of RAS training on walking decreased duration of double support (a measure of requirement for stability while walking) compared to those without RAS. There was no effect on any other gait

parameters (Conklyn et al., 2010). However, this study utilized a home-based program, which may have resulted in compliance variability. With a paucity of studies for comparison, conclusions are difficult to make from one study. Wittwer and colleagues (2013) also scored this RCT as low quality and concluded the the “application of best evidence synthesis therefore shows only indicative findings for the effect of RAS and only on double support in this clinical population” (Wittwer et al., 2013). Thus, this evidence is not sufficient to confirm the benefits of RAS in MS.

Since this review in 2013, there have only been two studies in the field of RAS and MS. The first was a large RCT that investigated the effects of both music-cued and metronome cued motor imagery among people with MS compared to a control group (Seebacher, Kuisma, Glynn, & Berger, 2017). Seebacher et al. (2017) found that combined music-cued and metronome-cued motor imagery for four weeks improved walking speed on the T25FWT in individuals with MS more effectively than the control group. Also, these interventions improved subjective fatigue, walking confidence and health related quality of life (Seebacher et al., 2017). This study was one of the first large trials to provide evidence that RAS training may have a positive impact for individuals with MS. However, it was unable to be distinguished whether the positive effects could be attributed to RAS. The intervention group performed both RAS and motor imagery, whereas the control group did neither intervention. Thus, it cannot be determined whether the positive effects on gait were due to RAS or motor imagery, or a combination of both since the control group did neither.

Most recently, an RCT has been published investigating the effects of RAS training during walking in MS compared to walking training without stimulus. Shahraki et al. (2017) found that stride length, stride time, cadence and gait speed increased significantly more in the RAS group than walking training alone (Shahraki, Sohrabi, Taheri Torbati, Nikkhah, & NaeimiKia, 2017). Thus, providing evidence that RAS training may indeed be beneficial for individuals with MS. However, there were several limitations to this study. All of the gait improvements were velocity dependent variables. This could be caused by experimental design, as the metronome cadence was set to 10% above a participant's self-selected cadence, whereas the control group trained at their self-selected pace. Thus, there is bias that the RAS group were pushed to practice at a speed faster than the control group, thereby influencing gait parameters directly related to velocity. We therefore cannot conclude whether the effects of RAS on gait can be attributed to plasticity is occurring in the motor entrainment circuits, as described in the neural mechanisms of motor entrainment and other neurological disorders, or whether these effects were simply due to practicing at a faster cadence.

Although the effects of RAS training on gait parameters in individuals with MS are beginning to emerge, there is a paucity of evidence describing the underpinnings of neural timing in MS. As stated by Schaefer et al. (2014), "As varied movement disorders are addressed using cueing interventions, the way different afflictions may impact these mechanisms is crucial" (Schaefer, 2014). We still do not know whether individuals with MS tend to have an anticipatory motor timing inclination (similar to individuals with PD) or a delayed motor reaction to a cue (similar to individuals with Huntington's disease). Also, an important point to consider is that MS has vast heterogeneity within the disease. Unlike individuals with PD, who all have very

similar basal ganglia involvement, people with MS have a wide range of affected areas in the brain due to scattered lesions. These various lesions can be difficult to track and monitor, as previously discussed, and lesions on MRI imaging are not consistently predictive of clinical symptoms (Amato et al., 2004; Arnett et al., 1994; Calabrese, Rocca, et al., 2009; Comi et al., 1999; De Stefano et al., 2003; Deloire et al., 2005; Foong et al., 1997; Miki et al., 1999; Nijeholt et al., 1998; Portaccio et al., 2006; Rovaris et al., 1998; Schreiber et al., 2001; Summers et al., 2008; Swirsky-Sacchetti et al., 1992). Therefore, by understanding the basic neural underpinnings of sensorimotor synchronization, we may be able to use various parameters of metronome timing to determine and monitor the affected areas of the brain in individuals with MS. For instance, individuals with MS with timing difficulties would indicate basal ganglia circuitry involvement, whereas those who are unable to perform error correction would suggest the cerebellum is involved. Thus, metronome timing could be a useful tool in this population, not only as a rehabilitation intervention, but as a measurement tool to track and monitor various sensorimotor cortical and sub-cortical circuitry.

1.7.9 How to Measure Timed Hopping

Hopping variables can be calculated using data collected from an instrumented walkway such as the Zeno Protokinetic Walkway (Protokinetics, Havertown, PA, USA). The walkway acts similarly to a force plate, with pressure sensors forming a grid over the mat and information about the number of sensors activated and pressure on specific sensors, transmitted to a computer. Location and degree of pressure sensor activation are processed by the accompanying software to produce footprints on the walkway, and thus calculations can be made to ascertain various hopping variables. These variables include integral pressure, hop length, hop width, hop

time, percent time in stance, velocity and measures of balance. Hop length (cm) is considered as the average distance from the midpoint of the heel, to the same location on the subsequent heel contact (or toe to toe; Figure 1.4). Hop width (cm) is considered as the distance between the feet upon landing a hop. Hop time (s) is the amount of time when both feet are on the ground between hops (termed 'stance' when considering walking parameters). Percentage time in stance is the amount of time that both feet are on the ground, relative to when only one foot or no feet (when in flight during hop) are in contact with the walkway. Velocity (cm/s) is considered as the time it takes for a participant to transverse the walkway distance. Lastly, CoP can be used to quantify balance. CoP path length is the total distance that CoP moves; greater excursions indicating more whole-body sway and likely more difficulty balancing. Range of CoP in both x and y direction can also be quantified, as a wider range also indicates more sway towards the bounds of stability. Lastly, CoP path efficiency can be considered. A perfectly efficient CoP path would create a straight line from the middle of two footfalls to the middle of the subsequent two footfalls (100% efficiency). Deviations from this path would be considered less efficient due to increase in whole body movement; greater deviations result in decreased efficiency scores. Furthermore, since hopping usually takes into consideration multiple hops, the coefficient of variability (CV) can be calculated for each of the parameters which provides a measure of consistency. As well, one would expect the feet to behave similarly during a bipedal hop so symmetry between the feet in terms of hop length and integral pressure can be calculated as a ratio value.

In addition to hopping variables, metronome timing variables can be considered including the average delay and the ability to adjust timing (adaptation or learning). The metronome is a

feature within the Zeno Protoketic Walkway, and thus metronome signals are synchronized with the pressure sensor data through the accompanying software (Protokinetics, Havertown, PA, USA). The average delay from the metronome, also known as timing error, is considered the amount of time between the metronome signal and both feet pressure reaching zero (indicating that both feet have lifted from the walkway). If foot pressure reaches zero before the metronome cue, then the participant anticipated the beat and the timing error is negative. If the foot pressure reached zero following the metronome cue, then the participant reacted to the stimulus and the timing error is positive. Timing adaptation considers how a participant adapts their timing error over the course of subsequent cues. This variable is calculated as the difference between the timing error on the last hop in the trial and the first hop in the trial. Ideally, participants will have a negative adaptation learning value, as that would indicate they used error correction to reduce the amount of time between the cue and response in order to anticipate the cue. This method of quantifying metronome timing is depicted in Figure 1.4.

