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NEUROPHYSIOLOGICAL CORRELATES OF FATIGUE AND THE FEASIBILITY OF PROGRESSIVE RESISTANCE EXERCISE FOR AMELIORATING SYMPTOMS OF FATIGUE IN PEOPLE WITH MULTIPLE SCLEROSIS

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PHD

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NEUROPHYSIOLOGICAL CORRELATE OF FATIGUE AND THE FEASIBILITY OF PROGRESSIVE RESISTANCE EXERCISE FOR AMELIORATING SYMPTOMS OF FATIGUE IN PEOPLE WITH MULTIPLE SCLEROSIS

By

Paula Mary Ellison

A thesis submitted in partial fulfilment of the requirements of University of Northumbria at Newcastle for the degree of Doctor of Philosophy

Research undertaken in the Faculty of Health and Life Sciences

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ABSTRACT

Clinicians are continually looking for effective treatments for multiple sclerosis (MS)-fatigue, but this has been hampered by unclear definitions of fatigue and studies of heterogeneous people with MS, including those who are highly-fatigued (MS-HF) and those who are less-fatigued (MS-LF). By directly comparing neuromuscular and transcranial magnetic stimulation measures between MS-HF and MS-LF, more light could be shed on the underpinning mechanisms of MS fatigue, and this could serve as a stronger foundation for therapeutic interventions. In addition, progressive resistance exercise has shown potential as an accessible exercise intervention for alleviating MS fatigue, but most studies have not recruited MS-HF or did not include MS fatigue as a primary outcome measure. In addition to positively impacting a range of other functional and mental health outcomes in PwMS, an individually tailored progressive resistance exercise (PRE) intervention has the potential to improve symptoms of fatigue and fatigability by helping to promote the development of new neural pathways (neuroplasticity). Thus, the overarching aim of this thesis was to establish whether neurophysiological differences between MS-HF and MS-LF could be reliably distinguished, and to investigate the feasibility and potential of PRE as a therapeutic exercise intervention for ameliorating perceived MS-fatigue in MS-HF. The series of investigations that set out to address this aim have led to many novel and interesting findings. Firstly, study 1 was the first systematic review and meta-analysis to synthesis the current evidence base comprising studies which used a dichotomised model (MS-HF versus MS-LF) to provide insights into structural and neurophysiological correlates of MS-fatigue. Secondly, Study 2 reports on the good to excellent test-retest reliability for a range of neuromuscular and transcranial magnetic stimulation measures assessed in the upper- and lower-limb muscles in MS-HF and MS-LF. Thirdly, based on the test-retest reliability findings of study 2, study 3 presents data for the differences between MS-HF compared to MS-LF and HC on a range of neuromuscular measures, including an isometric fatiguing exercise task in the upper- and lower-limb (performance fatigability measure). Finally, Study 4 presents important feasibility data regarding the utility of PRE as a therapeutic exercise option for MS-HF. In addition, this study provides preliminary evidence of the efficacy of PRE for ameliorating perceived MS-fatigue, a range of other patient-reported health outcomes and indices of neuromuscular function.

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LIST OF ABBREVATIONS

Abbreviation	Meaning
AMT	Active Motor Threshold
BPF	Brain Parenchymal Fraction
Cho-Cr	Choline -Creatine
CI	Confidence Interval
cm^3	Cubic Centimeter
CMC	Cortico-Muscular Coherence
CMCT	Central Motor Conduction Time
CSP	Cortical Silent Period
CT	Contraction Time
CTh	Cortical Thickness
CV	Coefficient of Variation
DTI	Diffusion Tensor Imaging
GM	Grey Matter
HC	Healthy Control
ECR	Extensor Carpi Radialis
EDSS	Extended Disability Status Scale
EEG	Electroencephalogram
EMG	Surface Electromyography
ERT	Estimated Resting Twitch
FA	Fractional Anisotropy
FSS	Fatigue Severity Scale
HC	Healthy Control
ICC	Intraclass Correlation
ICI	Intracortical Inhibition
ICF	Intracortical Facilitation
ICV	Intracranial Volume
IHSym	Interhemispheric Symmetry
KG	Kilogram
M1	Primary Motor Cortex
MD	Mean Diffusivity
MEP	Motor Evoked Potential

Abbreviation	Meaning
MESH	Medical Subject Headings
MFIS	Modified Fatigue Impact Scale
Mmax	Maximal Compound Muscle Action Potential
mm	Millimetre
ml	Millilitre
MRFD	Maximal Rate of Force Development
MRR	Maximal Relaxation Rate
MRS	Magnetic Resonance Spectroscopy
MS	Multiple Sclerosis
ms	Millisecond
MS-HF	Multiple Sclerosis with High Fatigue
MS-LF	Multiple Sclerosis with Low Fatigue
MS-NF	Multiple Sclerosis No Fatigue
MSO	Maximal Stimulator Output
MS-PF	Multiple Sclerosis Primary Fatigue
MS-SF	Multiple Sclerosis Secondary Fatigue
MTI	Magnetization Transfer Imaging
MVC	Maximal Voluntary Contraction (Isometric)
mV	Millivolt
M-wave	Compound Muscle Action Potential
NA+	Sodium Ions
NAA-Cho	N-Acetyl Aspartate-Choline
NAA-Cr	N-Acetyl Aspartate-Creatine
NABT	Normally Appearing Brain Tissue
Nm	Newton Meter
nLthal	Left Thalamus
nRthal	Right Thalamus
PwMS	People with Multiple Sclerosis
POT	Potentiated Twitch
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
Qtw,pot	Potentiated Quadriceps Twitch Force
RMT	Resting Motor Threshold

Abbreviation	Meaning
$RT_{0.5}$	One-Half Relaxation Time
SCP	Superior Cerebellar Peduncle
SD	Standard Deviation
SEM	Standard Error of the Mean
SICI	Short Interval Intracortical Inhibition
TBV	Total Brain Volume
TTF	Time to Task Failure
VA	Voluntary Activation
VL	Vastus Lateralis
WM	White Matter

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PwMS. The ICC was used to assess the relationship of each measure across the two experiential visits days and was defined as: <0.5 = poor, 0.5-0.75 = moderate, 0.75-0.9 = good, >0.9 = excellent, in accordance with Koo and Li (2016).

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While PhD's are known for being challenging, I can whole heartily say that mine has felt like an 'Everest of a task'. I want to thank my close friends and PhD colleagues for their continued assistance and support throughout my PhD. A very special thank you goes to Dr Gillian Barry; you began providing me with lecturing experience which has developed into a very close friendship, which I will treasure forever. I also thank my parents Dave and Sue and my brother Chris. They have been my rock throughout this experience with their never-ending support and irrefutable belief in me, thank you Ellison's.

Lastly and most importantly, a big thank you to all the participants who have taken part in my research. I have enjoyed every assessment, group discussions and exercise session. I have developed so much as a person from all our one-on-one chats. To quote Arnold Toynbee: "*no tool is omnicompetent. There is no such thing as a master-key that will unlock all doors*". Multiple Sclerosis is a debilitating disease, but through this PhD I have witnessed so much courage and determination to overcome the daily battles, that I will keep with me throughout my career.

DECLARATION

I declare that the work contained in this thesis has not been submitted for any other award and that it is all my own work. I also confirm that this work fully acknowledges opinions, ideas and contributions from the work of others.

Any ethical clearance for the research presented in this thesis has been approved. Approval has been sought and granted by the Faculty of Health and Life Sciences Ethics Committee and Newcastle National Health Service Ethical Committee for each study.

Name: Paula M Ellison

Signature: *P.M.ELLISON*

Date: Monday 2nd October 2020

“If we could give every individual the right amount of nourishment and exercise, we would have found the safest way to health”.

~ Hippocrates

CHAPTER 1 – INTRODUCTION

1.1 Introduction

Fatigue is one of the most common and severe symptoms, experienced in up to 75% of people with multiple sclerosis (PwMS; (Fisk et al., 1994b; Lerdal et al., 2007; Loy et al., 2017; Penner & Paul, 2017). In proposing a unified taxonomy of fatigue in neurologic illness, Kluger et al. (2013a) highlighted the importance of differentiating between perceived fatigue and fatigability. Perceived fatigue includes subjective perceptions of weariness and an increased perception of effort needed to perform everyday tasks (irrespective of recent physical exertion). In contrast, fatigability is defined as the rate of change in a performance criterion (e.g., maximum voluntary contraction force [MVC]) relative to a reference (baseline) value over a given time of task performance or measure of mechanical output. The consequences of fatigue have been well-described in the literature, and include profound impacts on quality of life (Aronson, 1997; Amato et al., 2001) and mental alertness (Weinges-Evers et al., 2010), cognitive processing (Andreasen et al., 2010b), poorer general health and increased disability (Janardhan & Bakshi, 2002; Krause et al., 2013). MS-fatigue is also a major contributor to the high levels of unemployment in PwMS (Krupp et al., 1988; Pompeii et al., 2005). As such, MS-fatigue is a leading cause of increased healthcare visits (Khan et al., 2014), inactivity and future comorbidities, and presents a significant economic burden to the National Health Service and wider society.

Despite widespread research efforts, the underpinning cause(s) of MS-fatigue is poorly understood and is an area of debate, partly due to unclear definitions of fatigue (Kluger et al., 2013a). However, there is general agreement that disease pathology plays an important role, including axonal degeneration, inflammation and/or myelin destruction at multiple levels of the central and peripheral nervous system (Kos et al., 2008). Such underlying disease pathology compromises the integrity of sensory pathways, as well as causing muscle weakness, lack of movement coordination and neuroplasticity impairments (Lublin & Reingold, 1996; Compston & Coles, 2008; Trapp & Nave, 2008; Kister et al., 2013). As revealed by magnetic resonance imagery, neurostructural damage to multiple brain areas and altered activity and connectivity of brain regions are the central stimuli considered to be implicated in the perception of MS-fatigue (Tanasescu et al., 2014; Biberacher et al., 2018). As such, this widespread damage and resultant dysfunctional brain connectivity is thought to underpin fatigue perceptions at rest and increase the perception of effort during simple motor tasks

(Filippi et al., 2002; Novo et al., 2018). Everyday tasks such as walking, balance and performing simple errands require muscle strength, coordination and constant neuromuscular adjustments (Dobkin, 2009; Dall & Kerr, 2010); however, because of the underlying neuropathology, such movements require greater effort in PwMS.

While only a few investigations have investigated the relationship between fatigue and functional imaging (Filippi et al., 2002), studies involving stimulation have found that impaired central motor activation is present in MS-fatigue (Andreasen et al., 2009; Morgante et al., 2011; Steens et al., 2012c). Other investigations have reported increased central activation or altered activation of brain regions at rest and during motor task, probably reflecting additional compensatory central activation (Thickbroom et al., 2008; Andreasen et al., 2009; Andreasen et al., 2010a). In addition, neurophysiological studies using the superimposed twitch (Merton (1954b) interpolation technique have reported a progressive impairment of central motor drive during sustained upper- and lower-limb maximum voluntary muscle actions in fatigued PwMS (Sheean et al., 1997; Andreasen et al., 2009; Steens et al., 2012b; Steens et al., 2012c). In one study, this was accompanied by an inability to increase cortical activation during sustained maximal muscle actions, in contrast to what was observed in healthy age-matched controls (Steens et al., 2012c). An attenuation of cortical inhibitory pathways in fatigued PwMS (Liepert et al., 2005; Morgante et al., 2011), is consistent with an augmentation of cortical activation at rest and during sub-maximal motor tasks, and an inability to increase cortical activation during sustained maximal muscle actions. It has been argued that excess cortical activity or a mismatch between the estimated and actual "neural work" needed during sub-maximal motor tasks could contribute to the clinical symptoms of fatigue in PwMS (Leocani et al., 2008). Although this altered neurophysiological function could underpin increased perceived effort and MS-fatigue, it might also reflect compensatory adaptations for the neurostructural damage associated with the disease, which requires further exploration.

Pharmacological and psychosocial interventions for fatigue management are reported to be ineffective or modest at best (Lee et al., 2008; Phyo et al., 2018). However, exercise has shown considerable promise as an intervention for helping PwMS to manage fatigue symptoms. Most of the studied therapeutic interventions in clinical

and exercise science research have been aerobic exercise or combined aerobic and resistance exercise. More recently, a growing body of research has been aimed at delineating the physiological and psychosocial effects of exercise (aerobic or combined aerobic and resistance exercise programmes), and how exercise programmes can be tailored to improve muscle function/performance and quality of life (Rietberg et al., 2005a; Motl & Gosney, 2008; Asano et al., 2009). There is evidence that resistance exercise can improve muscle power, strength/force generating capacity, physical and psychosocial functioning and quality of life in PwMS (Rietberg et al., 2005a; Motl & Gosney, 2008; Asano et al., 2009). Although, less well studied, an emerging body of work has also shown that resistance exercise can improve self-reported MS-fatigue (Dalgas et al., 2010; Dodd et al., 2011; Hayes et al., 2011b; Sabapathy et al., 2011). However, it is yet to be explored whether the magnitude of fatigue in highly fatigued PwMS can be attenuated following a programme of progressive resistance exercise and if so, what practical recommendations should be provided to optimise efficacy and adherence to such programmes, in order to preserve the health benefits to PwMS. The proposed relationship between MS-fatigue, neural lesions and muscle function/activation loss means that (hypothetically) an individually tailored progressive resistance exercise intervention has the potential to improve symptoms of fatigue and fatigability by helping to promote the development of new neural pathways (neuroplasticity).

Despite the high prevalence and pronounced impact of MS-fatigue on the lives of PwMS, techniques for improving our understanding of the different underlying causes of fatigue are limited and therefore, opportunities for mechanism-guided MS-fatigue treatment in PwMS are lacking. Therefore, this thesis comprises a set of interrelated but standalone studies, which have the objectives of (i) synthesising current evidence of the neuro-structural and neurophysiological correlates of MS-fatigue; (ii) ascertaining whether neurophysiological correlates of MS-fatigue differ between highly-fatigued and less-fatigued PwMS, and (iii) reporting on the feasibility of a progressive resistance exercise programmes in highly-fatigued PwMS, as well as providing early indicative evidence of changes MS-fatigue symptoms and neurophysiological correlates of MS-fatigue.

1.2 Statement of Thesis Aims

1.2.1 Study 1 (Chapter 4)

Title: Neurostructural and Neurophysiological Correlates of Multiple Sclerosis Fatigue: Systematic Review and Meta-Analysis of Cross-Sectional Studies

Aim: The aim of this study was to provide the most precise estimates of cross-sectional neurostructural and neurophysiological differences between people experiencing high and low levels of MS-fatigue.

1.2.2 Study 2 (Chapter 5)

Title: Test-Retest Reliability of Transcranial Magnetic Stimulation and Motor Nerve Stimulation Measures of Neurophysiological function in People Experiencing High and Low Levels of Multiple Sclerosis Fatigue

Aim: The aim of this study was to establish the test-retest reliability, variability and measurement error of a comprehensive battery of upper- and lower-limb transcranial magnetic stimulation and neurophysiological measures (knee-extensors and wrist-flexors, respectively) in people experiencing high and low levels of MS-fatigue.

1.2.3 Study 3 (Chapter 6)

Title: Neurophysiological Responses to a Sub-maximal Isometric Task in Highly Fatigued and Less Fatigued People with Multiple Sclerosis and healthy individuals: A Cross-Sectional Study

Aim: The aim of this study was to compare baseline neurophysiological responses and neurophysiological responses to a fatiguing exercise task between PwMS experiencing high and low levels of fatigue and a group of healthy controls.