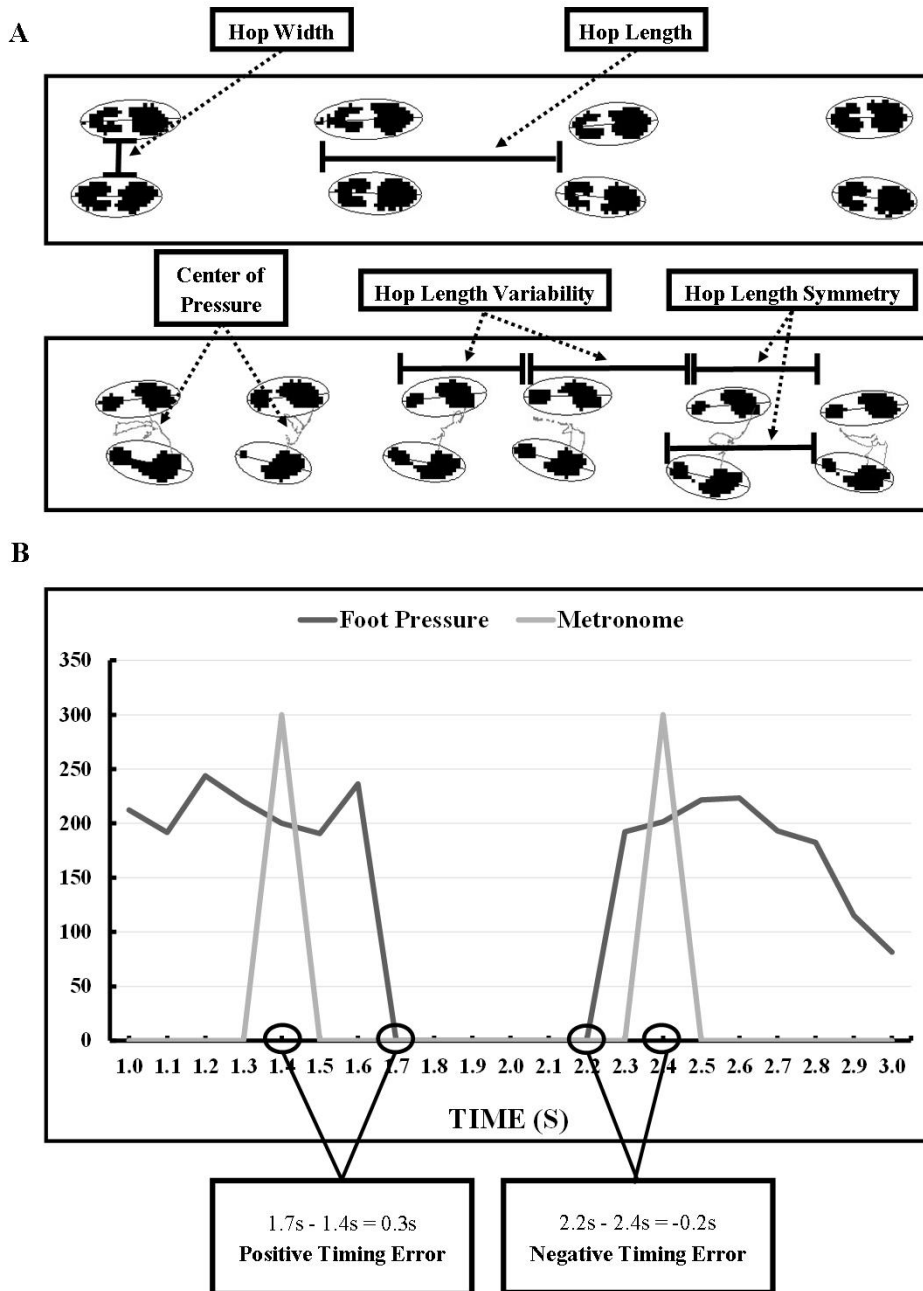


Figure 1.4: Quantifying Metronome Hopping

(A) Detailing calculation of various walkway variables, including hop width, hop length, center of pressure, hop length variability and hop length symmetry. These measurements were depicted using

footprint output from Zeno Protokinetic Walkway Software; (B) Detailing metronome timing error and distinguishing between positive and negative timing error in relation to foot pressure.

1.8 THESIS OBJECTIVE

The objective of this thesis was to characterize the ability of individuals with mild MS to synchronize a challenging motor task (bipedal hopping) to a metronome beat at various frequencies in comparison to age matched controls and elderly individuals. This study was part of an overarching goal to develop a challenging, clinically relevant measure to detect and monitor subtle impairment in people with mild MS. I aimed to answer the following research questions:

- (1) Do individuals with MS differ in metronome timing ability compared to control and elderly participants?
- (2) Are there differences between timing at a metronome frequency of 40 beats per minute (bpm) compared to 60-bpm?
- (3) Are metronome hopping variables related to physical and cognitive impairment in participants with MS?

1.9 CO-AUTHORSHIP STATEMENT

As research is often collaborative, I would like to acknowledge the contributions of co-authors on this manuscript. Dr. Michelle Ploughman, my supervisor, was mainly responsible for the design and identification of research proposal and contributed guidance to all aspects of the project. Co-authors Matthew B. Downer, Brett J. Holloway, Evan J. Lockyer, Natasha C.M. Buckle and Courtney L. Abbott played a role in the practical aspects of the research, including assisting with recruitment, data collection and data extraction.

Chapter 2: Manuscript

2.0 INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disorder of the central nervous system, affecting over 2.3 million people worldwide (Farinotti et al., 2012). It is typically diagnosed during the early ages of adulthood (20-40 years old) when many people are beginning their careers and families (Confavreux & Vukusic, 2006). Although clinical disability may take time to progress, people in the early stages of the disease often report problems that affect their day-to-day living, resulting in balance impairments and difficulty in multitasking (Ploughman et al., 2012). They experience subtle and subclinical muscle atrophy and weakness (Wens et al., 2014), similar to those that occur with aging (Stephenson et al., 2015). Unfortunately, current clinical assessment tools are often not sensitive enough to detect these self-reported problems until they have progressed into disability easily detected by an observer.

The current clinical gold standard for measuring motor ability in people with MS (PwMS) is the Timed 25 Foot Walk Test (T25FWT) (Bethoux & Bennett, 2011). The T25FWT is a test of walking ability, timing how long it takes for a participant to transverse a 25 foot walkway, with six seconds or less indicating 'normal' performance (Goldman et al., 2013). Many PwMS perform in the normal range (a floor effect) and changes up to 20% on this measure are needed to be considered clinically significant (Hobart, Blight, Goodman, Lynn, & Putzki, 2013). Several groups are developing more complex motor tasks in order to detect subtle deficits, such as dual-tasking (Downer, Kirkland, Wallack, & Ploughman, 2016; Kirkland, Wallack, Rancourt, & Ploughman, 2015) and standing balance (Spain et al., 2012). Kirkland et al. (2016) demonstrated that a bipedal hopping task can reveal motor deficits in a measurable way, even in participants who do not surpass the six-second clinical cut-off of the T25FWT (Kirkland et al.,

2016). In the bipedal hop test, PwMS in their 40's demonstrated neuromuscular deficits reminiscent of subjects 30 years their senior (Kirkland et al., 2016). This similarity to early aging may be related to changes in anticipatory motor control; the ability of the sensory-motor system to respond and adapt to changes in the environment (Krause, Weber, & Pollok, 2014). Early in the disease progression, PwMS have reduced anticipatory postural adjustments and smaller magnitudes of anticipatory muscle activation (Krishnan, Kanekar, & Aruin, 2012), which could be caused by subtle cerebellar network dysfunction (Romascano et al., 2015). Importantly, signs of cerebellar impairment are a significant predictor of more rapid walking disability and increased likelihood of a progressive disease course (Jacobs & Kasser, 2012). However, by the time cerebellar dysfunctions are detected on a magnetic resonance image (MRI), there are already clinical symptoms present (Weier et al., 2015). An assessment tool to detect subtle cerebellar deficits before they manifest into significant disability could identify PwMS who are more likely to have a progressive, rapid disease course and are in need of early rehabilitation. Earlier prescription of intense rehabilitation may then help delay the time to disability and slow progression in these high-risk patients.

A metronome timed task is useful in detecting impairments in anticipatory control. When PwMS were asked to synchronize finger tapping to a metronome beat, impairments in timing were related to widespread cortical thinning (Bonzano et al., 2013). Additionally, ability to time this finger tapping test could distinguish PwMS from healthy controls even at very low disability levels (Bonzano et al., 2013). Although some of the muscle weakness and balance difficulties in MS could be related to advanced neuromuscular aging (Kirkland et al., 2016), synchronization of movement to a stimulus seems to be preserved in aged individuals (Elliott, Wing, & Welchman, 2011). A timed complex motor task such as hopping has the potential to uncover unique

impairments in both physical function (hop characteristics) and anticipatory motor control (metronome timing).

As part of an overarching goal to develop a clinically relevant complex motor control test (strength and balance as well as anticipatory motor control), a task was developed that combines the hopping motor task timed with a metronome. Our aim was to characterize both the ability to anticipate and coordinate hopping at two metronome frequencies (60-bpm and 40-bpm) in a sample of people with MS, matched controls and elderly subjects.

2.1 METHODS

2.1.1 Participants

Following approval by the Health Research Ethics Board (HREB#14.231), MS participants were recruited from outpatient services with the help of physiotherapist, nurse, and neurologist collaborators. Both control groups, matched control (here on referred to as controls) and elderly control (here on referred to as elderly) groups, were recruited via word-of-mouth and posters. As this was a pilot study of a novel measurement, participants were recruited based on convenience and a priori sample size was not calculated.

Inclusion criteria for MS participants were: (a) an EDSS \leq 3.5 (the cut-off score for walking impairment), (b) the ability to walk without the use of an assistive device, (c) the ability to hop in place two times consecutively, (d) age between 18-64 years (e) relapse free in the previous three months, and (f) confirmed diagnosis of MS according to the McDonald criteria (Polman et al., 2011). Both the control and elderly subjects were required to walk without the use of an assistive device and hop in place two times. Control subjects were matched to MS subjects

by age, gender, and education, while the subjects in the elderly group had to be over the age of 70 years. Participants were excluded if they had any underlying diseases or injuries that could potentially affect bilateral hopping performance or a history of falls within the past month.

2.1.2 Procedure

After obtaining consent and gathering demographic information (age, gender, and level of education), participants completed the Montreal Cognitive Assessment (MoCA), T25FWT and the two hopping tests at different frequencies.

The MoCA is a brief, cognitive screening test that accurately measures overall cognition in individuals with MS (Dagenais et al., 2013). The T25FWT was administered as per the Multiple Sclerosis Functional Composite Instructions (Polman & Rudick, 2010). Participants walked a 25-foot linear course and average times were calculated. Walk times on the T25FWT slower than six seconds represent clinically meaningful and distinct performance benchmarks for impairment in the MS population (Goldman et al., 2013).

An instrumented walkway (Zeno Protokinetics, Havertown, PA, USA) and accompanying software was used to collect walking and hopping parameters. Participants completed a total of two hopping trials to the beat of a metronome (in randomized order) with two-minute rest periods between each trial. The metronome signal was recorded by the walkway for synchronization purposes. Previous research in Parkinson's disease suggested that 60-bpm was natural rhythm for human movement (Cubo, Leurgans, & Goetz, 2004) so we tested both 60-bpm and 40-bpm. Participants were instructed to hop forward along the walkway when they

heard the beat, while keeping both hands positioned on their hips throughout the trial. All participants received the same scripted instructions. Participants completed two passes over the 14-foot walkway for each condition. A ten beat familiarization period preceded each trial (Cubo et al., 2004).

2.1.3 Anticipatory Motor Control

Timing of the hop to the metronome beat was analyzed by extracting (to the thousandth second) the start of the metronome beat and when the participants' feet lifted from the mat (considered when both foot pressure equalled zero). Time delay was calculated such that, if a participant hopped before the beat (anticipation), their delay would be negative and after the beat, a positive delay. The average delay from the metronome (in seconds) was calculated from all the complete hops in the two trials. To determine the change in anticipatory motor control (adaptation), the difference between the delay on the last hop and the delay on the first hop for each condition was calculated. A change of 0 indicated no adaptation; with smaller values indicating improved anticipation. The number of hops per trial varied between participants, depending on how many hops it took to transverse the 14-foot walkway. On average, the number of hops per pass (14-feet) was 5-7.

2.1.4 Hopping Variables

Hopping parameters were divided into three categories, including measures of hopping capacity (integral pressure, hop length, hop width, hop time, percentage of time in stance (stance %), velocity, and centre of pressure (CoP) path efficiency), consistency (percent coefficient of variability (CV)), and symmetry (absolute difference from one of ratios). Details of the

parameters used are described elsewhere (Kirkland et al., 2016) as well as on page 48-49 of this thesis. Balance was quantified by extracting information on the x and y coordinates of CoP. Total CoP path length and range in both x and y directions was calculated for each hop, as demonstrated by others (Kalisch, Kattenstroth, Noth, Tegenthoff, & Dinse, 2011).

2.1.5 Data analysis

Descriptive statistics were reported as mean \pm standard deviation. One-way ANOVA tests were used to compare MS, elderly and control groups on demographic characteristics and scores on the clinical assessments (MoCA and T25FWT). A 3x2 repeated measures ANOVA was used to compare MS, control and elderly subjects between hopping conditions (40-bpm and 60-bpm). Bonferroni post-hoc corrections were applied if significance was observed. Relationships between hopping variables and clinical assessments were analyzed using simple linear regression. All data were analysed using SPSS version 21.0 (IBM SPSS Statistics, Chicago, Illinois, USA), with a significance set at $p < 0.05$.

2.3 RESULTS

2.3.1 Participants

We recruited 13 PwMS (10 females, 3 males; EDSS \leq 3.5), 9 matched controls (7 females, 2 males) and 13 elderly participants (7 females, 6 males). Some controls matched more than one MS participant. There were no differences in age ($F=51.85$, $p=1.00$) between the MS group and matched controls. There were also no differences in gender ($F=1.01$, $p=0.38$) or years of education ($F=0.33$, $p=0.72$) between groups (Table 2.1). Also, cognitive ability as measured

by MoCA did not differ between groups ($F=1.93$, $p=0.16$). There was only one MS subject who took longer than six seconds (cut off score) to complete the T25FWT.

Table 2.1 Demographic Information for Control, MS and Elderly groups

	Control	MS	Elderly
Age (years)	42.44 (11.13) ^a	42.00 (10.52) ^a	74.23 (4.76)
Gender	7 Female 2 Male	10 Female 3 Male	7 Female 6 Male
Post-secondary education (years)	4.11 (1.17)	3.46 (2.07)	4.00 (2.55)
EDSS Score	-	2.04 (1.16)	-
Years with MS (years)	-	12.25 (6.34)	-
MoCA	27.67 (1.66)	26.92 (3.10)	25.54 (2.60)
T25FWT (seconds)	3.90 (0.51) ^b	4.75 (0.65)	4.55 (0.60)

^a Different from elderly group at $p<0.01$; ^b Different from MS group at $p<0.05$; EDSS: Expanded disease severity scale; MoCA: Montreal Cognitive Assessment; T25FWT: Timed 25 Foot Walk Test; MS: multiple sclerosis; values are mean (standard deviation).

2.3.2 Comparing Metronome Frequencies

The average delay between the metronome beat and lifting off was significantly longer during 40-bpm than 60-bpm for all groups (Table 2.2); about 2.5 times longer in elderly and 8 times longer in MS and controls ($F=17.88$, $p<0.01$). There was no significant difference between groups ($F=1.05$, $p=0.36$) or an interaction effect between condition and group ($F=0.03$, $p=0.98$). In terms of adapting to the different frequencies of the metronome beat, at 60-bpm all groups showed no change over time (value at or about 0; Table 2.2). However, at 40-bpm, elderly group and controls lessened their delay while the MS group's delay was extended suggesting they had difficulty maintaining the 40-bpm pace (condition: $F=1.43$, $p=0.24$; group: $F=1.98$, $p=0.16$; condition x group: $F=3.58$, $p=0.04$; Figure 2.1). The 40-bpm frequency was slower, therefore, it was not surprising that there was significantly longer stance time between hops ($F=103.47$,

p<0.01) and significantly longer hop time compared to 60-bpm in all groups (F=144.71, p<0.01; Table 2.2). Additionally, total CoP path length per hop was greater during 40-bpm than 60-bpm for all groups (F=54.52, p<0.01), which could be attributed to increased time in stance during the 40-bpm condition.

Table 2.2 Hopping characteristics for Control, MS and Elderly groups

	bpm	Control	MS	Elderly
Metronome Timing				
Average Delay After Metronome (s) (positive=delay, negative=anticipate)	40	0.24 (0.35) ^c	0.32 (0.47) ^c	0.42 (0.42) ^c
	60	-0.03 (0.23)	0.04 (0.28)	0.17 (0.31)
Adaptation Learning (difference between last hop and first hop)	40	-0.07 (0.12)	0.11 (0.26) ^a	-0.18 (0.30)
	60	-0.02 (0.06)	0.00 (0.04)	0.03 (0.11)
Hopping characteristics				
Integral Pressure	40	166.29 (25.86) ^c	180.58 (42.92) ^c	186.40 (54.94) ^c
	60	111.82 (22.17)	130.64 (52.94)	134.60 (43.20)
Hop Length (cm)	40	70.02 (9.07) ^a	61.69 (22.62)	48.02 (12.29)
	60	71.48 (5.06) ^b	62.73 (25.41) ^a	45.16 (9.65)
Hop Width (cm)	40	21.22 (6.30)	21.45 (5.63)	15.00 (8.73)
	60	21.52 (6.37)	22.17 (5.09) ^a	16.53 (5.48)
Hop Time (s)	40	1.44 (0.07) ^c	1.46 (0.23) ^c	1.51 (0.28) ^c
	60	0.99 (0.05)	1.08 (0.33)	1.12 (0.26)
Stance (%)	40	83.51 (2.64) ^c	85.03 (5.11) ^c	85.80 (4.35) ^c
	60	77.30 (3.12)	79.93 (7.30)	81.94 (4.09)
Velocity (cm/s)	40	48.80 (7.39) ^{bc}	42.72 (14.77) ^c	32.61 (9.54) ^c
	60	72.28 (6.61) ^b	61.91 (29.87) ^a	41.29 (9.74)
Hopping consistency (%CV)				
Integral Pressure Variability	40	18.51 (3.56) ^a	26.30 (15.27)	33.46 (10.52)
	60	21.85 (6.02) ^a	21.02 (4.67) ^a	36.69 (21.00)
Hop Length Variability	40	10.36 (4.05)	16.54 (16.26)	20.73 (12.16)
	60	11.95 (6.89) ^a	12.49 (4.74) ^a	21.10 (11.48)
Hop Width Variability	40	8.05 (2.52)	14.15 (15.92)	28.68 (54.56)
	60	9.11 (4.23)	10.41 (4.90)	16.69 (9.90)
Hop Time Variability	40	10.18 (5.68) ^a	14.60 (13.88)	23.78 (13.64)
	60	9.42 (6.90)	9.35 (5.69)	26.05 (24.10)
Stance % Variability	40	2.79 (1.61)	3.82 (4.19)	4.92 (3.68)
	60	3.98 (2.00)	3.67 (1.47)	6.29 (4.58)
Hopping symmetry (ratio difference from 1)[#]				
Integral Pressure Symmetry	40	0.08 (0.07)	0.16 (0.17)	0.15 (0.10)
	60	0.14 (0.12)	0.11 (0.09)	0.21 (0.13)
Hop Length Symmetry	40	0.01 (0.02)	0.04 (0.08)	0.06 (0.06)
	60	0.02 (0.04)	0.01 (0.03)	0.04 (0.07)
Stance % Symmetry	40	0.01 (0.01)	0.03 (0.03)	0.02 (0.03)
	60	0.01 (0.01)	0.02 (0.03)	0.04 (0.03)
Hopping balance (CoP)				
CoP Path Length* (cm)	40	53.24 (8.66) ^c	58.24 (15.36) ^c	60.22 (13.04) ^c
	60	42.32 (6.99)	45.61 (10.87)	48.91 (11.81)
CoP Range X* (cm)	40	16.56 (3.95) ^c	16.85 (5.46)	19.50 (5.21)
	60	14.73 (4.85)	15.29 (5.46)	18.58 (5.04)
CoP Range Y* (cm)	40	12.71 (3.12)	16.32 (5.33)	14.25 (5.36)
	60	11.85 (2.95)	15.15 (4.46)	13.52 (4.61)
CoP Path Efficiency % (anterior/posterior)	40	73.29 (11.97) ^c	69.72 (12.19)	60.41 (15.00) ^c
	60	66.78 (15.37)	63.40 (14.19)	54.39 (15.17)