1.2.4 Study 4 (Chapter 7)

Title: Feasibility of External-Paced Resistance Training in Highly Fatigued People with Multiple Sclerosis

Aim: The aim of this study was to evaluate the feasibility and early efficacy of a supported (supervised and home-based) externally paced resistance training programme in people experiencing high levels of MS-fatigue via a randomised controlled feasibility trial.

CHAPTER 2 – REVIEW OF LITERATURE

2.1 Introduction to Review of Literature

This chapter provides a review of the literature, focusing on the following topics: 1) MS disease characteristics, 2) underlying mechanisms of MS-fatigue, 3) exercise training for the management of fatigue in PwMS. The chapter concludes with a rationale for undertaking this PhD research before stating the aims of the thesis.

2.2 Overview of Pathogenesis of MS

In 1868, Jean-Martin Charcot first recognised demyelination as the most striking pathologic feature of MS, and the interaction between inflammation and degeneration (Kumar et al., 2011). Subsequently, strong evidence suggested that relapses are the expression of acute, focal, disseminated and recurrent inflammation occurring within the central nervous system (Youl et al. (1991)). For example, for each clinical episode (MS relapse) there is an average of 10 new magnetic resonance imagery lesions (Chard & Trip, 2019), signifying the active nature of MS. Hence, relapses are a directclinical expression of inflammation and support the premise that MS is predominantly an inflammatory demyelinating disease (Tillema & Pirko, 2013). In recent years, studies investigating the pathology of MS have become increasingly widespread (Evangelou et al., 2000) and magnetic resonance imagery techniques (Losseff et al., 1996; Fu et al., 1998; Rudick et al., 1999; Tortorella et al., 2000; Brex et al., 2002; Filippi et al., 2003) have shown that progression and accumulation of disability correlate with early, diffuse, chronic and progressive axonal loss, which is the hallmark of the neurodegenerative process in MS.

MS disease activity can be divided into two phases, with the early phase characterised by inflammation of the central nervous system, caused by infiltration of activated T-cells, B-cells and Macrophages (Lipsy et al., 2009). The macrophages, T-cells, and antibodies secreted from the B-cells, attack selected neurons causing demyelination, progressing in severity, and leading to the second phase, characterised by axonal loss and neurodegeneration (Lipsy et al., 2009). See Figure 2.1 below.

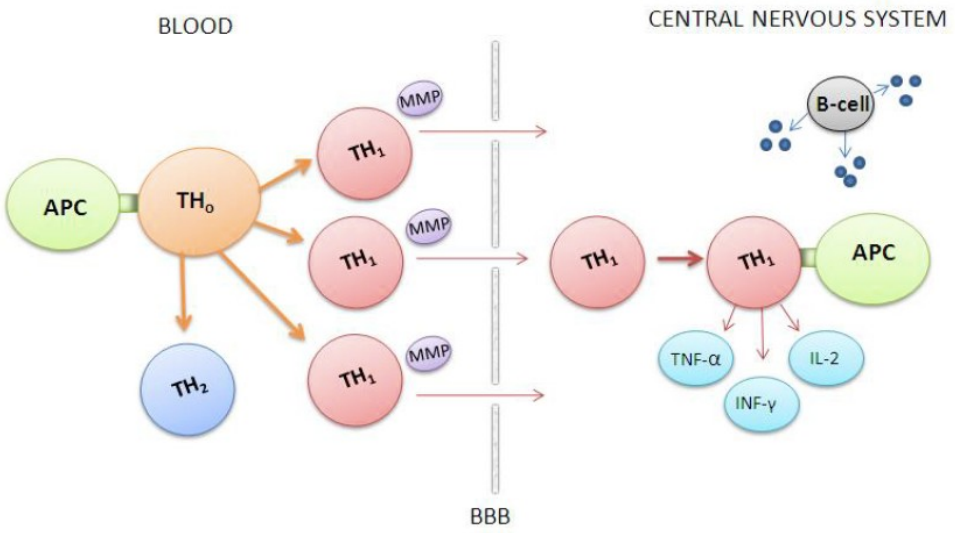

Figure 2.1 Multiple Sclerosis Pathology (adapted from Lipsy et al., 2006). APC: antigen presenting cell; TH: T helper cell; MMP: matrix metalloproteinases; BBB: blood brain barrier.

Therefore, MS is characterised by demyelinating lesions within the white matter of the central nervous system. This presents as a degradation of the myelin sheath, which normally serves as an insulator and speeds up conduction along nerve fibres to permit co-ordinated movements (Chang et al. (2011). However, once the myelin sheath of nerve fibers has been damaged, nerve signals become impeded. MS lesions (damaged areas as seen on magnetic resonance imagery) form with hardened scars or plaques that can impair normal myelin repair processes. Evidence suggests that PwMS have a slowing of nerve conduction and/or blocks in nerve conduction within the central nervous system and are unable to transmit high frequency electrical impulses to targeted muscles (Thickbroom et al., 2006). This causes impaired movement during motor tasks and a range of other neurological symptoms and clinical manifestations.

2.2.1 Epidemiology and Prevalence of MS

It is estimated that approximately 2.5 million people live with MS worldwide, signifying that MS is not a rare disease (Flachenecker & Stuke, 2008). In fact, MS is the most common cause of non-traumatic neurological disability in young adults, with a prevalence of around 1 in 1,000, and with evidence that incidence is increasing (Koch-Henriksen & Sørensen, 2010). Global prevalence rates are unevenly distributed and vary (see Figure 2.2), e.g. <5 cases per 100,000 in regions of Asia and South

America, 11-74 cases per 100,000 in Australia, and >100-200 cases per 100,000 in North America and Scotland (Tesar et al., 2003).

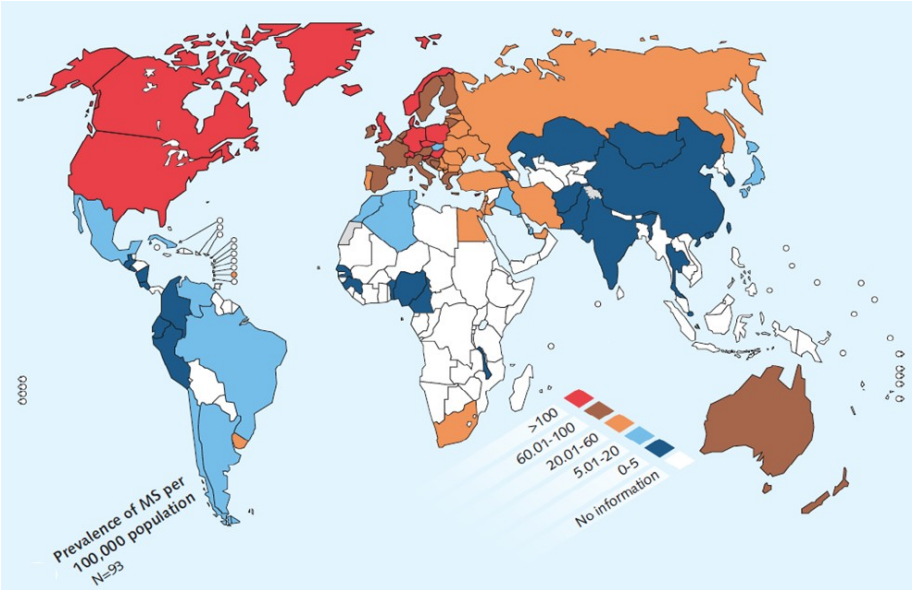

Figure 2.2 Worldwide prevalence of MS, per 100,000 population (Atlas multiple sclerosis resources in the world, 2008, page 15)

A population-based study using general practice databases also revealed that approximately 126,669 (203.4/100,000 population) people have MS in the UK (Mackenzie et al., 2014) and a large general practice will normally have between 10–20 patients with MS (Compston & Coles, 2002, 2008). Environmentally, MS is more prevalent in northern Europeans who live in a more temperate climate compared with people living in the tropics. This is believed to be due to lack of sunlight (necessary for mediating vitamin D synthesis), ultraviolet radiation and greater risk of infectious agents such as Epton-Barr virus (Compston & Coles, 2008; Milo & Kahana, 2010; Melcon et al., 2014). Likewise, there is an increased familial risk of MS occurrence of up to 20%, with the observed age-adjusted higher risk being in first degree relatives (siblings, 5%; parents, 2%; children, 2%) compared to second- and third-degree relatives (Compston & Coles, 2008). Gender and age bias affect MS risk, specifically with a ratio of 2:1 woman to men with MS (Compston & Coles, 2002; Koch-Henriksen & Sørensen, 2010) and an age-span of 15-75 years, with young adults being most frequently affected between 20 - 40 years. Additionally, a five-year difference in the peak incidence rate of MS is observed between men (45 years) and women (40 years) (Mackenzie et al., 2014). Thus, men tend to be diagnosed later in years and are thought

to have a more aggressive pattern of disease (Compston & Coles, 2002; Koch-Henriksen & Sørensen, 2010). While it has been reported that the average life span of PwMS is similar to the general population, a further study suggested that PwMS might have a reduced life span of approximately 5-10 years (Hurwitz, 2011). However, as the disease tends to be diagnosed in the prime of the individuals' life, there are physical, social and economic implications of living with MS (Patwardhan et al., 2005; McCrone et al., 2008).

2.2.2 Classification of MS

MS presents a highly heterogeneous disease course, with a number of distinct clinical subtypes defined by The National MS Society Advisory Committee on Clinical Trials in MS (1996). The most common subtype is relapsing remitting MS, which accounts for 80–90% of all cases (Compston & Coles, 2008) and is often characterised by demyelinating events where there is loss-of-function, inter-spaced by periods of partial or complete recovery. However, after 10 years approximately 50% of those with relapsing remitting MS will go onto develop secondary progressive MS with fewer relapses but a progressive worsening of disability. Yet around 10% of patients with MS have a progressive decline in disability from the outset, termed primary progressive MS. See Figure 2.3 for a visual representation of MS subtypes.

2.2.3 Symptoms of MS

People with MS experience a variety of symptoms, including impaired vision, sensations of numbness, pains, spasms and tingling, weakness (which can be unilateral), balance problems, and bladder, sexual and cognitive dysfunction issues. Fatigue is the most common symptom experienced by 75 to 92% of PwMS and is difficult to treat (Freal et al., 1984; Braley & Chervin, 2010; Berger et al., 2013). Fatigue is considered one of the most debilitating symptoms of MS and can significantly affect an individual's quality of life, interfere with activities of daily living, cause reduced work performance and contribute to loss of employment (Smith & Arnett, 2005; Blaney & Lowe-Strong, 2009; Göksel Karatepe et al., 2011; Glanz et al., 2012) . Additionally, fatigue in MS tends to follow a diurnal circadian pattern, with fatigue severity peaking in the afternoon (Schwid et al., 2002). Fatigue experienced by PwMS differs to that experienced by the general population, as shownby Kurtzke (1983) who interviewed 32 patients with MS and 33 control subjects and

found differences between the groups such as: MS-fatigue is worse with heat, causes an inability to sustain function, comes on suddenly and causes frequent problems in daily living. Whilst the disease process itself underpins symptoms of fatigue, other prevalent comorbidities likely contribute to fatigue in PwMS, include depression (Lobentanz et al., 2004; Siegert & Abernethy, 2005), sleep disorders (Bamer et al., 2008; Bol et al., 2009; Veauthier et al., 2011) and cognitive impairment. Thus, MS-related fatigue is a multi-dimensional phenomenon (Krupp & Elkins, 2000; Diamond et al., 2008; Bol et al., 2009; Weinges-Evers et al., 2010). Collectively the symptomatic manifestations of MS have been associated with barriers to engaging in exercise and physical activity within the home and community (Kayes et al., 2011; Asano et al., 2013). Although many of the initial symptoms may resolve, repeated attacks to the central nervous system often result in an exacerbation of MS-fatigue symptoms and a more pronounced decline in physical functioning, thereby affecting ability to engage in daily life activities as well as exercise and physical activity (Finlayson et al., 2004; Compston & Coles, 2008). This variation of clinical features and symptoms highlights some of the complexities in managing the disease and the importance of understanding how MS impacts the individual. Further detail of the underlying mechanisms of fatigue in PwMS will be explored in the next section.

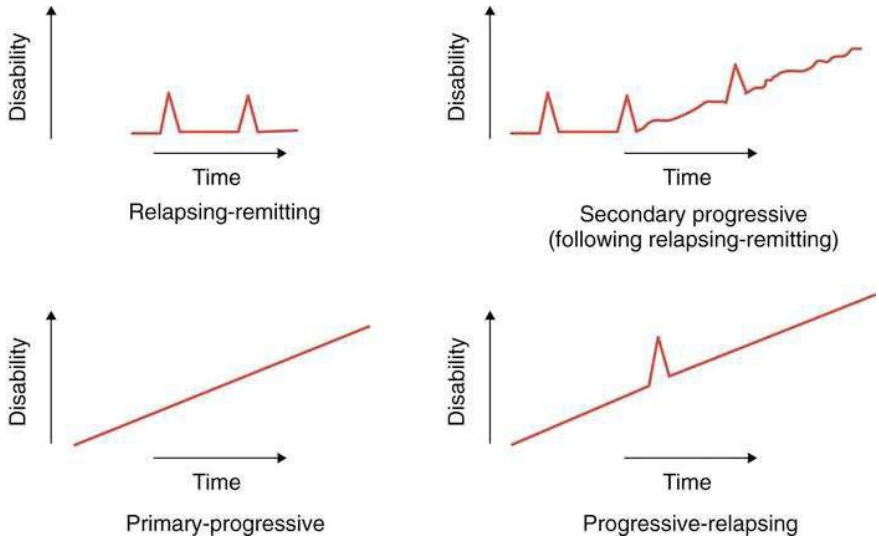

Figure 2.3 Clinical types of MS (Lublin and Reingold 1996).

2.3 Fatigue in Multiple Sclerosis

2.3.1 Perceived Fatigue and Fatigability Constructs

The term 'fatigue' has widespread generic use across populations and disciplines, often being used interchangeably and is relatively broad (Enoka & Duchateau, 2016). A physiological definition is: "*an exercise-induced reduction in the ability of a muscle to generate force or power*" (Bigland-Ritchie & Woods, 1984; Gandevia, 2001), whereby fatigue comes after prolonged muscular activity, and is a predictable symptom resolved by rest (Kluger et al., 2013a). In the case of MS, no universally accepted definition of fatigue has been established. However, a unified approach has been recommended by (Kluger et al., 2013a), which suggests two domains including, perceptions of fatigue and performance fatigue within a fatigue taxonomy (Kluger et al., 2013a; Finsterer & Mahjoub, 2014; Zijdewind et al., 2021). Their approach distinguishes fatigue, as experienced and described by the individual with MS, and fatigue as objectively quantified. The former is termed perceived fatigue; the latter is called fatigability (Kluger et al., 2013a). While studies acknowledge the complexity and multi-factorial nature of MS-related fatigue, a clear definition has been lacking.