^a Different from elderly group at $p < 0.05$; ^b Different from elderly group at $p < 0.01$; ^c Different from 60-bpm in same group at $p < 0.05$; [#] Ratios are absolute value difference from 1, therefore, closer to 0 is more symmetrical; *Average path length/range moved per hop; CV: coefficient of variation; DS: double support; CoP: center of pressure; MS: multiple sclerosis; bpm: beats per minute; values are mean (standard deviation).

2.3.3 Metronome Timing Adaptation

In terms of metronome timing, the average delay from the metronome was not different between groups; what distinguished PwMS from people their own age was their impaired ability to match the hop to the metronome beat over consecutive hops. The MS group had an opposite pattern of adaptation compared to the elderly and matched controls during 40-bpm (condition x group: $F=3.58$, $p=0.04$; Figure 2.1). The difference from last to first hop during 40-bpm for the MS group was 0.11 (SD 0.26); a positive value indicating that, on average, the MS group became further delayed from the metronome beat. This value was significantly different and the pattern opposite compared to the elderly group, who had a difference of -0.18 (SD 0.30). The elderly group anticipated the beat; becoming less delayed from the metronome by the end of the trial. The control group also had a negative value (-0.07 (SD 0.12)), indicating that they too learned to anticipate the beat. However, they were not significantly different from either group; their value fell between the MS and elderly groups (Figure 2.1). There were no differences between groups for the 60-bpm condition (condition: $F=1.43$, $p=0.24$; group: $F=1.98$, $p=0.15$).

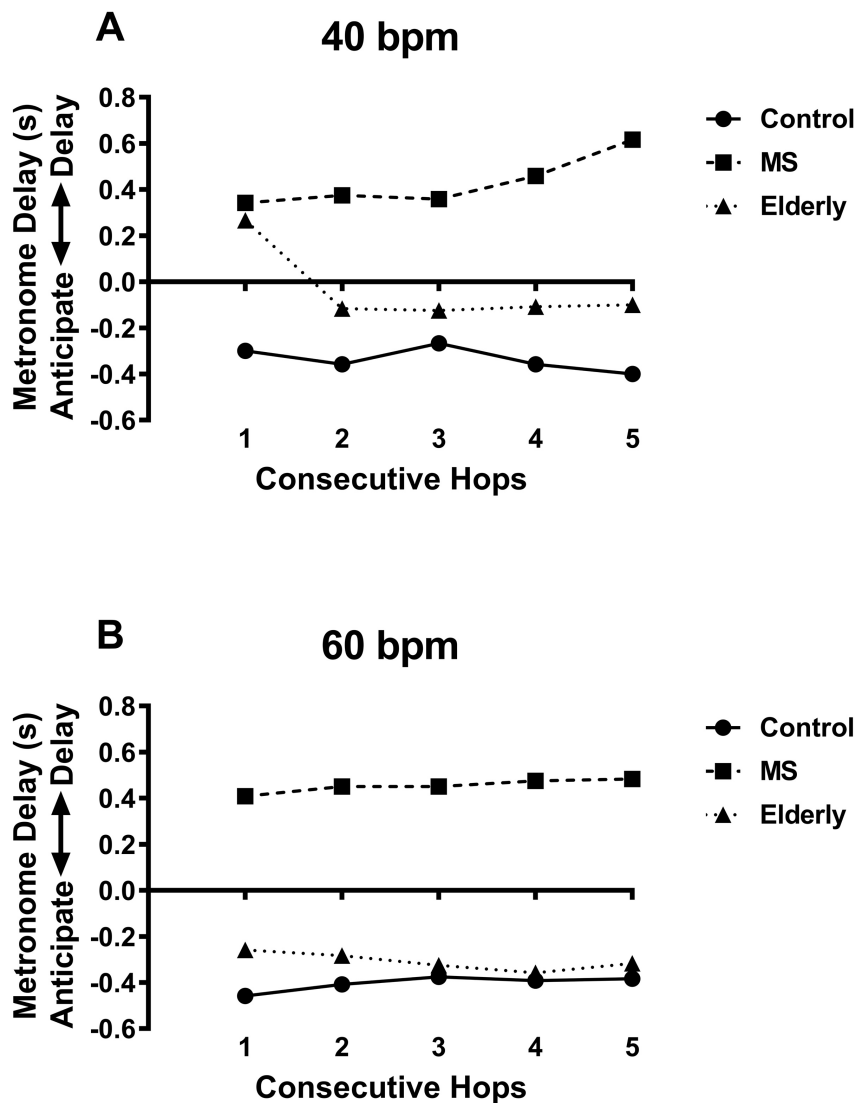


Figure 2.1: Representative metronome timing for Control, MS and Elderly groups.

People with MS tended to be delayed from the metronome beat with no anticipation during 4-bpm, whereas the control group consistently anticipated the beat. The elderly group learned over time to anticipate the beat. All groups had similar adaptation learning patterns for the 60-bpm condition. Numbers labeling the x-axis represent consecutive hops in a continuous sequence. Data used was from one subject from each group that represented the group average in adaptation learning. MS: multiple sclerosis; bpm: beats per minute.

2.3.4 Motor Performance During Metronome-Timed Hopping

In most measured hopping variables, the MS group's values fell between the matched control and elderly groups. The MS group performed more like the elderly group during the 40-bpm hop than the 60-bpm hop. For example, at 60-bpm, hop length of the control and MS groups were significantly longer than the elderly group (Control: 70.02cm (SD 9.07), MS: 61.69cm (SD 22.62), Elderly: 48.02cm (SD 12.29)). At 40-bpm, the MS group were no longer significantly different from the elderly group (condition: $F=0.01$, $p=0.91$; group: $F=6.32$, $p=0.01$; condition x group: $F=1.74$, $p=0.19$; Table 2.2 and Figure 2.2A). Similarly, when analyzing hopping velocity, even though speed was set by the metronome beat, at 40-bpm the control group (but not the MS group) were significantly faster than the elderly (condition: $F=78.63$, $p<0.01$; group: $F=7.21$, $p<0.01$; condition x group: $F=5.25$, $p=0.01$; Table 2.2). In terms of measures of hopping consistency (%CV), the results at 40-bpm and 60-bpm were similar to those described above. For example, at 60-bpm, integral pressure variability of the control and MS groups were significantly less than the elderly group (Control: 18.51 (SD 3.56), MS: 26.30 (SD 15.27), Elderly: 33.46 (SD 10.52); Table 2.2 and Figure 2.2B). At 40-bpm, the MS group were no longer significantly different from the elderly group (condition: $F=0.03$, $p=0.88$; group: $F=251.12$, $p<0.01$; condition x group: $F=1.17$, $p=0.32$; Table 2.2 and Figure 2.2A).