The subjective nature and severity of fatigue (i.e., perceived fatigue) in healthcare is assessed using psychometric tools such as self-report questionnaires and scales (Whitehead, 2009; Elbers et al., 2012; Enoka & Duchateau, 2016). Whilst multiple self-reported scales have been used to assess perceived fatigue in PwMS, such scales can be limited in their ability to adequately capture the multi-dimensional nature of fatigue (Flachenecker et al., 2002b; Mota & Pimenta, 2006). The most commonly used fatigue scales are the Modified Fatigue Impact Scale (MFIS) (Fisk et al., 1994b), the Fatigue Severity Scale (FSS) (Krupp et al., 1989), and the Visual Analogue Fatigue Scale (VAFS) (Lee et al., 1991). Some current definitions of perceived fatigue include "*overwhelming sense of tiredness, lack of energy or feeling of exhaustion*" (Leocani et al., 2008) or "*difficulty initiating or sustaining voluntary effort*" (Chaudhuri & Behan, 2004) and "*feelings of physical tiredness and lack of energy distinct from sadness or weakness*" (Krupp et al., 1988). These example definitions of fatigue are incomplete, and use simplified and unclear terms to describe the complex symptom of fatigue. Moreover, some definitions encompass the perceived nature of fatigue but neglect fatigability (e.g. Leocani et al. (2008)), whereas others (e.g. Chaudhuri and Behan (2004)) include only the fatiguability component. For the purpose of this thesis,

fatigue will be defined as "*a subjective lack of physical and mental energy that is perceived by the individual and caregiver to intervene with usual and desired activities*", in accordance with The MS Council for Clinical Practice Guidelines (1998). This definition is heavily biased towards the subjective experience of perceived fatigue. However, this thesis will also explore fatigability in PwMS, as assessed using objective measures of physical effort, to help capture the multi-dimensionality of MS-fatigue (Mills et al., 2010; Kluger et al., 2013a) and understand the relationship between them in this population.

Fatigability has been defined as the magnitude of change in the performance of a physical or a cognitive task over a period of time (Kluger et al., 2013a; Finsterer & Mahjoub, 2014). Fatigability interferes with the individual's everyday life, as it diminishes the individual's ability to efficiently perform tasks that requires prolonged or effortful activity such as walking or engaging in a conversation (Kluger et al., 2013a; Murphy & Schepens Niemiec, 2014). Physical fatigability is the measured change in the continuous performance of a prolonged physical task, such as repetitive or sustained movements and walking speed over a period of time. Fatigability is distinguished from perceived fatigue by the concept of change, i.e., a measurable difference in the performance of a task over a period of time (Schnelle et al., 2012; Zijdewind et al., 2021). Therefore, fatigability and perceived fatigue may be related but are different constructs. Development of the concept, classification and task preference of fatigability is ongoing (Eldadah, 2010; Zijdewind et al., 2016; Zijdewind et al., 2021). The definition and domain specification for fatigability used in this thesis were introduced recently by Kluger et al. and other researchers (Eldadah, 2010; Schnelle et al., 2012; Kluger et al., 2013a; Finsterer & Mahjoub, 2014; Murphy & Schepens Niemiec, 2014).

2.3.2 The Neurophysiology of MS Perceived Fatigue

In a recent review, Vucic et al. (2010) reported several neurophysiological mechanisms of MS-fatigue perceptions related to central nervous system dysfunction, from decreased gamma-aminobutyric acid activity, sodium (Na^+) channel dysfunction, increased cortical activation and reduced glucose metabolism. Particularly in transcranial magnetic stimulation studies, an observation of intracortical inhibition in both the pre- and post- exercise is shown in PwMS who are

experiencing high levels of perceived fatigue (Perretti et al., 2004; Liepert et al., 2005). Intracortical inhibition is mediated by gamma-aminobutyric acid -generic inhibitory interneurons and -activity may be down regulated to compensate for the conduction that occurs in demyelinated pyramidal tract fibres (Vucic et al., 2010). Additionally, it has been shown that in highly fatigued PwMS, motor thresholds take longer to normalise during a post-exercise period compared to less-fatigued PwMS (Liepert et al., 2005). Motor threshold measures reflect membrane excitability, so this suggests a possible role of Na^+ channel dysfunction in perceived fatigue.

Magnetic resonance imagery studies have found that when conducting a simple motor task, PwMS have widespread cortical activation, including non-cortical areas (Reddy et al., 2000; Filippi et al., 2002; Rocca et al., 2002; Vucic et al., 2010). Notably, the increase in cortical activation may be an adaptive response to weakness that results from dysfunction in the motor pathways, thereby causing inducement of perceived fatigue (Vucic et al., 2010). Other studies reported impairments in cortico-subcortical interactions (which are utilised in motor planning and execution) and increased activation of the anterior cingulate cortex and basal ganglia in fatigued PwMS (Filippi et al., 2002; Calabrese et al., 2010; Rocca et al., 2014), leading to a higher perceived effort when executing a motor task (Filippi et al., 2002; Vucic et al., 2010). Functional brain imaging has also demonstrated that reduced glucose metabolism exists in the prefrontal cortex and basal ganglia in highly-fatigued PwMS compared to less-fatigued PwMS (Roelcke et al., 1997). Furthermore, this reduction in glucose metabolism was found to correlate with perceived fatigue severity (Roelcke et al., 1997). Hypometabolism within grey matter structures might be a result of plaque deposits, iron deposition and neurodegeneration in people with MS (Haider et al., 2014). For further details of neurostructural and neurophysiological differences between highly-fatigued (MS-HF) and less-fatigued (MS-LF) PwMS, see Chapter 4.

2.3.3 The Neurophysiology of MS Fatiguability

One of the main symptomatic manifestations of MS is muscle weakness and loss of strength and it is likely that the underpinning pathophysiology causing loss of strength is also linked to fatigability. Fatigability studies in PwMS have investigated changes in hand grip strength across repetitive movements, change in walking speed across time, and changes in sustained attention over time (Goldman et al., 2008a; Bruce et

al., 2010; Walker et al., 2012; Severijns et al., 2015; Wolkorte et al., 2015a, 2015b; Leone et al., 2016). Lower extremity muscles are more affected by muscle weakness than upper extremity muscles in PwMS (Benedetti et al., 1999; Dalgas et al., 2008; Souza et al., 2010), with 75% of PwMS reporting a lower-limb muscle strength defect (Benedetti et al., 1999; White et al., 2004; Dalgas et al., 2008; Souza et al., 2010), and 66% reporting that upper-limb impairments have a dramatic effect on activities of daily living (Spooren et al., 2012). PwMS often exhibit reduced muscle strength during both dynamic (Armstrong et al., 1983; Lambert et al., 2001) and static(Armstrong et al., 1983; Schwid et al., 1999) muscle actions. The mechanisms underlying the observed strength deficit in PwMS are considered to be of both muscular and neural origin. Some studies (Formica et al., 1997; Kent-Braun et al., 1997; Garner & Widrick, 2003) but not all (Lambert et al., 2002; Ng et al., 2004; Carroll et al., 2005) have indicated a loss of muscle mass in PwMS, which inevitablyleads to relative reductions in muscle strength. Furthermore, the distribution of muscle fibre types may differ between PwMS and healthy controls, but the findings are inconsistent (Kent-Braun et al., 1997; de Haan et al., 2000; Garner & Widrick, 2003;Zijdewind et al., 2021). Neural mechanisms influencing loss of muscular strength in PwMS result from a reduced ability to fully activate motor units in the thigh and lowerleg muscles (47–93%) during maximal voluntary contractions (MVCs) when compared with healthy controls (94–100%; (Rice et al., 1992; de Haan et al., 2000; Ng et al., 2004). Other studies have shown an increased central motor drive during muscular contractions, which is likely to be a compensatory strategy allowing PwMSto generate a desired force despite the underlying neural pathology (Ng et al., 2004; Thickbroom et al., 2006) but potentially, with a concomitant increase in the perception of effort and consequent increase in fatigability. Thus, the underpinning physiological mechanisms causing impaired strength and physical function, in conjunction with an altered sense of effort to engage in everyday tasks, probably influence the magnitudeof fatigability experienced by PwMS.

2.4 Other Contributing Factors to MS-related Fatigue

A broad range of secondary factors can contribute to MS-related fatigue and are important to consider in both assessment and management. Fatigue as a symptom may arise and be amplified as a result of numerous factors such as medical conditions including infections, injury to the brain, medication, psychiatric disorders (e.g.,

depression, anxiety, etc.), pain, sleep disorders and unhealthy lifestyles (DeLuca, 2005; DeLuca et al., 2008; Kos et al., 2008). This form a fatigue is referred to as secondary fatigue. Triggers and underpinning contributors of secondary fatigue can be identified by guided interviews (Ayache & Chalah, 2017). Factors such as depression and anxiety may be identified by key warning signs such as sadness, anhedonia, motivation loss, social isolation, nervousness and irritability. Sleep disorders such as sleep apnea, nocturia, nocturnal spasms, neuropathic pain, snoring or restless leg syndrome may also be a contributory cause of secondary MS-fatigue. Thyroid dysfunction (hypo- & hyper-thyroidism) could also cause conditions which influence symptoms of secondary fatigue, such as constipation, diarrhea, restlessnessand cold or heat intolerance. Medications such as analgesics, anti-epileptics, anti- spasmodics or even immunosuppressants can have side effects which include fatigue.Other clinical deficiencies, such as anemia and vitamin D deficiency, have also been shown to lead to feelings of fatigue (Roy et al., 2014; Johnson & Sattari, 2015).

2.4.1 Fatigue and Depression

Depression is very common in PwMS, affecting almost half of the MS population (Feinstein, 2011; Giordano et al., 2011). Several studies have found an association between depression and MS-fatigue (Lobentanz et al., 2004; Bol et al., 2009; Kinsinger et al., 2010). In fact, depression and fatigue are two components of MS which often appear in conjunction and are strongly related (Bakshi et al., 2000; Kroencke et al., 2000; Chwastiak et al., 2002; Schreurs et al., 2002; Voss et al., 2002; Lobentanz et al., 2004; Patrick et al., 2009), although the causality of the relationship has not yet been established (Kos et al., 2008). In addition, mood and behavioral changes may be prominent symptoms at MS presentation but can remain under-diagnosed in PwMS (Skegg et al., 1988) and may also be observed in early stages of the disease (Sullivan et al., 1995). It has also been found that anxiety and depression levels can be elevated during peri-diagnostic periods (Mattarozzi et al., 2012) or during periods of increased MS activity (Legge et al., 2003; Moore et al., 2012). In a longitudinal follow-up study including 236 PwMS over a period of 5 years, it was found that clinical anxiety, depression and fatigue were frequent in the early stages of the disease and that the co-occurrence of these three conditions was in total 3.76 times higher than the expectation under statistical independence, suggesting these three symptoms tend to cluster together in the disease process (Simpson et al., 2016).

Interestingly, a magnetic resonance imagery study which investigated the involvement of specific regional patterns of lesion distribution and GM, as well as WM atrophy, on the experience of fatigue in PwMS, revealed an interesting link with symptoms of depression (Gobbi et al., 2014b). The researchers recruited 123 PwMS and 90 controls and acquired 3D T1-weighted images on which Voxel-based morphometry was performed to assess lesion distribution, GM and WM atrophy. They found that GM atrophy within the frontal, parietal and occipital lobes showed a mutual effect for depressed as well as fatigue patients. Additionally, atrophy specifically in the left middle frontal and right inferior frontal gyrus was found to be solely related to depression, concluding that atrophy within the aforementioned cortical areas is linked to depression and that more distributed GM atrophy contributes to the concomitant occurrence of fatigue and depression in PwMS (Gobbi et al., 2014a; Gobbi et al., 2014b). Thus, it seems that GM atrophy in specific brain regions is more linked to symptoms of depression rather than fatigue. A further positron emission tomography study (Brody et al., 2001) examined the association between change in depressive symptoms and change in regional brain metabolism following treatment for depression. The findings indicated that a decrease in bilateral ventral prefrontal cortex activity correlated with a decrease in fatigue before and after treatment.

2.4.2 Fatigue and Sleep Disorders

Sleep quality is an important factor to consider in the assessment of MS-related fatigue. Sleep disturbances are common in PwMS (Fleming & Pollak, 2005; Bamer et al., 2008) and are associated with an increase in the perception of fatigue in this population (Veauthier et al., 2011; Veauthier & Paul, 2014). Around 87% of PwMS have reported poor sleep (Ghaem & Borhani Haghighi, 2008) and whilst the exact relationship and interaction between fatigue and sleep quality, including the disorders of sleep and quantity of sleep are meaningful, it remains to be fully understood (Induruwa et al., 2012). An increasing appreciation for the importance of the influence of sleep disorders on MS-fatigue has arisen over the last few years, with reports of reduced sleep quality in PwMS being twice as high as in healthy controls and often being associated with pain, spasms, medication, disorders of bladder control, anxiety and other external factors (Clark et al., 1992; Tachibana et al., 1994; Lobentanz et al., 2004; Stanton et al., 2006). Some studies investigating the relationship between

fatigue and sleep in PwMS found no relation between fatigue and sleep-wake rhythm, difficulties falling asleep, early wakening and nocturnal apneas or oxygen desaturations (Taphoorn et al., 1993; Wunderlin et al., 1997; Stanton et al., 2006), whilst moderate correlations between fatigue and disruptions of sleep by nocturnal activity and middle insomnia (i.e. waking during the night; Stanton et al. (2006)) could be identified. Other studies indicated that disruptions and deviations of circadian rhythm, sleep architecture and cycles, daytime sleepiness, nocturnal activity and waking due to nocturia were important factors in the relationship between fatigue and sleep disorders amongst PwMS (Attarian et al., 2004; Hossain et al., 2005; Kaynak et al., 2006; Stanton et al., 2006; Braley & Chervin, 2010; Kaminska et al., 2012).

The causality between fatigue and sleep disorders is not explained by the abovementioned relationships (Kos et al., 2008) and many studies have come to the conclusion, that a differentiation between fatigue and daytime sleepiness is necessary (Hossain et al., 2005; Stankoff et al., 2005; Merkelbach et al., 2006; Stanton et al., 2006). In light of the above, the importance and potentially confounding influence of depressive symptoms on the complex interaction between sleep disorders and fatigue has been highlighted (Kaynak et al., 2006). This exemplifies the complexity of MS-fatigue and attempts to delineate primary (disease pathology-related) from secondary factors brought about by other accompanying disorders such as depression and poor sleep quality. Improved sleep quality recently has been shown to be a relieving factor, and poor sleep quality as an aggravating factor of self-reported MS-fatigue (Mills & Young, 2008). However, no studies as yet give evidence if and how sleep quality contributes to fatigability.

2.4.3 Fatigue, Pain and Quality of Life

Pain has been recognised as a symptom of MS since the first descriptions of the disease and can broadly be classified as nociceptive or neuropathic (O'Connor et al., 2008). The overall point prevalence of pain in MS is around 50% (O'Connor et al., 2008) and it is often ranked by patients as one of the most distressing symptoms of the disease (Kalia & O'Connor, 2005). In spite of the prevalence and clinical importance of pain in MS, its mechanisms remain poorly understood. One case-control study in women with relapsing remitting MS found that pain and pain intensity were significantly greater in the relapsing remitting MS group in comparison to healthy controls

(Newland et al., 2009), likely due to the clinical disease of MS. Additionally, five different MS body pain syndromes were identified within the literature, all neuropathic from pseudo-radicular pain (Ramirez-Lassepas et al., 1992; Tosi et al., 1998; Marchettini et al., 2006), dysesthetic pain (Burkey & Abla-Yao, 2010; Deppe et al., 2013), painful itching (Hellwig et al., 2006), painful tonic spasms (Andrade et al., 2012) and visceral pain (Marchettini et al., 2006). The identification/location of neurological lesions was thought to explain the body pain syndromes, as these were located in the spinal cord, except for painful tonic spasms, where lesions were identified in the pyramidal tract in the brain (Andrade et al., 2012). In this sense, pain is likely to be linked to fatigue due to the central origin and might be directly disturbing sensory afferent pathways, or by disrupting descending inhibitory pathways (Svendsen et al., 2011). Further investigations are warranted.

Quality-of-life (QoL) is defined as individual perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals expectations, standards and concerns (Huh et al., 2014). Several studies have reported that QoL is worse in PwMS in comparison with healthy controls with a higher prevalence of depression and fatigue (Murphy et al., 1998; Amato et al., 2001; Lobentanz et al., 2004; Pittion-Vouyovitch et al., 2006; Kargarfard et al., 2012). One small study of 31 PwMS showed that increased fatigue intensity was a predictor of decreased physical QoL (Newland et al., 2009). The aforementioned symptoms are important, and all play a role in MS-fatigue, as such the thesis will measure them accordingly.

2.4.4 Relationship Between Perceived Fatigue and Fatiguability

Some studies have failed to associate perceived fatigue and fatigability (Krupp & Elkins, 2000; Lou et al., 2003; Bailey et al., 2007), while others have shown an association (Goldman et al., 2008b; Bruce et al., 2010; Severijns et al., 2015) . These previous studies may have failed to establish a relationship because fatigue and fatigability are poorly understood, and self-reported fatigue scales do not accurately capture the perception of fatigue (perceived fatigue) in relation to change in physical performance (fatigability). The extent to which high levels of MS perceived fatigue and more pronounced fatigability are the result of the disease process *per se* (i.e., demyelination and axonal degeneration in the central nervous system) or secondary

factors is difficult to delineate at the individual level, and the extent to which both constructs can be modulated by therapeutic interventions (e.g., exercise rehabilitation) is unknown.

2.5 Exercise Therapy for Fatigue in MS

2.5.1 Introduction to Therapeutic Exercises

Clinical fatigue treatments for PwMS have primarily focused on the effectiveness of pharmacological and psychosocial interventions, however, their efficacy has been found to be modest at best and most often reported to be ineffective (refer to review (Lee et al., 2008). Alternative approaches to fatigue management are clearly needed and treatment modalities that can be incorporated into long-term self-management strategies would have particular appeal to PwMS, their carers and healthcare providers. One highly promising approach to managing MS-fatigue is exercise (Pilutti et al., 2013; Heine et al., 2015). Exercise is reported as a safe, non-pharmacological treatment strategy for P*w*MS, with numerous systematic reviews highlighting many health benefits, including improvements in muscle power, fatigue, physical and psychosocial functioning and quality of life (Rietberg et al., 2005a; Motl & Gosney, 2008; Asano et al., 2009; Kluger et al., 2013a). However, despite the known health benefits of exercise, PwMS are considered to be relatively inactive (Motl et al., 2005; Sandroff et al., 2012), which might place them at a higher risk of developing secondary health complications associated with inactivity (Motl & Goldman, 2011), in particular cardiovascular disease (including, stroke, peripheral artery disease etc.) and type 2 diabetes (Motl et al., 2005; Lee et al., 2012). Other studies have explored the barriers and facilitators of exercise in PwMS (Kayes et al., 2011; Asano et al., 2013) but there is a lack of in-depth understanding about how these translate to MS-fatigue management.

Nowadays, a combination of pharmacological and/or non-pharmacological treatments (which may include exercise) are often recommended in the fatigue management plan. Medications such as Amantadine, Pemoline, and Modafinil are frequently used in an attempt to lessen fatigue and its effects in PwMS (Krupp et al., 1988; Janardhan & Bakshi, 2002), whereas non-pharmacological interventions include education to avoid extreme weather conditions like heat and humidity, addressing lifestyle factors like diet and exercise, learning strategies for energy conservation, and adapting to work

and household environments (Krupp et al., 1988; Merkelbach et al., 2002; Shah, 2009). However, a review by Khan et al. (2014) showed that the effects of pharmacological and non-pharmacological treatments of fatigue in the MS population vary considerably, and that the best treatment option for MS-fatigue is often difficult to determine. There is no standardised agreement for the recommended dose of structured exercise or physical activity for fatigue management in PwMS. World Health Organisation Guidelines on physical activity and sedentary behaviour (published 25th November 2020) recommends similar to the general population, that the traditional interventions are based around 30–60 minutes of moderate-intensity aerobic activity, 3 days per week, and/or 2–3 sessions of resistance training per week to enhance functional capacity and prevent falls (https://www.who.int/publications/i/item/9789240015128). Similarly for PwMS, Dalgas et al. (2008) recommended 10 to 40 minutes of moderate intensity aerobic activity (2-3 days per week) and moderate intensity (1-4 sets of 8-15 repetition) resistance training (2-3) days per week. The American College of Sports Medicine (ACSM) recommends 30 min of moderate intensity aerobic activity (3 days per week; Ferguson (2014)). Latimer-Cheung et al. (2013) recommend 30 min of moderate intensity aerobic exercise (2 days per week) and strength training for major muscle groups (2 days per week). These guidelines are aimed at PwMS who are mildly or moderately affected by the condition and the activities used in the guidance are structured forms of exercise. Nonetheless, there is no specific MS guidance that considers how the broad range of physical activity options should be used to manage MS-fatigue. Clinical guidance in the UK recommends the use of exercise as one strategy in the management of PwMS, including MS-fatigue (NICE, 2014). These recommendations focus on moderate progressive resistance training, aerobic, balance and stretching exercises to improve mobility and symptom severity.

2.5.2 Resistance Exercise

Prior to 1990, resistance exercise was not a part of the recommended guidelines for exercise training and rehabilitation for either the American Heart Association or the ACSM. In 1990, the ACSM first recognized resistance training as a significant component of a comprehensive fitness program for healthy adults of all ages (Ferguson, 2014). In this respect, resistance training shows particular promise for reducing the impact of MS, including symptoms of fatigue (Dalgas et al., 2010; Dodd

et al., 2011). The optimal method of achieving a resistance training effect depends on many factors and approaches have varied in the literature, with many studies using resistance machines, some using body weight, and one study using resistance bands. From these, no single form suggests particular benefits over the other, however, access to resistance machines may be limited for some PwMS due to either geographical location or physical ability. Thus, free weights or exercises which use body weight or resistance bands as the form of resistance may offer a more practical solution. Furthermore, resistance training offers advantages in that it can easily be done at home for individuals with mobility difficulties, and the intensity/amount of resistance applied can easily be modified throughout. However, a major limitation of current studies examining the effects of exercise training, including resistance training, on fatigue is that participants have not been recruited on the basis that they are experiencing severe levels of fatigue (Pilutti et al., 2013; Motl et al., 2017) and in many studies, fatigue has been a secondary outcome.

A systematic review of exercise therapy and fatigue in PwMS suggested that resistance training may have more consistent fatigue-reducing effects than aerobic exercise but fewer well controlled trials have studied this exercise modality (Andreasen et al., 2011). One single-blind randomised controlled trial trained severe fatigue PwMS three times a week for duration of 16 weeks of high activity aerobic exercise, and did not show a clinically meaningful reduction in fatigue or societal participation when compared to a low-intensity control intervention (Heine et al., 2017). Randomised controlled trials that have investigated the effects of resistance training on fatigue in P*w*MS have reported significant improvements in symptoms (Dalgas et al., 2010; Ushiyama et al., 2010; Dodd et al., 2011; Hayes et al., 2011b; Sabapathy et al., 2011). These studies and others showed improvements in self-reported fatigue following 8-12-week programmes of twice-weekly resistance exercise (White et al., 2004; Gutierrez et al., 2005; Dalgas et al., 2010; Dodd et al., 2011), whereas other studies incorporating higher volumes of aerobic exercise (e.g. thrice-weekly aerobic exercise for 12-15 weeks) showed no effect (Petajan et al., 1996; Geddes et al., 2009). A randomised controlled trial that did not to show an effect on fatigue symptoms compared thrice-weekly high-intensity eccentric resistance exercise with standard exercises (Hayes et al., 2011b) but this type of high intensity resistance exercise is atypical and might not be suitable for all patients.

Several further resistance training studies adopted an experimental methodology with no control group (White et al., 2004; Gutierrez et al., 2005; Taylor et al., 2006b; Ayán Pérez et al., 2007; Filipi et al., 2010). Another study used a "within subjects"controlled design (de Souza-Teixeira et al., 2009). The remainder adopted a randomised controlled trial design (DeBolt & McCubbin, 2004; Dalgas et al., 2010; Broekmans et al., 2011; Dodd et al., 2011; Hayes et al., 2011a). However, there is a risk of bias with studies often not achieving assessor blinding and failing to use an intention to treat paradigm when analysing results from a fatigued group of PwMS. Inaddition, more studies that exclusively recruit highly fatigued PwMS are needed to better understand the impact of exercise programmes on this debilitating symptom. Additionally, differences between studies with respect to training variables included, the intensity of resistance exercise (Muellbacher et al., 2000), type of muscle contractions (Howatson et al., 2011), degree of fatigue, and the external pacing of muscular contractions (Leung et al., 2015) might affect the adaptations in motor cortex and perception of fatigue experienced in PwMS.

Resistance exercise training may be a better system of exercise training for evoking sustained improvements in fatigue as it is easily transferrable to the home environment through body resistance, weighted vest and thera-band exercises (Taylor et al., 2006b). There is evidence of high adherence to home-based resistance training as well as improvements in leg extensor power (White et al., 2004; Taylor et al., 2006b). One study that encouraged PwMS to maintain progressive resistance exercise (PRE) after a 12-week period of supervision at home showed a sustained improvement in fatigue up to 24 weeks, though this was not significant (Fimland et al., 2010). The venue of many of the studies has been hospital or university laboratories, however these studies show that it may be more effective for long term continuation of the exercise programme to allow study participants to undertake exercise in the home-environment or community leisure facility – particularly if participants can somehow be remotely supported. Doing so, also fits well with government guidelines which encourages community rehabilitation (Scottish Executive, 2007). Taylor et al. (2006b) and Dodd et al. (2011) have shown this is feasible by carrying out interventions in community spaces. Furthermore, a systematic review did not find any evidence of adverse events or symptom exacerbations in studies of resistance training in PwMS (Motl et al., 2008;

Asano et al., 2009). Another potentially important issue is that aerobic exercise can present problems for PwMS with ambulatory difficulties and can raise the body's core temperature to levels that can exacerbate symptoms in thermosensitive PwMS. Resistance training overcomes both these problems, as exercises can be performed in fully supported (or seated) positions and core temperature does not increase to the same extent (White et al., 2004).

2.5.3 External Pacing of Resistance Training

Co-coordinated movements and rhythmic perception are intuitively connected. Cognitive neuroimaging studies have found motor areas in the brain are involved in perceiving the beat when listening to musical rhythms, suggesting a connection between the cerebral auditory and motor system (Grahn & Brett, 2007; Chen et al., 2008). Hence, resistance training using simple movements might be synchronised to sound and therefore improve connectivity between motor and auditory areas (Thaut & Thaut, 2005). People with MS with low physical activity levels have been suggested to inappropriately use activity pacing as a reactionary response to their multiple sclerosis symptoms (Abonie et al., 2020). Hence, the use of pacing devices during resistance training (e.g., a metronome) might increase brain activation during movement, promote neuroplastic adaptations and pacing response (Abonie et al., 2021). The use of externally paced resistance training with an audible metronome was shown to produce a large magnitude of cross-education in the lower limb in healthy, untrained individuals (Goodwill & Kidgell, 2012). This may be due to the increased cognitive demand and control of movement pattern, which likely results in greater use-dependent neuroplasticity (Ackerley et al., 2011; Leung et al., 2015). For example, Leung et al. (2015) investigated the effects on excitability and inhibition of a single bout of visuomotor tracking compared with self-paced resistance training and metronome-based resistance training and found that both skilled training and metronome-paced resistance training, but not self-paced resistance training, increased excitability and released inhibition in both the trained limb and in the untrained limb. This has implications for rehabilitation: for example, an improved understanding of the methods that maximise the opportunity for neuroplasticity may result in an important progression in how we prescribe exercise-based rehabilitation for motor performance, fatigue perception and potentially restoration of the corticospinal control of the muscle in PwMS.

2.5.4 Neural Adaptation to Resistance Training

An increase in force is a common result of resistance training, even with studies of short duration (Hood & Forward, 1965; Gabriel et al., 1997; Holtermann et al., 2005; Schnelle et al., 2012). Some studies have reported an increase in rate of force development as a common finding (Aagaard et al., 2002a; Brown & Whitehurst, 2003; Gruber et al., 2007; Holtermann et al., 2007a; Holtermann et al., 2007b), with improvements seen in as little as two days (Brown & Whitehurst, 2003). Additionally, changes in muscle activation, such as increases in motor neuron firing rate (Van Cutsem et al., 1998; Patten et al., 2001; Klass et al., 2008) and decreases in motor neuron recruitment threshold (Cracraft & Petajan, 1977; Adam et al., 1998; Van Cutsem et al., 1998), are commonly implicated among early neural adaptations to strength training (Aagaard et al., 2002b; Holtermann et al., 2007a). Numerous studies have shown an increase in level of muscle activation, as measured via surface EMG, subsequent to strength training (Knight & Kamen, 2001; Aagaard et al., 2002a; Gruber et al., 2007).

Furthermore, there are a number of studies that have employed transcranial magnetic stimulation to investigate the integrity of the corticospinal pathway following a single session of strength training (Hendy & Kidgell, 2014; Leung et al., 2015; Latella et al., 2016; Nuzzo et al., 2016; Latella et al., 2018). For example, a single session of heavy-load elbow flexion strength training increased MEPs evoked by single-pulse transcranial magnetic stimulation (Leung et al., 2015). Neuroplastic adaptations evoked by resistance training could reduce or eliminate the need for compensatory downregulation of inhibitory cortical neural pathways, with evidence showing that SICI reduces following a single session of strength training in healthy controls, suggesting improved motor performance (Hendy & Kidgell, 2014; Leung et al., 2015; Latella et al., 2016; Latella et al., 2018). However, further investigation is needed to determine whether such resistance-training effects are possible in PwMS and if so, what impact they may have on MS-fatigue.

Several studies have provided evidence of neuroplasticity (including cortical plasticity) in response to habitual exercise and physical inactivity/immobilisation (Hortobagyi et al., 2009; Falvo et al., 2010; Kidgell & Pearce, 2010; Ushiyama et al., 2010; Carroll et al., 2011; Weibull et al., 2011; Langer et al., 2012). Interestingly,

short-term programmes of resistance training have shown an increase in central motor activation (Folland & Williams, 2007), enhanced neural economy (Falvo et al., 2010) and adaptations in corticospinal inhibitory mechanisms (Kidgell & Pearce, 2010) in healthy volunteers. In PwMS, a 3-week programme of lower-limb resistance training resulted in an increase in motor output from spinal motor neurons (Fimland et al., 2010), consistent with an augmented descending drive from higher centres (Aagaard et al., 2002b).