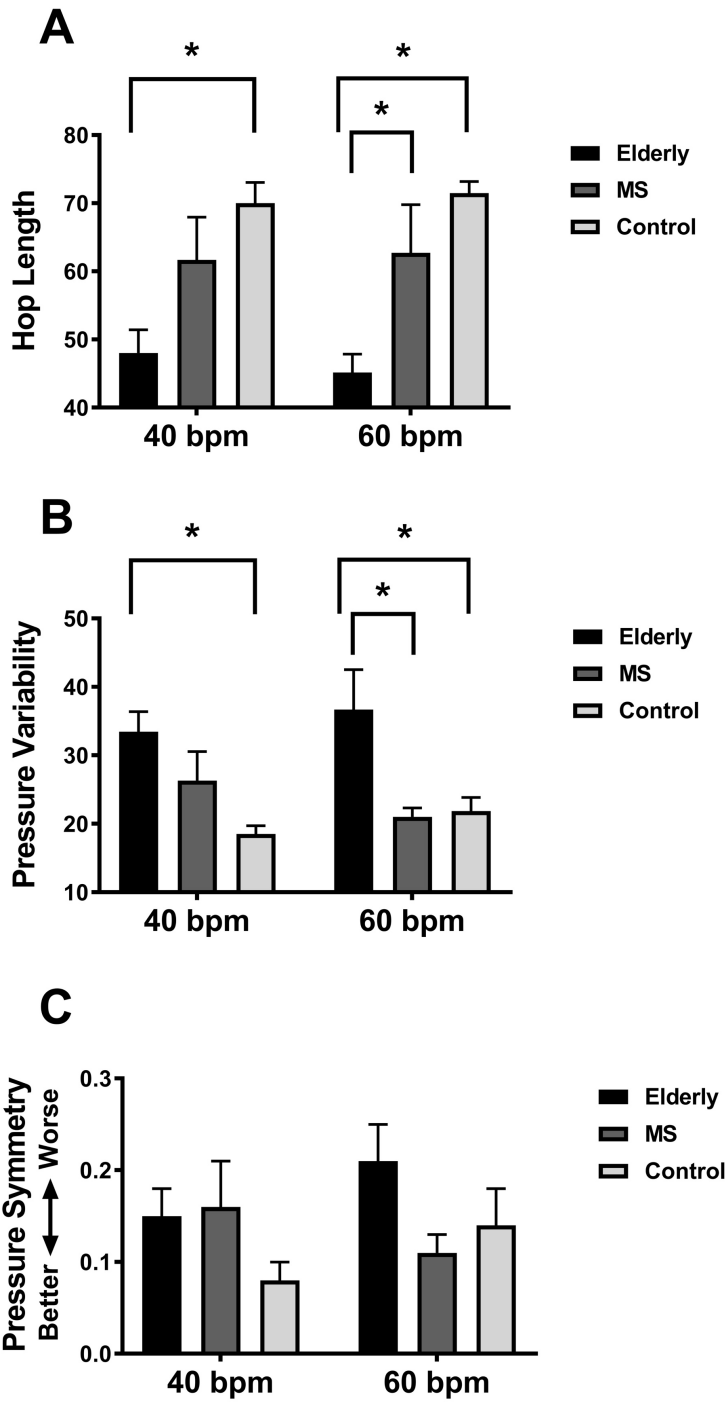


Figure 2.2: Difference in hopping characteristics between the Control, MS and Elderly groups.

(A) Hop length (cm) and (B) pressure variability (percent coefficient of variability) was significantly different ($p < 0.05$) between MS and elderly groups during only 60-bpm, but not 40-bpm. The control group was consistently different from the elderly group ($p < 0.05$). (C) Pressure symmetry (ratio calculated as absolute difference from 1 between both feet) did not differ between groups. MS: multiple sclerosis; bpm: beats per minute; error bars represent standard error of the mean.

2.3.5 Relationship between Metronome Delay and Cognition

Ability to time motor movement to the metronome was related to cognition in the MS group, but not the control or elderly groups. The delay from the metronome beat to the moment the participant's feet left the ground on the first hop at 60-bpm significantly predicted scores on MoCA in the MS group ($R=0.55$, $\beta=4.64$ (SD 4.63), $F=4.85$, $p=0.05$, Figure 2.3A). For every second delay from the metronome beat, their MoCA score was lowered about 4.5 points (15%). This effect was not seen in the control or elderly groups ($R=0.07$, $p=0.86$; $R=0.17$, $p=0.57$; Figure 2.3B and 2.3C).

2.3.6 Relationship between hopping characteristics and T25FWT

In terms of physical status (T25FWT), several hopping variables (but not timing variables) predicted walking in the MS group. For instance, in both 40-bpm and 60-bpm conditions, shorter hop length predicted longer time to complete the T25FWT (Figure 2.3D, 40-bpm: $R=0.68$, $\beta=-0.02$ (SD 0.01), $F=9.35$, $p=0.01$; 60-bpm: $R=0.68$, $\beta=-0.02$ (SD 0.01), $F=9.63$, $p=0.01$). Similarly, greater asymmetry in pressure between the feet predicted longer times on the T25FWT, but only during 40-bpm (Figure 2.3E, 40-bpm: $R=0.77$, $\beta=2.93$ (SD 1.63), $F=15.63$, $p < 0.01$; 60-bpm: $R=0.04$, $p=0.91$). Lastly, more variable pressure indicated longer time to complete the T25FWT (Figure 2.3F, 40-bpm: $R=0.58$, $\beta=0.02$ (SD 0.02), $F=5.49$, $p=0.04$; 60-bpm: $R=0.72$, $\beta=0.10$ (SD 0.03), $F=11.48$, $p < 0.01$). Overall, the relationships between bipedal

hopping ability and longer time to complete the T25FWT were stronger during hopping at 40-bpm than 60-bpm. However, these relationships were only within the MS group, as hopping variables did not significantly predict T25FWT in the control or elderly groups (data not shown). Interestingly, although predictive of the T25FWT, hopping variables were not predictive of the EDSS score in the MS group.

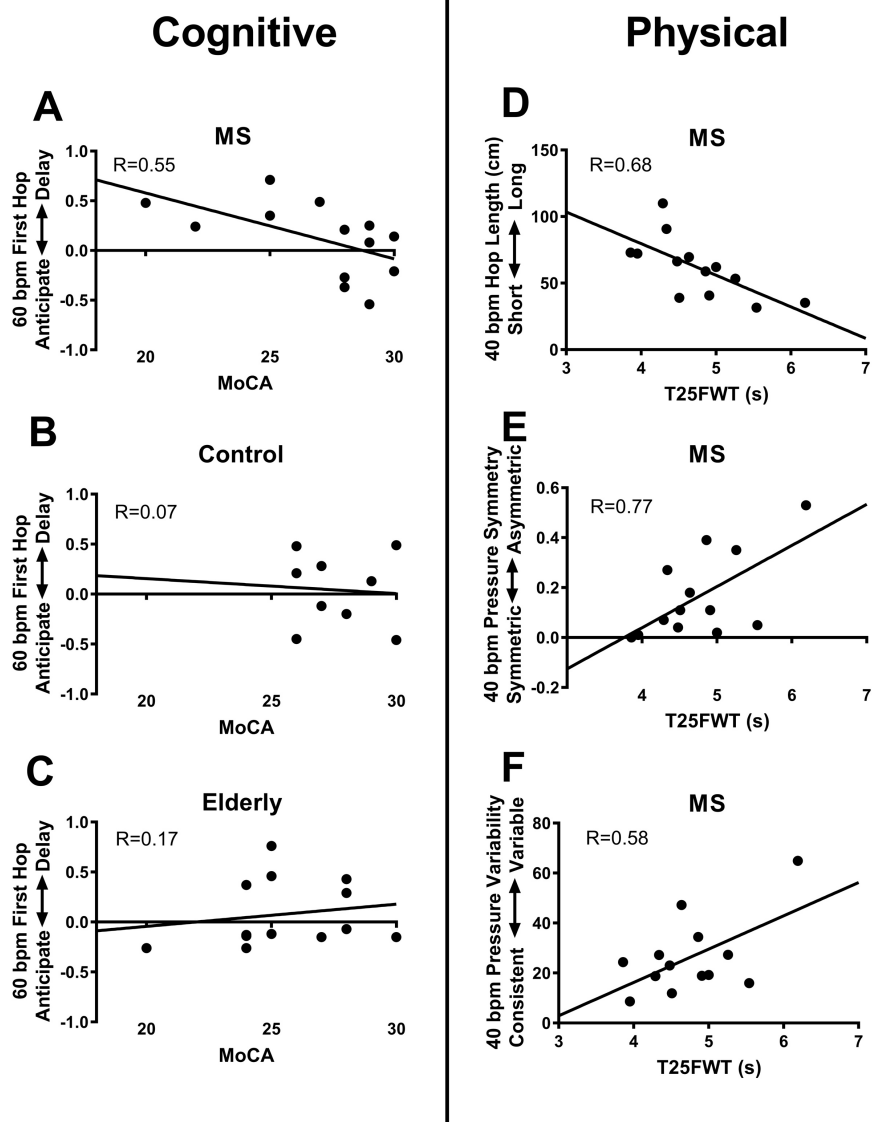


Figure 2.3: Metronome timing and hopping variables significantly predict cognition and walking ability in people with MS.