2.6 Summary

In an attempt to understand and reduce MS-related fatigue, this chapter has provided evidence that MS-fatigue is multi-factorial, with interplay of perceived (self-reported) and fatiguability components. Although there is still a lack of well-conducted trials which precludes any definitive conclusions as to the potential mechanisms underlying MS-fatigue, there is evidence to suggest that PwMS experiencing high levels of fatigue are 'neurophysiological different' to less-fatigued PwMS. Additionally, there is evidence that resistance exercise is capable of inducing neuroplastic adaptations which may have a positive impact on MS-fatigue symptoms. With these points in mind, the first aim of this thesis was to provide a greater understanding of the neurostructural and neurophysiological aetiology of MS-fatigue. Secondly, to investigate the feasibility and early indicative efficacy of externally paced resistance exercise training as a strategy for reducing MS-fatigue symptoms in PwMS.

CHAPTER 3 – GENERAL METHODS

3.1 Introduction

This chapter describes the common methods used for the experimental work contained within this thesis. Additional detail, which is only specific to individual chapters, is further described in the methods section of the relevant chapter.

3.2 Pre-Test Procedures

3.2.1 Ethical Approval

Institutional ethical approval was received from the Northumbria University, Faculty of Health & Life Sciences Ethics Committee (HLSPE111114: Chapters 5 and 6 and HLSPE010216: Chapter 7, Appendix 1), in accordance with the ethical standards and principles of local ethics committees, as established in the *Declaration of Helsinki* (1975, as revised in 2013). Chapters 5-7 received additional ethical approval from the respective Newcastle upon Tyne National Health Service Hospital Review Committee (14/LO/2290: Chapter 5 - 6 and 16/SS/0142 Chapter 7, Appendix 2).

3.2.2 Health and Safety

All experimental research was carried out in hospitals of the Newcastle upon Tyne national health service Foundation Trust (i.e., Royal Victoria Infirmary and the Newcastle General Hospital), in accordance with established Newcastle upon Tyne national health service Foundation Trust health and safety policies and standard operating procedures. Prior to, and following all experimental work, the assessment room and all apparatus were cleaned using alcohol wipes (PMC0062, Clinell Universal Sanitising Wipes), in accordance with relevant national health service guidelines. During each session of data collection, the lead researcher and one nurse (Band 6) were present throughout, both qualified in emergency first aid and use of an automated external defibrillator. Experiments were stopped prematurely if the participant displayed signs of discomfort, syncope or nausea. In the likelihood of an adverse event, the participant would be moved to the hospital ward on the same floor and monitored by the lead researcher and clinical team until any adverse physiological responses subsided. Participants were informed they could stop an experiment prematurely at any time and were under no obligation to provide a reason. Additionally, in Chapter 7, participant reasons for drop-out were recorded to ascertain feasibility outcomes. Participants were informed to contact the lead researcher if prior to the visits they felt unwell so that experimental sessions could be reorganised. In the

unlikely case that the participant presented any adverse symptoms related to their MS, the lead researcher contacted the clinical team for a review.

3.3 Participants

Clinically diagnosed people with definite relapsing-remitting multiple sclerosis (relapsing remitting MS) were selected and recruited according to the Poser criteria (Poser et al., 1983; McDonald et al., 2001). Disease severity was determined by a consultant neurologist using the Expanded Disability Status Scale (EDSS, refer to Figure 3.1) with 0.0 representing "normal neurological function" and 10.0representing "Death". A visual representation of the EDSS is shown in Figure 3.1 (Kurtzke, 1983). All PwMS had a mild to moderate level of disability (EDSS, 0.0 to 5.0).

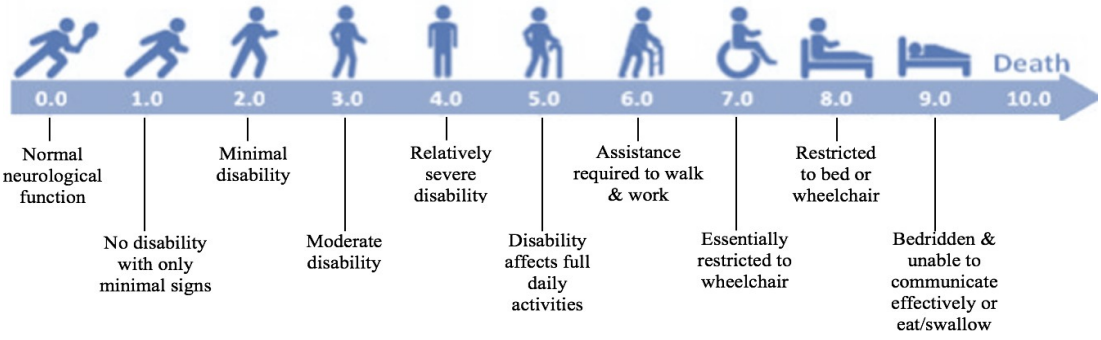

Figure 3.1 Visual representation of the EDSS (Adapted from Kurtzke, 1983).

In Chapters 6 and 7, PwMS were divided into two sub-groups, 'Highly-Fatigued PwMS' (MS-HF) and 'Less-Fatigued PwMS' (MS-LF). High levels of MS-fatigue were defined using a Fatigue Severity Scale (FSS) cut-off score ≥ 5 (Krupp et al., 1989). Please refer to the overview of thesis participant characteristics presented in Table 3.1.

Table 3.1 Overview of Thesis Participant characteristics (Mean ± SD).

	Chapter 6 and 7 Participants			**Chapter 8 Participants**	
Within Group Description	HC	MS-LF	MS-HF	Exercise	Control
N	20	20	20	16	17
Age (years)	44.8 ± 15.1	45.9 ± 9.0	43.6 ± 10.2	51.7 ± 9.3	48.2 ± 7.7
Gender (F/M)	13/7	15/5	15/5	12/4	11/6
EDSS (arbitrary units)	-	2.1 ± 1.2	2.4 ± 1.4	2.7 ± 1.4	3.3 ± 5.3
Disease Duration (years)	-	9.3 ± 3.8	9.9 ± 5.5	10.8 ± 4.5	8.8 ± 4.4
Disease Modification Therapy (Y/N)	-	17/3	14/6	13/3	15/2

FSS: Fatigue Severity Scale; HADS: Hospital and Anxiety Depression Scale; HC: Healthy Controls; MS-LF: Less-Fatigued People with Multiple Sclerosis; MS-HF: Highly-Fatigued People with Multiple Sclerosis N: Numbers; F: Females; M: Males; EDSS: Extended Disability Status Scale; Y: Yes; N: No. *One-way ANOVA significant group effect $p < 0.05$.

Furthermore, selection of participants was based on the participant's medical notes and the inclusion and exclusion criteria (see Table 3.2). For the experimental Chapters 5 and 6, a cohort of age- and gender- matched healthy participants were also recruited as a comparison group and assessed for eligibility to take part via study-specific inclusion and exclusion criteria (also provided in Table 3.2).

Table 3.2 Inclusion and Exclusion Criteria

Inclusion Criteria (PwMS)	■ Adults >18 years with definite multiple sclerosis (Poser criteria) ■ EDSS score of 0.0-5.0 (Kurtzke, 1983). ■ FSS ≥ 5 (highly-fatigued group); FSS < 5 (less-fatigued group) (Krupp et al., 1989) ■ Able to walk without rest or aid for 300 metres (as defined by EDSS). ■ Able to understand spoken and written English and stage two instructions. ■ Clinically stable (no relapses) for at least 4 weeks prior to entering the study. ■ Stable on disease modifying therapy (Interferon, Glatiramer Acetate, Mitoxantrone and Natalizumab) for at least 3 months prior to entering the study. ■ No contra-indications to transcranial magnetic stimulation or other neurophysiological measurements (Rossi et al., 2009). See Appendix 3. ■ Must be able to provide written informed consent. ■ Right handedness and have normal function of the right limbs (Oldfield, 1971). See Appendix 4.
Exclusion Criteria (PwMS)	■ Any other conditions that may be associated with fatigue, e.g., anaemia, dementia, alcoholism, implanted pacemaker, metal implants, and pregnancy. ■ Medication taken within the past 3 months, which may directly affect level of fatigue (Amantadine, Modafinil). ■ Change in medical treatment within the last 3 weeks.
Inclusion Criteria (age-matched controls)	■ Adults >18 years. ■ No contra-indications to transcranial magnetic stimulation or other neurophysiological measurements (Rossi et al., 2009). See Appendix 3. ■ Must be able to provide written informed consent. ■ Able to understand spoken and written English and stage two instructions. ■ Right handedness and have normal function of the right limbs (Oldfield, 1971). See Appendix 4.
Exclusion Criteria (age-matched controls)	■ Any other conditions that may be associated with fatigue, e.g., anaemia, dementia, alcoholism, implanted pacemaker, metal implants, and pregnancy. ■ Medication taken within the past 3 months, which may directly affect level of fatigue.

3.3.1 Recruitment

Participants were recruited from the Neurology Department outpatient's clinic at the Royal Victoria Infirmary Hospital, Newcastle upon Tyne, UK between April 2015 and June 2018 for Chapters 5 to 7 via voluntary response to advertising flyers, clinic attendance and postal letters of invitation, with further details being provided below:

- **Advertising flyers** were placed in the waiting room of the neurology outpatient clinics and day unit clinics (i.e., day unit for Lemtrada, an intravenous infusion disease modification treatment. Potential eligible PwMS were invited to speak to the lead researcher and/or a MS specialist nurse/consultant neurologist and a participant information sheet was sent out (Appendix 5). Followed two-weeks later with a follow-up phone call.
- **Patient referral from the neurology outpatient clinics.** Eligible PwMS were referred by an MS Specialist Nurse and/or Consultant Neurologist to the lead researcher, who attended three weekly clinics. A participant information sheet was provided, with a follow-up phone call two-weeks later.
- **Postal letters of invitation** were sent out to eligible PwMS who matched the inclusion and exclusion criteria assessed by an MS Research Nurse (see Appendix 6), followed two-weeks later with a follow-up phone call.

Further details of each recruitment method can be found within each chapter.

For Chapters 5 and 6, a cohort of healthy volunteers was recruited using flyers and posters in local community centres and universities and screened for eligibility by the lead researcher. For Chapter 7, participants from Chapters 5 and 6 who previously expressed interest in participating in further research, were identified from database records by the lead researcher and MS Specialist Nurse before the study information (i.e., letter of invitation and participant information sheet) was sent out. Thereafter, potential participants were advised to phone contact the MS Research Nurse for eligibility criteria screening and were then invited for an informed consent visit.

3.3.2 Informed Consent

Prior to entering the study and <5 days prior to the familiarisation visit, eligible participants were invited to attend a preliminary visit with the lead researcher and a MS Research Nurse in the Clinical Research Facility at the Royal Victoria Infirmary Hospital, Newcastle upon Tyne, to complete the informed consent documentation (Appendix 7). Participants were also required to complete the FSS (Appendix 8) and HADS (Appendix 9), as it is often reported that depression and anxiety are co-existing symptoms amongst PwMS and may explain some of the variance of MS-fatigue

(Bakshi et al., 2000). Thereafter, participants were invited for a study familiarisation visit.

3.4 Familiarisation

Participants attended a ~1-hour familiarisation visit to go through the experimental procedure of the measures to be assessed, to be screened for any contra-indications to transcranial magnetic stimulation and/or other neurophysiological measurements (Rossi et al., 2009) and to complete the patient-reported outcome questionnaires. Any participant presenting a contraindication was excluded and provided with an explanation for their exclusion, with any uncertainty being followed-up with the clinical research team, including the Consultant Neurologist and MS Specialist Nurse. Data collected during familiarisation were not used for subsequent analysis.

3.5 Experimental Criterion

Demographic data (including gender, age, disability, type of MS), comorbidities, disease modification treatment and additional medication were recorded. All experimental testing was performed at the same time of the day (± 2 h) to control for diurnal variations in corticospinal excitability and inhibition (Tamm et al., 2009; Lang et al., 2011) Participants were instructed to arrive at the hospital in a rested state, to avoid strenuous exercise in the 48-hours preceding assessment sessions and to refrain from caffeine intake 24-hours prior to testing (Taylor et al., 2006a; de Carvalho et al., 2010) Moreover, participants were advised to wear a loose-fitting short-sleeved top, shorts and sports trainers. For safety reasons, they were advised to contact the lead researcher if they felt an oncoming exacerbation of MS (i.e., relapse, attack or flare-up) and, in such circumstances, the experimental testing session would be reorganised. To encourage recruitment amongst participants living in Newcastle and surrounding areas of the North East of England, reimbursement of taxi travel was available for all roundtrips to hospital.

3.6 Neuromuscular Assessment

All neuromuscular assessments presented in Chapters 5 to 7 were performed at the Clinical Research Facility, located in the Royal Victoria Infirmary Hospital. Participants were required to visit the laboratory on two separate occasions for knee extensor and wrist flexor muscle assessments, performed in a randomised order with

a minimum of 48-h between visits. During the neurophysiological assessments, participants were comfortably seated upright with the involved limb fixed into position with a custom-made adjustable isometric dynamometer (see Figure 3.2). Additional detail on these procedures is provided below.

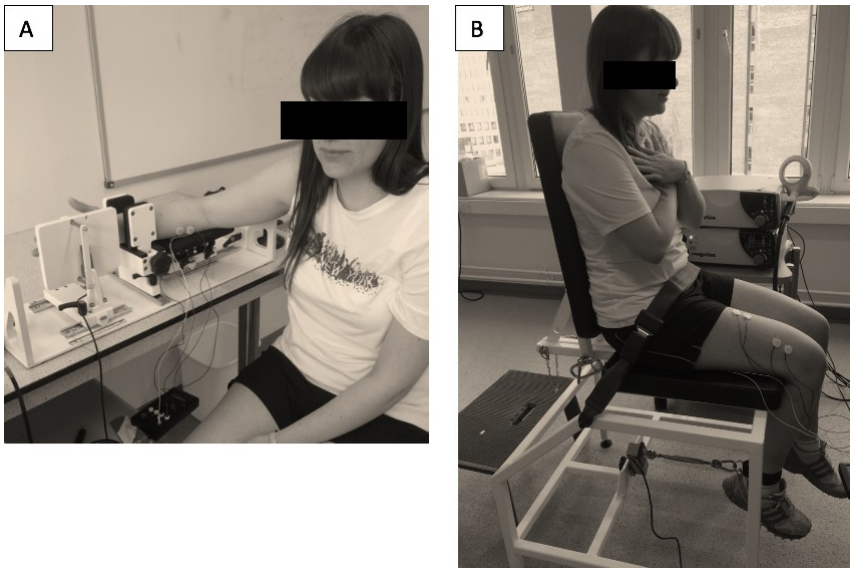

Figure 3.2 The custom-modified and adjustable isometric dynamometer set-up for the (A) wrist-flexor and (B) knee-extensor muscles.

3.6.1 Force and Electromyography Recordings

Calibrated load cells recorded muscle force in Newton's (N), during an isometric maximal voluntary contraction of the knee extensors and wrist flexors. For each participant, the height of the load cell was adjusted at the beginning of each trial to ensure that force was applied in a direct line tangentially to the joint axis of rotation. Wrist flexor force was measured using a calibrated load cell (NL62, Neurolog, Digitimer, Welwyn Garden City, Hertfordshire, UK) attached to a flat metal plate positioned midway in the palm of the right hand. The arm and wrist were immobilised and positioned using a goniometer at 45° angle away from the right shoulder during voluntary contraction (Langer et al., 2012; as shown in Figure 3.2.A). Knee extensor force was measured using a calibrated load cell (NL63, Neurolog, Digitimer, Welwyn Garden City, Hertfordshire, UK), connected to an adjustable strain gage and non-compliant strap, attached superior to the ankle malleoli. Hip, knee and ankle angle were measured using a goniometer and set at 90° of flexion, supported with a seatbelt to restrict rise of the hips during voluntary muscle actions of the knee-extensors.

Visual feedback was displayed on a screen in front of the participant during voluntary and evoked muscle actions, to assist in providing maximal efforts during MVC (Baltzopoulos et al., 1991).

Skeletal muscle activity during voluntary and evoked muscle actions of the *rectus femoris* (knee-extensor muscle) and *flexor carpi radialis* (wrist-flexor muscle) were recorded from pairs of surface Ag/AgCI electrodes (1041PTS-Kendall, Henley's medical supplies, Welyn Garden City, Herts, UK). Prior to attachment of electrodes and to reduce impedance, the participant's skin was shaved (if required) and cleaned with an alcohol wipe. Then, following palpation of the muscle under a resisted contraction, the electrodes were spaced parallel to the alignment of muscle fascicles and 2 cm apart over the muscle belly (Rainoldi et al., 2004). The placement of EMG electrodes was marked with indelible ink and recorded on acetate in relation to anatomical landmarks based on SENIAM guidelines to ensure they were placed in the same location at both assessment visits. Reference electrodes were placed over the patella and the olecranon process, respectively. In addition, antagonist muscle activity was recorded from the *biceps femoris* (knee-extensor muscle) and the *extensor carpi radialis* (wrist-flexor muscle), as antagonist activation can affect the measurement of agonist voluntary activation when using the interpolation twitch technique (Todd et al., 2004, 2016). The maximal EMG amplitude during the MVC was quantified as the root-mean-square (RMS) value during a 0.5 s interval that spanned the peak of the EMG. In other assessments, EMG responses were recorded from transcranial magnetic stimulation motor evoked potentials (MEPs) and compound muscle action potential (M-wave) from percutaneous nerve stimulation, these are explained infurther detail below. The EMG (gain × 1000; Cambridge Electronic Design [CED] 1401, Cambridge, UK) and force (gain × 300; CED 1902, Cambridge, UK) signals were amplified, then band-pass filtered (EMG only; 20-2000 Hz), digitised (4 kHz; CED micro1401, Cambridge, UK) and acquired for later off-line analysis on apassword secured laptop (Spike2 v6, CED, UK).

3.7 Percutaneous Nerve Stimulation

Percutaneous nerve stimulation of the femoral and ulnar nerve was administered using single electrical stimuli (200 μs pulse width, 100 Hz) via a constant-current stimulator (DS7AH, Digitimer Ltd., Hertfordshire, UK) to elicit a maximum M-wave (M_{max}) in

the *rectus femoris* and *flexor carpi radialis* muscles, used to assess changes in membrane excitability. Before placing the adhesive electrodes (ST50D [50 mm], Nidd Valley Medical Ltd., Bordon, UK), the skin was cleansed with an alcohol wipe to improve the signal-to-noise ratio. For the femoral nerve, the cathode was positioned high, over the femoral triangle and the anode was placed midway between the greater trochanter and the iliac crest (Sidhu et al., 2009; Weavil et al., 2015). For the ulnar nerve, a cathode was positioned 3-5 cm above the medial epicondyle and the anode was placed on the lateral epicondyle of the right elbow. The stimulation intensity was determined by applying a gradual increase, beginning at 100 mA and increasing by 20 mA until plateaus were evident in the resting muscle twitch and M-wave. To ensure supramaximal stimulation, the stimulation intensity was then increased by 30% (Oğuzhanoğlu et al., 2010). To determine the potentiated twitch force ($Q_{tw,pot}$) percutaneous nerve stimulation of the femoral and ulnar nerve was delivered 2 s after an MVC (McKenzie et al., 1992). The mean of three attempts was recorded pre- and post- the sub-maximal test. The $Q_{tw,pot}$ was used in the calculation of peripheral voluntary activation.

3.7.1 Voluntary Activation

Voluntary activation (VA) is defined as the level of neural drive to a muscle during exercise (Gandevia et al., 1995) and was estimated using the interpolation twitch technique, with a single electrical stimulation of the femoral and ulnar nerve delivered during and 2 s following a MVC (Merton, 1954b; Strojnik & Komi, 2000). If during an MVC, the super-imposed twitch is small or absent, it is suggested that this reflects an ability to drive most of the motorneurons voluntarily to produce maximal force (Belanger & McComas, 1981; Gandevia & McKenzie, 1988; Lyons et al., 1996; Allen et al., 1998; Herbert & Gandevia, 1999). To quantify VA, the amplitude of the potentiated twitch was compared with the super-imposed twitch evoked during an MVC, and VA was derived from the following equation:

$$\text{Voluntary Activation (\%)} = (1 - \text{super-imposed twitch} / Q_{tw,\,pot}) \times 100$$

3.7.2 Sub-maximal Test Protocol

In Chapters 5 and 6, a sub-maximal isometric test using intermittent muscle actions at 40% MVC was performed by all participants. The target force at 40% MVC was determined from the MVC obtained at the start of the visit. Participants performed intermittent isometric muscle actions (3 s on, 2 s off) until the target force could not be met. Participants were instructed to increase force to the target (40% MVC), matching the displayed force on the monitor screen in front of them and hold it as steady as possible. At the end of each minute, they were instructed to produce an MVC, before returning to targeted sub-maximal muscle actions (Bigland-Ritchie et al., 1986; Burnley et al., 2012). All sub-maximal and maximal muscle actions were prompted by an interval timer (Gymboss LLC Interval Timer) with the lead researcher providing verbal prompts for the participant to begin each muscle action with "push" and "rest". The test was continued for 60 minutes or until task failure, i.e.,the point at which a participant was unable to maintain the target force within ~5% of40% MVC for three muscle actions. Data acquisition for performance fatigabilitywas quantified as the change in MVC force before to after the sub-maximal test (Burnley et al., 2012). Ratings of perceived exertion were also measured using the Borg scale (6–20) after every set, with 6 representing "rest or no exertion", and 20 corresponding to the "maximal effort" (see section 3.9.6 for more details).

3.8 Transcranial Magnetic Stimulation

Single- and paired-pulse transcranial magnetic stimulation was applied over the left motor cortex (M1) projecting onto spinal motorneurons (i.e., corticospinal tract). Consequently, motorneuron activation in response to corticospinal volleys induced by transcranial magnetic stimulation leads to a contraction in the target muscle, evoking a MEP on EMG recorded with surface electrodes applied over the muscle belly. When the M_{max} is compared to the MEP peak-to-peak amplitude estimates of excitability of the corticospinal tract can be made (Figure 3.3). Transcranial magnetic stimulation was delivered through a concave double 110 mm cone coil (maximum output 1.4 T) for the knee-extensor muscle and an 8 cm figure-of-eight coil for the wrist-flexor muscles, powered by two Magstim 200^2 stimulators and a BiStim unit (The Magstim Company Ltd, Whitland, UK). Identification of the optimal coil position for the *rectus femoris* and *flexor carpi radialis* was found by the junction of the double-cone coil aligned tangentially to the sagittal plane, with its centre 1–2 cm to the left of the vertex

to stimulate the contralateral hemisphere of the chosen dominant muscle. The optimal position to stimulate the *flexor carpi radialis* was found using the figure of eight-shaped coil held over the left M1, with the handle pointing backwards at 45° away from the midline sagittal plane invoking a posterior–anterior current flow. The optimal coil placement was determined at the start of each trial as the position that elicited consistently large MEPs from separate spots for the right rectus fermoris and flex muscles. The position was then marked with indelible ink to ensure consistent placement throughout the trials. Specific details of the protocols used to assess cortical and subcortical drive are presented below. Stimulator intensity was based on the active motor threshold (AMT). The AMT was determined at the beginning of each assessment during a 10% MVC, with stimulator intensity set at 50% and increasing in 5% increments until consistent MEP with peak-to-peak amplitudes of ≥ 0.05 mV in three out of five stimulation attempts in the *rectus femoris* and *flexor carpi radialis* were evident (Sharshar et al., 2004; Groppa et al., 2012; Weier et al., 2012). Abnormal MEPs were noted, visually inspected and agreed for inclusion by the lead researcher and a clinical neurophysiologist (clinical team member).

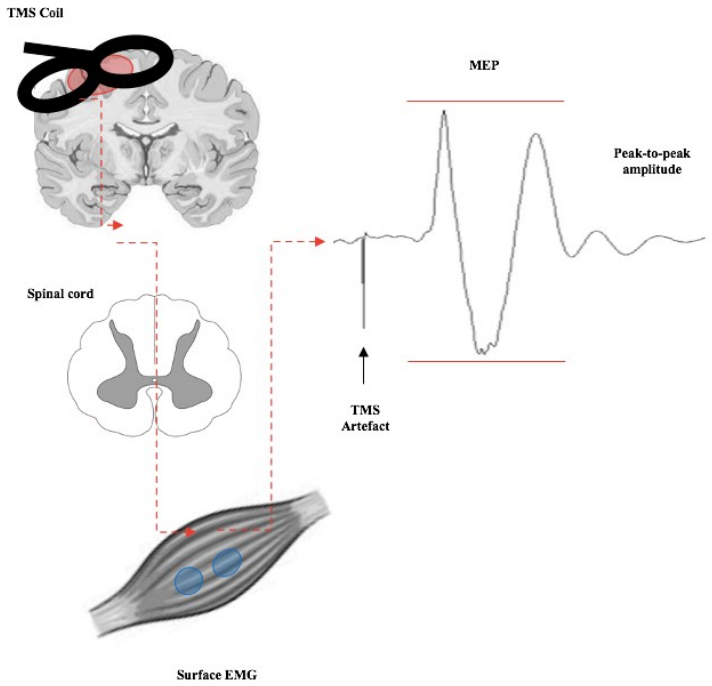

Figure 3.3 Transcranial magnetic stimulation applied over the motor cortex to the brain surface projecting on spinal motorneurons, also termed the corticospinal tract. Motorneuron activation in response to corticospinal volleys induced by transcranial magnetic stimulation leads to a contraction in the target muscle evoking a MEP, recorded by using surface EMG electrodes over the muscle belly.

3.8.1 Short-Interval Intracortical Inhibition

Paired pulse transcranial magnetic stimulation was used to quantify corticospinal inhibition performed during a 10% MVC and delivered by a Magstim 200^2 and a BiStim module (The Magstim Company Ltd, Whitland, UK). For single-pulse transcranial magnetic stimulation, the stimulus intensity was set at 120% AMT. The configuration used for short interval intracortical inhibition (SICI) consisted of a sub-threshold conditioning stimulus of 70% AMT, followed by supra-threshold of 120% AMT unconditioned test stimulus; test stimulus delivered in a randomised order of 20 stimuli (i.e., 10 single and 10 paired pulses (Conte et al., 2009; Garry & Thomson, 2009). The inter-stimulus interval was 2 ms, which has been shown to elicit the greatest amount of inhibition in the RF (Brownstein et al., 2018; Goodall et al., 2018). SICI was determined as the ratio between the test stimulus and conditioning stimulus using Spike2 (v6, CED, UK). A conditioned versus unconditioned ratio of 100% indicates facilitation. If the ratio for SICI was >100% or the ratio for ICF was <100%, the data from the corresponding participant were removed from analysis.

3.8.2 Corticospinal Silent Period

The corticospinal silent period (CSP) was measured during 50% MVC contractions where single-pulse transcranial magnetic stimulation was applied with an intensity of 140% AMT. The CSP was quantified as the duration (ms) from the point of stimulation to the resumption of pre-stimulus EMG. There is some inconsistency in the literature in relation to identifying the resumption of pre-stim EMG with visual inspection techniques having previously been used (Todd et al., 2005; Sidhu et al., 2009; Astorino et al., 2015). In this thesis, CSP was quantified as the duration from stimulation to the continuous resumption of post-stimulus EMG, which is as reliable as an automated procedure (Hermsen et al., 2016b). The mean of three evoked responses was used for subsequent analysis.

3.9 Perceptual Scales

In Chapters 5-7, participants were asked to complete several perceptual scales of patient reported outcomes on fatigue, mood, sleep, pain and quality of life.

3.9.1 Perceived Fatigue

Fatigue Severity Scale

The FSS was developed for use in PwMS (Krupp et al., 1989) and comprises 9-items that rate the level of agreement with statements about the severity, frequency and impact of fatigue in everyday life. A total FSS score ≥ 5 (Likert Scale) classifies P*w*MS as experiencing clinically-important levels of fatigue (Krupp et al., 1989). The FSS enables two sub-groups to be classified as 'highly-fatigued' and 'less-fatigued', as reported in previous studies with cut off > 5 (Liepert et al., 2005; Tellez et al., 2005; Andreasen et al., 2009). Chipchase et al. (2003) reported good discernment between PwMS and healthy controls and good test-retest reliability (Intraclass correlation=0.84; (Krupp et al., 1989; Chipchase et al., 2003). The FSS requires five minutes to complete and no prior training, supporting the feasibility of this scale in clinical research (Appendix 8).

Modified Fatigue Impact Scale

The Modified Fatigue Impact Scale (MFIS) is a modified form of the Fatigue Impact Scale, developed by Fisk et al. (1994) and is a measure of the impact of fatigue experienced in everyday life (Fisk et al., 1994b). The MFIS comprises 21-items, with patients required to rate agreement with each statement (0 “never” to 4 “almost always”, Appendix 10). A recommended global MFIS score cut-off of ≥ 38 classifies PwMS as experiencing clinically important levels of fatigue (Tellez et al., 2005; Johansson et al., 2008). Rietberg, (2010) reported good test-retest reliability (ICC = 0.85, (Rietberg et al., 2010)) and good internal consistency (Cronbach’s alpha = 0.80). Furthermore, correlation between the MFIS and FSS in PwMS has been reported as *r* = 0.66 (Rietberg et al., 2010), suggestive of good convergent validity, with similar results also reported in an alternative MS study (Tellez et al., 2005).

Chalder Fatigue Scale

The Chalder Fatigue Scale (CFS) measures a composite of physical and mental fatigue (i.e. a total score) as a measure of fatigue severity in PwMS (Chalder et al., 1993). The CFS comprises 11-items that measure fatigue intensity (Appendix 11). A total CFS score of ≥ 4 (bimodal scale) classifies PwMS as experiencing clinically important levels of fatigue (Johansson et al., 2008). The CFS has reported high internal consistency, with small to moderate correlations with impact of fatigue and mood, and

it is sensitive to change across low and high intensity behavioural interventions (Chilcot et al., 2016).