(A) Timing of the first hop of 60-bpm significantly predicted MoCA score ($R=0.55$, $\beta=4.64\pm 4.63$, $F=4.85$, $p=0.05$). (B, C) Timing of the first hop of 60-bpm did not significantly predict MoCA score in either control ($R=0.07$, $p=0.86$) or elderly groups ($R=0.17$, $p=0.57$). (D) Hop length significantly predicted T25FWT ($R=0.68$, $\beta=-0.02\pm 0.01$, $F=9.35$, $p=0.01$). (E) Pressure asymmetry significantly predicted T25FWT ($R=0.77$, $\beta=2.93\pm 1.63$, $F=15.63$, $p<0.01$). (F) Pressure variability significantly predicted T25FWT ($R=0.58$, $\beta=0.02\pm 0.02$, $F=5.49$, $p=0.04$). MoCA: Montreal Cognitive Assessment; T25FWT: Timed 25 Foot Walk Test; MS: multiple sclerosis; bpm: beats per minute.

2.4 DISCUSSION

Our study aimed to determine whether metronome timed bipedal hopping could detect anticipatory motor control impairments among PwMS in comparison to matched controls and an elderly group. In terms of neuromuscular control of timed hopping, we found that although controls performed better than the elderly group in most hopping variables, MS subjects ≤ 3.5 EDSS were not significantly different from either control or elderly participants. This finding aligns with our prior results in self-paced hopping (Kirkland et al., 2016). Requiring the subject to hop to the beat of a metronome provided the additive ability to detect impairments in feed forward control. Delay in timing was related to cognitive rather than physical symptoms in MS.

2.4.1 Does the Metronome Frequency Matter?

We examined two metronome frequencies: 40-bpm and 60-bpm. We expected more challenges during 40-bpm since 60-bpm is considered to be a more natural rhythm (Cubo et al., 2004). We found that during the more rhythmical 60-bpm, MS participants performed at a level similar to matched controls. Similarly, rhythmic auditory stimulation has been shown to improve gait, fatigue, and quality of life in individuals with MS when using natural gait rhythms (Conklyn et al., 2010; Seebacher et al., 2017). Time structure of a rhythm is an essential element relating sound specifically to motor behaviour (Thaut, Kenyon, Schauer, & McIntosh, 1999). Therefore, in the same way that a natural rhythm stabilizes gait (Conklyn et al., 2010; Seebacher et al., 2017), it also seems to improve hopping performance. Hopping at 40-bpm may challenge the system more by involving more cognitive processing and active timing, potentially exposing

more hopping deficits. Moving forward, 40-bpm may be the optimal metronome frequency to use for a clinical test.

2.4.2 Impaired anticipatory feed-forward control in people with MS

We found that despite very low levels of disability, PwMS did not learn to match their hop and anticipate the metronome beat in comparison to the other groups tested. The elderly and control groups became closer to the metronome beat over time while the MS group actually became further delayed from the beat during the 40-bpm condition. Audio cues paired with sensory and motor input to the cerebellum allow learning and feed-forward control in order to anticipate the next beat (Penhune & Doyon, 2005). The cerebellum in connection with the posterior parietal cortex is the main center responsible for this adaptation (Krause et al., 2014; Penhune & Doyon, 2005). In PwMS, even in the earlier days of symptom onset, there is neurodegeneration in the cerebellum (Rocca & Filippi, 2017), specifically in the dentate nucleus (Albert et al., 2016; Sbardella et al., 2017) and the middle and superior peduncles (Preziosa et al., 2014). Consequently, this neurodegeneration causes a functional disruption of cortico-ponto-cerebellar and spino-cerebellar inputs (Dogonowski et al., 2014). Disintegration of regional processing in the cerebellum and disruption of input into the cerebellum dramatically affects motor learning, which could be one of the contributing factors towards this deficit in timing adaptation. Although we did not examine MS lesions in this study, MS participants even early in disease, often exhibit cerebellar dysfunction and consequent problems with anticipatory control, which may be one of the mechanisms causing subtle disability in people in the early stages of MS. Rehabilitation has the potential to offset self-reported impairments. With further

refinements, a metronome hopping test could help clinicians measure impairment and target appropriate rehabilitation programs earlier in MS.

2.4.3 Metronome hopping as a potential rehabilitation outcome measure in MS

Our overarching goal was to build a potentially useful clinical measure of neuromotor control in order to measure the benefit of future rehabilitation interventions. Neuroplasticity exists, and therefore rehabilitation has the potential to improve impairment and disability in MS (Snodgrass et al., 2014). However, due to the heterogeneous nature of MS, therapists need useful tools to help focus their interventions. For example, therapy to address physical impairments would focus on measurements of strength and balance whereas therapy to improve anticipatory motor control would utilize complex tasks requiring agility and timing (O'Sullivan, Schmitz, & Fulk, 2013). Largely due to heterogeneity between individuals with MS, we were not able to differentiate PwMS from controls in terms of timing delays and adaptation. However, we did observe patterns in which individuals with MS had difficulty matching the hop to the metronome beat over time as well as a significant relationship between this delay and cognition measured by MoCA. Our study represents a first step in creating a relatively simple tool to provide greater granularity and clinical phenotyping in the early stages of the disease. With further refinement, validity of a clinically-measured version of this test could be created and translated into the clinical setting.

2.4.4 Limitations

A major limitation in this study was the small sample size. As a pilot study, we were unable to examine outcomes based on disability level. For example, it would be important to

examine how a metronome bipedal hopping test detected impairment in people who have EDSS of 0 (no observable deficits). Future studies should investigate the applicability of this measure in a larger cohort to determine whether differences actually exist. Also, we did not quantify grey or white matter lesions in the cerebellum or cerebellar circuitry. Lastly, mass, leg length or height was not measured, and we were therefore unable to control for these factors when comparing hop length and width as well as pressure on the walkway.

2.5 CONCLUSION

During a metronome hop test, PwMS performed similarly to the matched controls during 60-bpm, but shifted towards the elderly group's ability during 40-bpm. PwMS trended to become more delayed from the metronome beat over time, whereas both control and elderly groups learned to anticipate the beat. This suggests that PwMS do have subtle impairments in both motor characteristics and anticipatory feed-forward control that can be detected by a metronome hop test.

2.6 SOURCE OF FUNDING

This study was supported by the Dean's Innovation Award, Faculty of Medicine, Memorial University (MP), the Ignite Research Award Research and Development Corporation of NL (MP), the Canada Research Chairs Program (MP) and the Translational and Personalized Medicine Initiative, Faculty of Medicine, Memorial University (MK).

2.7 CONFLICT OF INTEREST

The authors report no conflicts.

Chapter 3: Discussion

3.1 OVERVIEW

The goal of this thesis was to characterize the ability of individuals with MS to synchronize hopping to a metronome, and to determine whether this ability differed from control and elderly participants. We found that individuals with MS were not able to learn and adapt to the metronome over time during the 40-bpm condition; both control and elderly groups were able to adapt to shorten synchronization error from the metronome beat. This finding could indicate subtle cerebellar impairment in these individuals with mild MS. We also aimed to determine whether the frequency of the metronome had an impact on metronome timing and hopping variables. We found that individuals with MS performed closer to the control group when hopping at a more natural rhythm (60-bpm), while they exhibited more synchronization error and displayed hopping characteristics resembling the elderly group at 40-bpm.

In this chapter, potential mechanisms underlying differences in timing ability and variation between metronome frequencies will be discussed. Also, impairments typical among MS patients will be compared to senescence, in the context of impaired hopping ability. Lastly, the importance of having sensitive, reliable and accurate measurement tools will be discussed followed by future directions in translating metronome hopping into both a research outcome measure and clinical measurement tool.

3.2 METRONOME TIMING

3.2.1 40-bpm versus 60-bpm

Participants with MS seemed to be able to better synchronize their movement over time during the 60-bpm condition than during the 40-bpm metronome. Although faster, the 60-bpm metronome is a natural rhythm, as it is similar to internally generated rhythm for gait within the brain (Cubo et al., 2004). As previously stated, if the external trigger for timing is similar to the naturally generated internal timing beat, then internal timing mechanisms in the basal ganglia will become more involved, and the cerebellar circuit will not be as active (Merchant & de Lafuente, 2014). The frequency of 60-bpm is very close to what a participant would hop without a metronome (internally generated) as shown previously in self-selected hopping (Kirkland et al., 2016). Therefore, the participant may be able to turn on ‘auto-pilot’ more during the 60-bpm condition, as it is a recognized beat and thus basal ganglia can control this autonomic timing. Since the natural timing so closely matches this beat, there is little error to detect and correct, so responsibility is withdrawn from the cerebellar circuitry (Merchant & de Lafuente, 2014). In this way, comparing the ability to synchronize movement to 60-bpm versus 40-bpm is comparing the ability of basal ganglia circuitry to generate timing rhythm versus cerebellar ability to detect and correct synchronization error, respectively. Other researchers have compared frequencies for biomechanical purposes such as leg stiffness (Hobara, Kobayashi, Yoshida, & Mochimaru, 2015), however, metronome frequencies have never been compared for purposes of comparing integrity of various neural circuitry in individuals with neurological disorders. Therefore, the novelty of the current study was in demonstrating that the ability to synchronize hopping differed depending on metronome frequency, which may be attributable to differences between the integrity of the basal ganglia and cerebellar circuitry. Specifically, we found that participants with MS did not perform at the level of controls when cerebellar circuitry was more dominantly relied upon. This is logical, as the basal ganglia circuitry seems to be preserved in the early

stages of the disease; participants with MS could compensate by relying more heavily on basal ganglia circuitry during 60-bpm than cerebellar circuitry, and thus synchronized their movement to the metronome similarly to control and elderly subjects during the 60-bpm condition. Since there was very little error during 60-bpm, subjects retained similar timing delay across all hops in the trial, with very little error detection and correction suggesting there was little cerebellar processing required. Even though 60-bpm is actually faster, all groups had shorter initial timing delays during 60-bpm, than 40-bpm, which was also shown by Shin and Demura (2009) in a group of elderly individuals (Shin & Demura, 2009). However, when the beat was slowed from the natural timing rhythm to 40-bpm, basal ganglia internally generated timing could no longer be extensively relied upon and resultant synchronization errors were likely detected and relayed to the thalamus by the cerebellum. Individuals with MS differed from control subjects in this trial of 40-bpm, possibly indicating impairment in the cerebellar circuit. Future work using near-infrared spectroscopy or electroencephalography would help to determine differences in brain activation during rhythmic timing.

3.2.2 Metronome Adaptation May Indicate Early Cerebellar Impairment

We found that participants with MS were unable to adjust their hopping frequency to better synchronize their movement with the metronome over subsequent cues, which could indicate early involvement of cerebellar processing networks. Following a metronome cue and subsequent motor movement, the cerebellum is responsible for recognizing any delay between these two events as a timing error and feeding information forward to the thalamus on adjustments to minimize this inaccuracy (Molinari et al., 2007). The control and elderly subjects could achieve this, as they adjusted their hopping frequency to become closer to the beat over

time and anticipated the beat. The MS subjects, however, did not adjust their timing throughout the trial. The first time the metronome is heard, basal ganglia circuitry and motor entrainment circuits are responsible for minimizing the delay from metronome cue to movement onset (Thaut et al., 2014). The MS group did not differ from control or elderly individuals in terms of overall timing. However, during the adaptation phase, when greater reliance should be placed on cerebellar circuitry, participants with MS were challenged to adapt. They maintained the same timing delay throughout all the hops in the trial, which could be attributed to early GML's in the cerebellum (Geurts et al., 2007; Gilmore et al., 2009; Kincses et al., 2011; Kutzelnigg et al., 2007; Kutzelnigg et al., 2005; Papadopoulos et al., 2009). Even though GMLs may not be visible on an MRI, GMLs can often precede the formation of WMLs (Calabrese et al., 2010; Calabrese et al., 2007). Additionally, there is evidence to support neurodegeneration in the cerebellum early in the disease course, possibly even from the onset of CIS (Rocca & Filippi, 2017). Specifically, this early neurodegeneration occurs in the dentate nucleus and middle and superior peduncles (Albert et al., 2016; Preziosa et al., 2014; Sbardella et al., 2017). The superior peduncle is the main connection for feedforward information to be relayed to the thalamus (Preziosa et al., 2014). Therefore, degeneration in this area would result in a disruption of this pathway and consequent disintegration of error correction adjustments during rhythmic synchronization. Thus, there could be clinically silent lesion activity and degeneration occurring in the cerebellum, which could explain why the MS group were unable to adapt their timing. Previous studies have suggested cerebellar impairment occurs early in the disease course (Rocca & Filippi, 2017), but this impairment has yet to be clinically measured. This study provides the first evidence that a clinical measurement has the potential to detect possible cerebellar impairment prior to obvious clinical symptoms (as evidenced by EDSS score ≤ 3.5). Therefore, this novel measurement tool

has the potential to expand the range of disability levels in which clinicians can detect cerebellar impairment within a clinical setting.

3.3 MULTIPLE SCLEROSIS AND EARLY SENESCENCE

Another novel aspect of this study was the comparison between individuals with MS and an elderly group. Since several of the impairments and pathology of MS are also characteristic of early senescence, it is logical to compare clinical functioning to an elderly group to examine how similar pathologies translate to clinical functioning. Although logical, there is a paucity of evidence that directly compares individuals with MS to elderly individuals. We found that hopping ability in individuals with MS shifted towards that of elderly individuals, however, inability to adapt to metronome timing was an impairment unique to individuals with MS.

3.3.1 Elderly Display Accurate Sensorimotor Synchronization

In terms of metronome timing ability, the elderly group could adjust their timing to synchronize the beat. Although there is significant age-related decline in both grey and white matter in the cerebellum after age 50, most of this atrophy occurs in the cerebellar vermis (Luft et al., 1999). The medial and lateral hemispheres are very minimally or insignificantly affected by aging (Luft et al., 1999). When measuring movement synchronization abilities in individuals with cerebellar lesions, Ivry et al. (1988) found that the medial hemisphere of the cerebellum is associated with the ongoing regulation of the motor response, as individuals with medial cerebellar lesions could elicit a timed motor response but were not able to adjust their movement to increase accuracy over time (Ivry, Keele, & Diener, 1988). Therefore, because the medial hemisphere, important for error detection and adjustment in rhythmic timing, is not the region of

the cerebellum affected by aging, this ability is likely preserved. Our study aligns with this theory, as the elderly group could adapt over time to become closer to the metronome cue similar to that of the control group. This difference in ability to adapt suggests that elderly individuals and individuals with MS seem to have different areas of the cerebellum affected, which possibly creates differences in the ability to perform sensorimotor synchronization. Metronome hopping may therefore be a useful measure in individuals with MS particularly as they age; declines in the two aspects of this measure (delay vs. adaptation) could be attributed to cerebellar dysfunction due to either MS, as we have learned from this study, or due to the natural process of aging.

3.3.2 People with MS Display Aging Muscle Characteristics

Although we demonstrated that metronome timing is preserved in older adults, many of the motor hopping variables were influenced by age-related deficits, which were also present in younger individuals with MS. For instance, we found that participants with MS hopped greater distances than elderly individuals, but still shorter than participants their own age. Shorter hop length could be due to insufficient propulsion since based on findings from other studies it is possible that even in this early disease state, muscle atrophy of type IIa muscle fibres (fast-twitch fatigue resistant) has already been initiated (Garner & Widrick, 2003). One of the muscles required for producing strength for a long hop is the quadriceps, which is heavily comprised of type IIa muscle fibres (Smith, 2014). Therefore, early atrophy of these fibres could be an underlying contributing factor to a shorter hop. Similar atrophy also occurs with aging, and therefore it is likely that elderly individuals' quadriceps strength would also be affected in a similar fashion (Nilwik et al., 2013). Our findings confirmed that, in fact, elderly participants

produced the shortest hop of any of the groups. It was interesting that MS participants also exhibited a shorter hop than their age and gender matched controls, which suggests that they may be beginning to manifest muscle atrophy reminiscent of people 30 years their senior.

Resistance training has a large positive impact on muscle strength, and can help to withstand the effects of atrophy that occurs with aging (Nilwik et al., 2013; Stevens et al., 2013). Although we did not collect information regarding participation in resistance-based exercise, it is reasonable to think that progressive resisted exercise could help alleviate or stall muscle fibre atrophy associated with MS and with the natural course of aging. Several studies have confirmed that targeted lower extremity resistance exercise can improve lower extremity strength among people with MS (Dalgas, 2011). However, it is important to note that strength declines once training ceases. This suggests that adherence to exercise in MS must be lifelong to avoid excessive muscle atrophy. In any case, hopping may be a useful tool to track and monitor the progression of muscle strength due to resistance training in individuals with MS.

3.3.3 Balance and Coordination During Hopping

Although both individuals with MS and elderly individuals experience balance and coordination impairments, neither of these impairments were able to be detected using bipedal hopping. There were no differences between MS, control or elderly groups when examining hopping variables such as CoP (balance) or symmetry (bilateral coordination). Among MS subjects, balance and coordination impairments emerge with increasing disability, and become obvious once walking disability is evident (Martin et al., 2006). It is likely that our MS cohort have yet to experience these impairments. However, it is also likely that there was heterogeneity

within the small sample we measured. Furthermore, balance and coordination impairments are also dependent upon specific location of lesions (vestibular system or corpus callosum). The substantial heterogeneity possibly contributed to lack of significance in hopping balance. A larger sample size would provide greater scientific rigor in comparing deficits in variables suggestive of balance/coordination such as variability and symmetry measures in individuals who have specific lesions of interest. In terms of the elderly group, as previously stated, since only one in every five elderly individuals experience problems with their balance (Lin & Bhattacharyya, 2012), it is possible that our sample size was too small and likely only consisted of a few individuals who had balance impairment.