3.9.2 The Hospital Anxiety and Depression Scale

People with MS often report depression and anxiety, and this may exacerbate and explain some of the variance of fatigue (Ehde et al., 2003). The Hospital Anxiety and Depression Scale (HADS) is an appropriate screening measure for major depression and generalized anxiety disorder in PwMS (Honarmand & Feinstein, 2009; Watson et al., 2014). Global mood, depression and anxiety were assessed using the self-administered HADS questionnaire (Zigmond & Snaith, 1983), a 14-item self-assessment questionnaire, with responses scored on a 4-point (0–3) scale, (3 indicating a high-frequency of experienced symptoms, Appendix 9). The HADS consists of two subscales, anxiety (HADS-Anxiety) and depression (HADS-Depression) with each subscale consisting of seven items and the total score ranging from 0 to 21 (Zigmond & Snaith, 1983; AS, 1994). An applied cut-off score of :;7 indicates non-cases, and with scores >7 indicating possible and definite cases (Zigmond & Snaith, 1983). To score global mood, a score between 0 and 7 is “normal,” between 8 and 10 “mild,” between 11 and 14 “moderate,” and between 15 and 21 “severe” mood. The MFIS takes 2–5 minutes to complete, which supports the feasibility of this scale in clinical research.

3.9.3 Sleep Quality

Poor quality of sleep is very common in PwMS (Veauthier et al., 2011) and has been reported to relate to fatigue, as well as being associated with impairments in cognitive function (Cameron et al., 2014). Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) over a 1-month time interval (Buysse et al., 1989). The PSQI is a self-rated questionnaire which consists of 19-items generating 7 component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction (Appendix 12. Each component has a possible score of 0–3, where a higher score indicates a greater sleep problem. The global PSQI score was used in all analyses and was the sum of all component scores (range: 0–21); a score ≥5 represents poor sleepers; <5 represents patients with normal sleep quality.

3.9.4 Pain

Throughout the course of MS, >50% of P*w*MS report pain as a common and varying symptom. Pain influences quality of life, mood, behaviour and the ability to partake in physical activity and structured exercise (Archibald et al., 1994; Ehde et al., 2003). Pain was measured by the recommended North American Research Committee on Multiple Sclerosis (NARCOMS) registry, which reports pain with one question; "*in the past months, how intense was your pain?".* The score ranges from 0 "*no pain*" to 5 "*totally disabling pain*". The NARCOMS pain questionnaire is an easy and efficient measure (Appendix 13), has good test-retest reliability (r = 0.84) and has been validated with the MS Pain Effects Scale criterion measure (Marrie et al., 2005).

3.9.5 Quality of Life

QOL was assessed using the Multiple Sclerosis Quality of Life (MSQOL)-54, comprising the generic Short-Form 36-item (SF-36) instrument (Ware & Sherbourne, 1992) in addition to 18 MS-specific items derived from professional opinion and a literature review (Vickrey et al., 1995). These enquire about QOL over the preceding month, except item 2 (Change in Health) which refers to the preceding year. Two composite scores (Physical Health Composite and Mental Health Composite) are derived by combining scores of the relevant subscales (Vickrey et al., 1995). MSQOL-54 scale scores were created using the Likert method by averaging items within the scales and, then row scores were linearly transformed into 0–100 scales. Higher values are indicative of a better quality of life. The MSQOL-54 has well documented validity, in terms of content, constructs, reliability, discrimination (Vickrey et al., 1995; Solari et al., 1999; Füvesi et al., 2008) and responsiveness (Giordano et al., 2010).

3.9.6 Ratings of Perceived Exertion

The Borg rating perceived exertion Scale quantifies perceived exertion during exercise (G., 1985) (6 = Very Very light – 20 =Maximal, see Appendix 14). The Borg rating perceived exertion Scale has been shown to be a reliable measure for functional tests such as the 6 Minute Walk Test, Functional Stair Test, Static Standing Balance Test and Sit-to-Stand Test in PwMS (Wetzel et al., 2011). To standardise the procedure and improve the accuracy of the rating perceived exertion scale, it was important that participants understand both the verbal anchors and the numerical value and as such, the same verbal instructions were given to each participant.

3.10 Statistical Analysis

Data are presented in this thesis as mean ± SD and mean ± SEM in figures unless stated otherwise. All data were analysed using SPSS (version 20, SPSS Inc., Chicago, IL, USA). Statistical significance was set at $p < 0.05$. Normal Gaussian distribution of data was confirmed using the Kolmogorov-Smirnov test and in the likely event a violation was detected, the data was logarithmically transformed.

3.10.1 Sample Size

Chapters 5 and 6 included the same cohort of participants. In accordance with previous cross-sectional studies that have provided preliminary evidence of neurophysiological differences between 'fatigued' and 'less-fatigued' people with MS, a sample size of ~20 participants are sufficient to show differences in measures of central and peripheral activation between the groups (Chalder et al., 1993; Greim et al., 2007). Thus, a sample of 20 participants per group (3 groups, 60 participants in total) was recruited to assess the test re-test reliability of the measures. In Chapter 7, consecutive sampling was used to recruit 30 participants (2 groups, 15 participants per group). This conforms to guidance on feasibility and pilot studies, with justification that a sample size ranging 24–50 has been recommended as sufficient and appropriate for determining the variability data of key outcome measures for use in sample size calculations for a larger trial (Sim & Lewis, 2012). Allowing for 20% attrition, 36 participants were aimed to be recruited and randomised.

3.10.2 Analysis of Variance

Chapter 5

In Chapter 5, between session test-retest reliability of all measures was assessed using reliability indices; intra-class correlation coefficient (ICC), coefficient of variation and typical error. According to the guidelines recommended by Koo and Li (2016), ICCs less than 0.5 were considered low agreement, between 0.5 and 0.75 were considered as moderate agreement, values between 0.75 and 0.9 as good agreement, and values >0.9 considered as excellent agreement (Bruton et al., 2000).

Chapter 6

In Chapter 6, in order to ensure equivalence between groups, all baseline variables (demographic, disease-related, fatigue, and physical measures) were compared

between groups using t-tests or chi-square tests where appropriate and using a significance threshold of $p < 0.05$. Analysis of variance (ANOVA) was used to compare neurophysiological outcomes between 'highly-fatigued' and 'less-fatigued' PwMS and healthy controls (Portney, 2000). Following a significant main effect from ANOVA, post-hoc comparisons were made using Bonferroni test using a critical value for the studentised range statistic of $\alpha = 0.05$.

Chapter 7

In Chapter 7, process and scientific feasibility was determined by the recruitment, (i.e., willingness to be randomised, optimal recruitment method, expected recruitment, refusal rates), acceptability of outcome measures, retention, adherence rates of attendance at supervised and home-based sessions and any adverse advents. Process and scientific feasibility were examined via percentage and descriptive statistics. The proportion of sessions completed by each participant was determined by taking the number of supervised sessions attended divided by the total number supervised sessions offered. This information is important because it provides acceptability and highlights considerations for alterations. Determining compliance will further allow correct conclusions to be drawn from the results. Specific details of the feasibility measures are outlined in the respective experimental chapter. Exploratory analysis was conducted using intent-to-treat analysis to determine change in neurophysiological and patient report outcomes, with missing data points checked to be random (Little's Chi Squared test), and then imputed using the SPSS Expectation Maximisation method. Outcome data were analysed using analysis of covariance (ANCOVA), with baseline values used as the covariate, to compare differences between groups at each time point (Follow-up 1/6 weeks and Follow-up 2/12 weeks). Results are presented as mean (± SD) at each time point and changes in outcome data are considered to be preliminary, and a cautious approach to interpretation has been taken.

CHAPTER 4 Neurostructural and Neurophysiological Correlates of Multiple Sclerosis Fatigue: Systematic Review and Meta-Analysis of Cross-Sectional Studies

4.1 Introduction

Studies show that ≥75% of people with multiple sclerosis experience fatigue symptoms persistently or sporadically (Lerdal et al., 2007) and over half the MS population describe it as their most severe symptom (Fisk et al., 1994a). In proposing a unified taxonomy for fatigue in neurologic illness, (Kluger et al., 2013b) highlighted the importance of differentiating between *perceived fatigue* and *fatigability* and the application of neuroimaging, neurophysiology and neuropathologic measures to improve our understanding of these two constructs was identified as a research priority. Perceived fatigue and fatigability are analogous to the constructs of 'central' and 'peripheral' fatigue proposed by (Chaudhuri & Behan, 2000). *Perceived fatigue* includes subjective feelings of weariness and an increased subjective perception of effort for everyday tasks (irrespective of recent physical exertion) and is commonly rated in PwMS with the FSS and MFIS (Krupp et al., 1989; Fisk et al., 1994b). The FSS is a 9-item scale which focuses on the severity, frequency and impact of fatigue on daily life during the past seven days, whereas the MFIS is a 21-item scale yielding data on the level of cognitive, physical, psychosocial and total fatigue experienced during the past 4 weeks. Validated cut-points of >4 and ≥38 for the FSS (Krupp et al., 1995) and MFIS (Flachenecker et al., 2002a), respectively, have been used to classify people experiencing higher (MS-HF) versus lower (MS-LF) levels of perceived MS fatigue. However, other threshold scores have been used as the criterion for higher levels of perceived fatigue in some studies (Colombo et al., 2000; Niepel et al., 2006; Tomasevic et al., 2013; Cogliati Dezza et al., 2015). In contrast, *fatigability*, sometimes referred to as motor fatigability or performance fatigability (Zijdewind et al., 2016; Severijns et al., 2017), is defined as the rate of change in a performance criterion, e.g. an objective measure of voluntary force relative to a reference (baseline) value over a given time of task performance or measured mechanical output (Kluger et al., 2013b).

Neuroimaging studies that have investigated associations between perceived fatigue severity and morphometric measures of global brain atrophy or regional atrophy within grey or white matter structures have yielded conflicting results (Tedeschi et al., 2007; Pellicano et al., 2010; Cruz Gomez et al., 2013; Rocca et al., 2014). Nevertheless, evidence of impaired functional connectivity between cortical and sub-cortical regions, implicates basal ganglia structures, the thalamus, and specific areas

within the frontal, parietal, and temporal lobes in *perceived* MS fatigue (Roelcke et al., 1997; Filippi et al., 2002; Tartaglia et al., 2004; Wilting et al., 2016; Jaeger et al., 2018). Although neuromuscular studies have yielded inconsistent data for voluntary activation of the upper- and lower-limb skeletal muscles in PwMS versus healthy controls (Ng et al., 2000a; Andreasen et al., 2009; Steens et al., 2012a), neurophysiological impairments could underpin the reductions in maximal voluntary force (Ng et al., 2004; Liepert et al., 2005; Wolkorte et al., 2016) and motor function (Ng et al., 2004) and the more pronounced levels of fatigability (Sheean et al., 1997; Liepert et al., 2005; Wolkorte et al., 2016) that have been reported in PwMS. Such neurophysiological changes are likely to have a direct bearing on perceived effort for everyday tasks and perceptions of fatigue amongst PwMS.

Current knowledge on the underlying neurobiological substrate of MS fatigue, as assessed by neuroimaging and neurophysiological measures, is impeded by inconsistent findings, insufficiently powered cross-sectional studies and comparisons between healthy controls and PwMS, without partitioning the latter by fatigue status. This makes it difficult to draw definitive conclusions about neurobiological differences between MS-HF and MS-LF and there is a need to consolidate anextensive and somewhat conflicting evidence-base. This systematic review and accompanying meta-analyses addressed these limitations by synthesizing all current evidence, including peer-reviewed (published) neuroimaging and neurophysiological data acquired from senior authors which were not originally presented by fatigue statusof PwMS in the published report. By meta-analysing previously reported dichotomised data for MS-HF versus MS-LF, the main aim was to gain an improved insight into structural and neurophysiological correlates of MS fatigue.

4.2 Methods

4.2.1 Search Strategy

This systematic review and meta-analysis was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (Liberati et al., 2009) and the protocol was pre-registered with the PROSPERO International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=17934). A systematic literature search of PubMed/MEDLINE, ProQuest, CINAHL and Web of

Science from inception until 31st December 2019 was undertaken, blinded to title and authorship, by two reviewers (PE & SG). The search strategy was conducted using Medical Subject Headings and search terms included those related to MS, fatigue, neurophysiology, neuroimaging, voluntary contractions, transcranial magnetic stimulation and motor nerve stimulation (Table 4.1). We also searched the grey literature (theses, conference abstracts/posters), along with the reference lists of retrieved systematic reviews and included studies to identify other pertinent articles.

Table 4.1. Databases and Search Terms

Database Up to December 31st, 2019	Search
PubMed/MEDLINE	(("multiple sclerosis"[MeSH Terms] OR ("multiple"[All Fields] AND "sclerosis"[All Fields]) OR "multiple sclerosis"[All Fields]) AND (twitch[All Fields] AND interpolation[All Fields])) AND central[All Fields] AND ("transcranial magnetic stimulation"[MeSH Terms] OR ("transcranial"[All Fields] AND "magnetic"[All Fields] AND "stimulation"[All Fields]) OR "transcranial magnetic stimulation"[All Fields] OR ("transcranial"[All Fields] AND "magnetic"[All Fields] AND "stimulation"[All Fields] AND "paired"[All Fields] AND "pulse"[All Fields])))) AND (intracortical[All Fields] AND excitability[All Fields]) AND (("nerve tissue"[MeSH Terms] OR ("nerve"[All Fields] AND "tissue"[All Fields]) OR "nerve tissue"[All Fields] OR "nerve"[All Fields]) AND stimulation[All Fields])) AND (maximal[All Fields] AND contraction[All Fields]) AND (motor[All Fields] AND execution[All Fields]) AND (maximal[All Fields] AND contraction[All Fields]) AND force[All Fields] AND (motor[All Fields] AND execution[All Fields]) AND motor fatigue AND force AND/OR (multiple sclerosis) AND motor fatigue AND fatigue scores AND ("neurophysiology"[MeSH Terms] OR "neurophysiology"[All Fields])) AND ("fatigue"[MeSH Terms] OR "fatigue"[All Fields]) AND muscle action potentials AND neural activity AND ("motor activity"[MeSH Terms] OR ("motor"[All Fields] AND "activity"[All Fields]) (10) "magnetic resonance imaging" MeSH Terms] OR ("magnetic"[All Fields] AND "resonance"[All Fields] AND "imaging"[All Fields]) OR "magnetic resonance imaging"[All Fields] OR "functional magnetic resonance imagery "[All Fields]) "functional magnetic resonance imaging"[All Fields]) "functional"[All Fields] OR "volumetric" AND "brain structures" (("brain"[MeSH Terms] OR "brain"[All Fields]) AND structures[All Fields]) OR "brain function" (("brain"[MeSH Terms] OR "brain"[All Fields]) AND ("physiology"[Subheading] OR "physiology"[All Fields] OR "function"[All Fields] OR "physiology"[MeSH Terms] OR "function"[All Fields])) AND "brain activation "brain"[MeSH Terms] OR "brain"[All Fields]) AND activation [All Fields].
ProQuest,	multiple sclerosis, nerve stimulation, twitch interpolation, transcranial magnetic stimulation, motor cortical excitability, muscle strength, peripheral and central fatigue, maximal voluntary contraction, motor task, maximal force, motor fatigue, fatigue scores, neurophysiology,muscle action potential, neural activity, magnetic resonance imaging, functional magnetic resonance imaging, volumetric, brain structures, brain function, brain activation.
CINAHL	multiple sclerosis, nerve stimulation, twitch interpolation, transcranial magnetic stimulation, motor cortical excitability, muscle strength, peripheral and central fatigue, maximal voluntary contraction, motor task, maximal force, motor fatigue, fatigue scores, neurophysiology,muscle action potential, neural activity, magnetic resonance imaging, functional magnetic resonance imaging, volumetric, brain structures, brain function, brain activation.
Web of Science	TS=('multiple sclerosis' AND 'transcranial magnetic stimulation, paired pulse') TS=('multiple sclerosis' AND 'transcranial magnetic stimulation, single pulse') TS=('multiple sclerosis' AND 'twitch interpolation') TS=('multiple sclerosis' AND 'muscle strength') TS=('multiple sclerosis' AND 'muscle fatigue, peripheral') TS=('multiple sclerosis' AND 'muscle fatigue, central') TS=('multiple sclerosis' AND 'motor performance') TS=('multiple sclerosis' AND 'nerve stimulation') TS=('multiple sclerosis' AND 'brain stimulation') TS=('multiple sclerosis' AND 'fatigue scales') TS=('multiple sclerosis' AND 'magnetic brain imaging') TS=('multiple sclerosis' AND 'functional magnetic brain imaging') TS=('multiple sclerosis' AND 'brain function, brain structures') TS=('multiple sclerosis' AND 'brain activation') TS=('multiple sclerosis' AND 'neurophysiology')

4.2.2 Study Selection

Eligible articles reported data from cross-sectional studies using a validated fatigue scale and defined cut-points for differentiating MS-HF from MS-LF. Adults >18 years with definite multiple sclerosis (Poser or McDonald criteria) and all types of MS (relapsing-remitting; secondary progressive; primary progressive) were eligible for inclusion. The included studies must have reported neuroimaging measures or neurophysiological variables for MS-HF and MS-LF. However, 14 authors of 16 peer-reviewed published studies provided original data (neurofunctional or neurophysiological) partitioned by *perceived fatigue* status of PwMS (MS-HF versus MS-LF), where it was available but not reported as such in the published article, and these authors have been acknowledged. In the case of the same cohort data being reported in >1 article, only the most recent publication was included. Non-English animal studies, case studies, review articles, randomised controlled trials and other controlled trials, pharmacological trials and studies that only reported other physical/psychological outcomes (e.g., gait analysis variables, mental health status, disability, cognitive impairment and spiro-ergometric) were excluded.