3.4 METRONOME HOPPING AS A MEASUREMENT TOOL

3.4.1 Importance of Measurement

Measurement is extremely important in both clinical care and research, as the outcomes provided by the measurement tool provide knowledge and guidance for treatment and progress. Since MS presents a variable, progressive disease course, measurement is a crucial aspect to track progression over time (Bowden et al., 2012). Performance on repeated clinical measures guides medication prescription and advises treatment plans and their modifications (Rannisto et al., 2015). Sensitive measurement tools not only provide key information for clinicians, but also researchers who use them to determine the effectiveness of interventions under consideration (Bowden et al., 2012). There are a variety of measurement tools available for individuals with MS; many of which focus on walking ability as walking is expected to decline throughout the disease course (Kalron et al., 2015). However, with emerging technology, our ability to detect and diagnose subtle changes is improving with the use of high resolution MRI, for example,

leading to earlier diagnosis and intervention (Karabudak, 2015). Therefore, individuals are now being diagnosed with MS before major clinical symptoms arise (such as in radiologically isolated syndrome) (Rojas et al., 2015). However, a measurement problem still exists in that in both MS clinical and research settings, many currently used measurement tools have floor effects (Karabudak et al., 2015); participants are excelling on all the measures and appear to have no disability. However, using MRI and other biomarkers, we can appreciate that there is a mismatch between radiological findings and clinical findings and blunted ability to detect subtle cognitive and sensorimotor impairments that are the sequelae of new MS lesions and neurodegeneration. It is important to appreciate that this underlying pathology will eventually manifest into disability. Therefore, many researchers and clinicians aim to target these individuals with MS with no disability, in order to slow or halt accumulation of lesions and degeneration before disability begins to progress (Campbell et al., 2016). The objective of this study was to develop a test that could expand this range of measurement, and expose subtle disability in individuals with MS early in the disease course whose problems would go unnoticed using the current clinical assessment. Metronome hopping achieved this goal. This challenging motor task of hopping demonstrated that people with MS with low EDSS scores and no apparent walking disability did not hop with the same ease as people their own age, but were beginning to demonstrate some of the deficits associated with muscle senescence. Additionally, adding a metronome to hopping also exposed those who had cerebellar dysfunction by measuring timing difficulty, thus providing an indication of cerebellar connectivity impairment. Moving forward, this measure has the potential to widen the assessment window so that individuals with MS can be targeted and accurately monitored for treatment and rehabilitation. With further refinement, this innovative measure can be useful in both the research and clinical settings, which will be discussed below.

3.4.2 Metronome Hopping as an Outcome Measure

Emerging rehabilitation trials are focusing on various interventions (such as medication and exercise) to delay the onset and slow the progression of disability. For individuals with MS with minimal disability, it is difficult to measure change when impairment is not detected. Hence, interventions are difficult to prove efficacious. We demonstrated that metronome hopping can help address this issue because it can provide more specificity to detect changes induced by interventions (such as strength, coordination and symmetry), thereby reducing the floor effect commonly seen in outcome measurements. As mentioned, precise measurement helps clinicians and researchers develop and test more effective and targeted interventions. In this study, we have the benefit of using a highly sensitive instrumented walkway (Zeno Protokinetic Walkway) providing extremely precise measurements with low measurement error. It would be important in future studies to develop its clinical validity, reliability and usefulness in a clinical setting perhaps without using an instrumented walkway.

3.4.3 Metronome Hopping as Clinical Assessment Tool

There are five main requirements to consider when developing any measurement tool: (a) the ability to detect differences, (b) determine the minimal clinically important difference (MCID), (c) validity, (d) reliability and (e) usable in clinical settings. This study provided the first evidence that metronome hopping can detect differences in individuals with MS from age and gender matched controls. The next step in developing this measure would be to determine what changes on this measure are indicative of clinically meaningful change in a large cohort of

individuals with MS. MCID is critical for interpreting whether changes on this measure due to an intervention are clinically meaningful for the patient's functioning. Additionally, test-retest reliability must be determined so that natural variability on the measure does not erroneously become attributed to an intervention effect. Due to the objectivity of the measurement technology (Protokinetic walkway), inter-rater reliability is not a pressing concern for this outcome measure in research settings. However, more importance should be placed on inter-rater reliability in the clinical setting, as changing the modality of measurement to use clinical tools (such as a ruler and smart-phone device) could result in a large increase in measurement error between raters and between measurement sessions. Thus, prior to using metronome hopping as an outcome measure in clinical trials, test-retest reliability and clinically important change metrics must be determined to allow for accurate interpretation of change on this measure due to an intervention.

To develop metronome hopping as a useful clinical measure, adaptations will need to be made to make the measure applicable to a wide range of clinical settings. Considerations include using available clinical tools for measurement and improving simplicity so that many different personnel can perform the test, while maintaining valid sensitivity as when measured using an instrumented walkway. For instance, a ruler could be used to measure hop length and width, while a metronome app could be played on a smartphone. All measurements would need to use tools available to a clinician. If simplicity and interrater reliability is accomplished, then experienced health professionals (i.e. MS nurse, physiotherapist) could easily and accurately perform the test. Additionally, it is important to consider length of time to conduct the assessment when making it applicable to clinical settings. Clinic visits are very short and the

clinicians must accomplish numerous tasks in each visit. Thus, to plausibly integrate metronome hopping into clinic, the amount of time to perform this assessment must be shortened and made more concise. However, once the appropriate chronometric measures are completed, the metronome hop test may have potential to detect progression in disability over other clinical measures, and perhaps provide an earlier indication of disease activity and subsequent need for changes in therapy.

3.5 LIMITATIONS

There are some limitations to this study that could influence the results we obtained. Primarily, the biggest limitation is a homogenous sample and a small sample size. The majority of the MS population in Newfoundland and Labrador are Caucasian, English speaking Canadians. Thus, our sample was extremely homogenous in terms of ethnicity which reduces generalizability to the global MS population. Also, as this was a pilot study, participants were recruited based on convenience, which resulted in large standard deviations and subsequent difficulty in concluding whether meaningful differences existed. As mentioned previously, MS is extremely heterogeneous and therefore it is difficult to obtain a homogeneous sample without sub-grouping individuals, and large sample sizes are needed to perform this type of sub-group analysis. This leads into another major limitation. People with MS have differing impairment; some have more motor impairments while others have sensory symptoms. The advantage, as stated previously, to metronome hopping is the potential to distinguish those with motor impairment vs. timing (cerebellar) problems. In this study, detailed MRI was not available, which could have provided a better indication of lesion-specific impairments. It would have been interesting to determine whether those with difficulty in metronome timing had cerebellar lesions

and those with shorter length of hopping were more likely to have corticospinal tract lesions. Future studies should use metronome timing in a large cohort of individuals with MS, stratifying by clinical data based on major area of impairment (motor, sensory, cognitive, etc.). Furthermore, in terms of hopping, we did not measure mass, leg length or height which could be confounding factors when comparing hop length and width. However, there was an even distribution in sex between MS and controls (most likely factor contributing to height differences), which would help lessen the impact of differences in leg length. Also, participation in resistance-based exercise was not measured, and could confound the results of hopping performance. Lastly, there are numerous studies that show that auditory entrainment pathways are more developed among musicians than in the general population (Thaut, 2015; Thaut et al., 2014). Those with musical backgrounds may excel at metronome timing due to stronger interconnectivity of auditory timing networks and thus could confound our results. Determining the impact of musical ability on metronome hopping would help define its reliability.

3.6 CONCLUSION

We are the first research group worldwide to utilize the task of bipedal hopping as a measurement tool among individuals with mild MS. We found that metronome hopping could detect subtle impairments in motor ability and cerebellar processing in individuals with mild MS, who otherwise had performed in the typical range of other walking tests (floor effect). Furthermore, using the bipedal test, in terms of the length of hopping, individuals with MS were beginning to demonstrate power deficits that were similar to participants who were 30 years their senior. In addition, our findings suggest that there are subtle, cerebellar processing impairments but not basal ganglia dysfunction in individuals with mild MS.

Taken together, the findings from this study suggest that we have succeeded in the first step of our overarching goal to create a challenging outcome measure to detect relevant, meaningful, subtle impairment in people with mild MS; we have identified a potential multifaceted measure in metronome hopping. The next steps in developing this measure as both a potential research outcome measure and clinical assessment tool involves determining reliability, validity and clinically meaningful change. With further refinement, this measure may provide critical information not previously available, by tracking subtle progression and improvement in MS.

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