4.2.3 Methodological Quality Assessment

The methodological quality of included studies was evaluated using the Cross-Sectional/Prevalence Study Quality Scale, recommended by the Agency for Healthcare Research and Quality (http://www.ncbi.nlm.nih.gov/books/NBK35156/) (Zeng et al., 2015). This scale is an 11-item tool that is used to evaluate study quality, with an item scoring "1" if it was answered "Yes" and "0" if it was answered "No", "Unclear" or "Not Applicable". Scores of 0-3 indicate "low quality", 4–7 "moderate quality" and 8–11 "high quality" (Appendix 17). Two reviewers (PE and SG) assessed each included study independently, with disagreements being resolved by consensus and the opinion of a third reviewer (JS).

4.2.4 Data Extraction and Analysis

Data were extracted independently by three reviewers (PE, SG and JS) as follows: (1) Study design; (2) Characteristics of the participants (number, subtype of MS, disease duration, age, gender and EDSS score, fatigue score); (3) Primary outcomes; (4) Secondary outcomes. Means and standard deviations for each variable were extracted for meta-analyses using RevMan 5.0 (http://www.cc-

ims.net/RevMan/download.htm). Due to variation in clinical and/or demographic characteristics and fatigue assessments across studies, a random-effects model was applied throughout. A p value <0.05 indicated statistical significance for an overall effect and the magnitude of heterogeneity across studies was tested using the I^2 statistic: I^2 values <25%, 25–50%, or >50% indicate low, moderate and high heterogeneity, respectively (Higgins et al., 2003). Funnel plots were not constructed, owing to the number of meta-analyses which included <10 studies (Sutton et al., 2000). Sub-group analyses were planned based on brain region and limb targeted. Data were not included in meta-analyses if means, standard deviations and number of participants allocated to each group were not reported or available.

4.3 Results

Figure 4.1 shows that the search yielded 66 studies, with data from 46 studies included in meta-analyses (42 neuroimaging studies, 19 neurophysiological studies and 5 combined neuroimaging and neurophysiological studies). Appendix 15 and 16 present details of each included study. A total of 1761 MS-HF and 1391 MS-LF participants were compared in the cross-sectional studies, with the majority (2345) having a definite relapsing remitting MS diagnosis, 150 being classified as PRIMARY PROGRESSIVE MS or secondary progressive MS and 575 participants of unspecified disease type. In 48 studies, healthy controls were included as an additional comparison. Studies which provided details of the gender balance for MS-HF and MS-LF (N=43) showed there were approximately twice as many women than men in each subgroup (729:357 and 657:387, respectively), reflecting the higher prevalence of MS amongst women (Harbo et al., 2013). The MS-HF and MS-LF groups were well-balanced for age, disease duration and EDSS score. The mean age was 40 years for MS-HF versus 38 years for MS-LF (reported in 56 studies). MS-HF had a mean disease duration (years) and EDSS score of 8.7 years (reported in 41 studies) and 2.6 (reported in 52 studies) respectively, versus 8.1 years and 2.0, respectively for MS-LF. EDSS scores indicated a mild to moderate level of disability with no impairment to walking for the majority of MS-HF and MS-LF participants (EDSS :; 3.5 in 85% of studies).

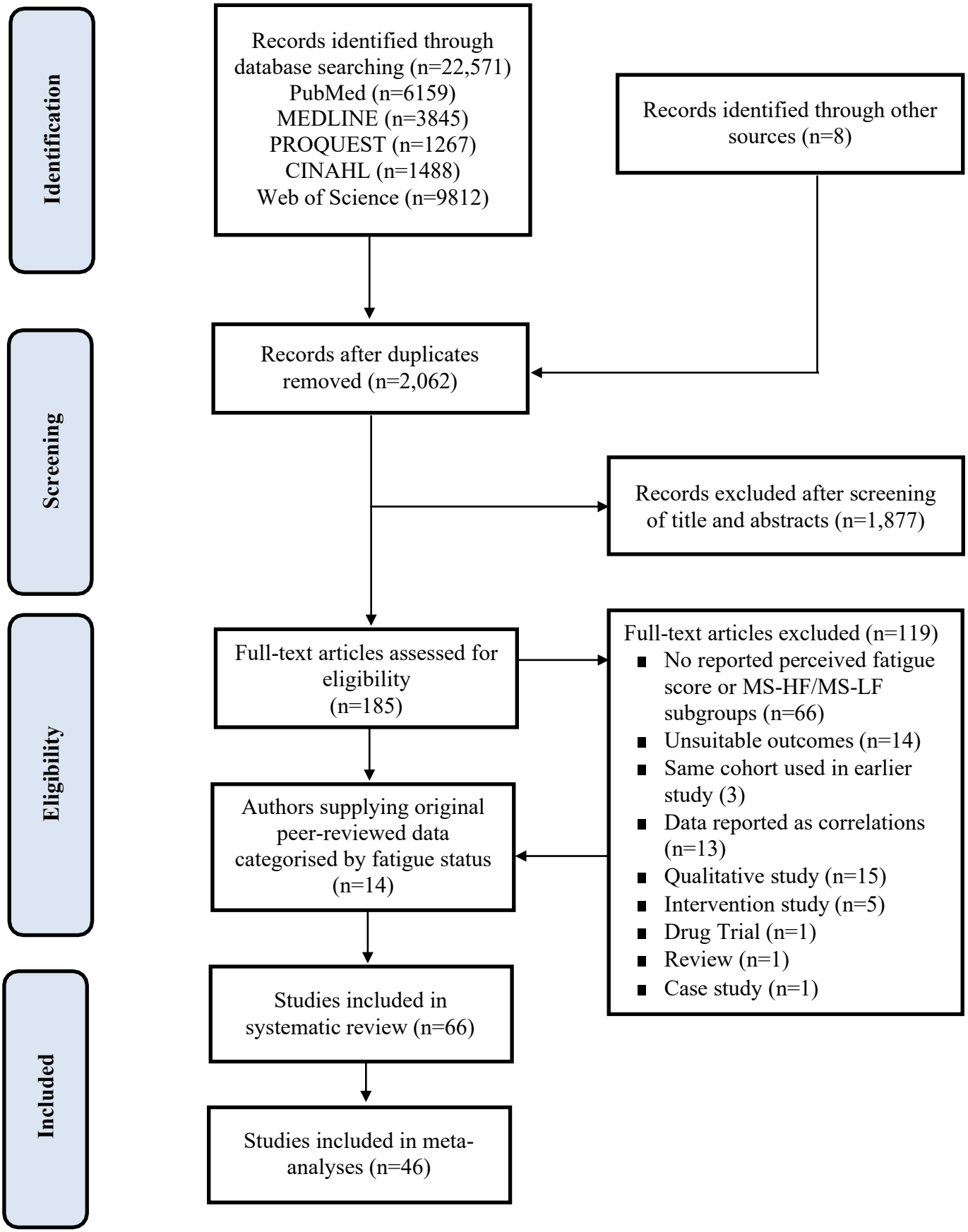

Figure 4.1. PRISMA flow chart for literature search and study selection

4.3.1 Perceived Fatigue Measures

The most frequently used scale to differentiate MS-HF from MS-LF was the FSS (Krupp et al., 1989), which was used in 48 of the included studies, using mean cut-off scores for MS-HF of >4 or >5 and total scores ranging from >25 to >36. A further 10 studies used the MFIS (Fisk et al., 1994a) with cut-off scores for MS-HF in the range of >35 to >38 or ≥16 for the MFIS physical scale. Three studies used the cognitive scale of the Fatigue Scale for Motor and Cognitive Functions using cut-points in the range of ≥22 to ≥28, two further studies used the MFIS-5 and a validated French version of the Fatigue Impact Scale, and three studies used subjective perceptions to classify MS-HF, e.g., "mostly or daily tired" (Appendix 15 and 16).

4.3.2 Neuroimaging and Neurophysiological Measures

Neuroimaging measures for meta-analyses were obtained using magnetic resonance imaging, diffusion tensor imaging and magnetic resonance spectroscopy (MRS). Measures included total normalised brain volume, grey and white matter volumes, T1-weighted hypointense and T2-weighted lesion volumes, white matter microstructural integrity (diffusion tensor imaging indices of fractional anisotropy and mean diffusivity) and neuronal/axonal integrity and function (N-acetylaspartate to creatine [NAA/Cr] ratio and choline to creatine [Cho/cr] ratio by MRS). Neurophysiological measures for meta-analyses were obtained using transcranial magnetic stimulation, electroencephalography (EEG), neuromuscular electrical stimulation (NMES) and electromyography (EMG) and included motor evoked potential (MEP) amplitude, MEP latency, MEP threshold, central motor conduction time, short-intervalintracortical inhibition (SICI), and voluntary activation (central motor drive) using the twitch-interpolation technique during MVC (Merton, 1954a). Brain region functional connectivity data determined using functional magnetic resonance imagery were not included in meta-analyses, but the key findings are reported in Supplementary Appendix 15. MVC force data were determined using upper- or lower-limb rigs that fixed the joint in position for isometric muscle actions, with fatigability being assessed using a sustained MVC or intermittent % MVC isometric fatiguing protocol and reported as percent of the baseline force.

4.3.3 Quality Assessment

Most of the included studies (70%) were classified as being of "moderate quality", 16 (24%) studies were rated as "low quality" and four studies (6%) as "high quality" (Figure 4.2; Appendix 17). Key limitations representing risk of bias included inadequate details of the time period used to identify and recruit participants, use of non-blinded evaluators and lack of quality control data for the methods used to compare MS-HF with MS-LF.

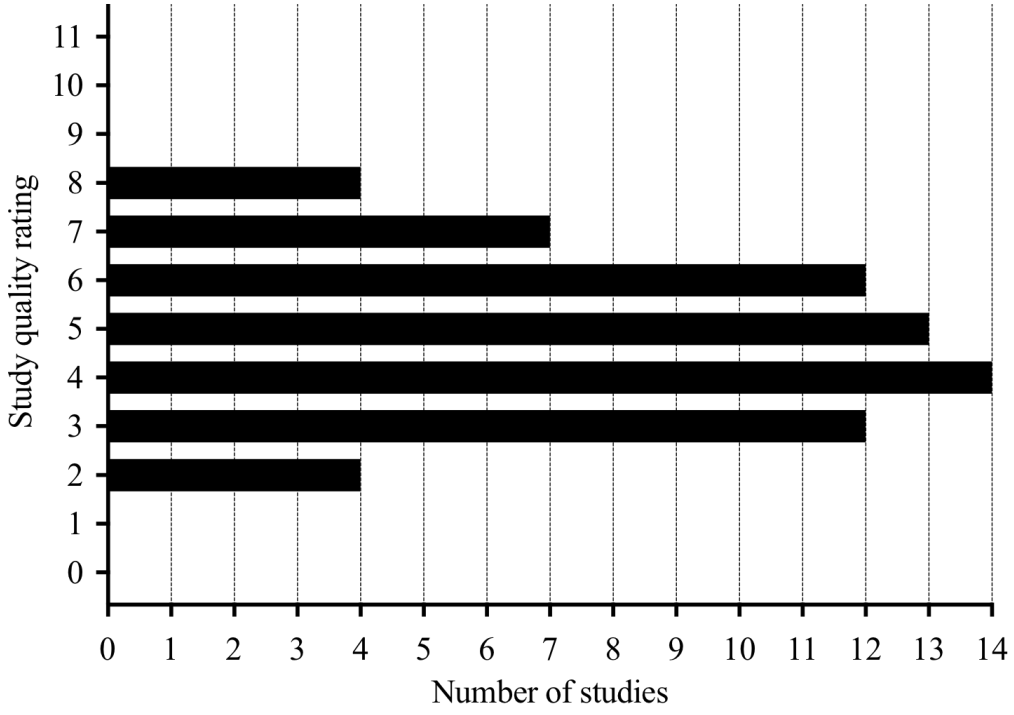

Figure 4.2. Methodological quality of the included studies evaluated using the Cross-Sectional/Prevalence Study Quality Scale, recommended by the Agency for Healthcare Research and Quality. Scores of 0-3 indicate "low quality", 4–7 "moderate quality" and 8–11 "high quality".

4.4 Meta-Analyses Overview

The results of meta-analyses are presented as absolute mean differences with 95% confidence intervals (CI). Detailed forest plots showing comparisons of MS-HF versus MS-LF, MS-HF versus HC and MS-LF versus HC are presented in Appendix 18-23. A summary of meta-analyses results for all neuroimaging and neurophysiological variables (MS-HF versus MS-LF) are presented as standardised mean difference (SMD) and 95% CI in Figures 4.3 and 4.4, with Cohen's categories (SMD = 0.2 - 0.5; 0.5 - 0.8; ≥ 0.8) indicating small, medium and large overall effect sizes, respectively.

4.5 Neuroimaging Meta-Analyses

4.5.1 Brain Volume

Meta-analysis indicated a reduction in mean normalised brain volume (-22.74 ml; 95% CI: -37.72 to -7.76 ml; p=0.003) in MS-HF versus MS-LF, accompanied by areduction in the volume of grey matter in MS-HF versus MS-LF (-18.81 ml; 95% CI: -29.60 to -8.03 ml; p<0.001). There was no significant difference in white matter volume between MS-HF and MS-LF (-6.41ml; 95% CI: -13.98 to 1.15 ml; p=0.10). Larger reductions in mean normalised brain volume, grey and white matter volumes (all p<0.001) were apparent for MS-LF and MS-HF versus HC (Figure 4.3, and Appendix 18, 20 and 22).

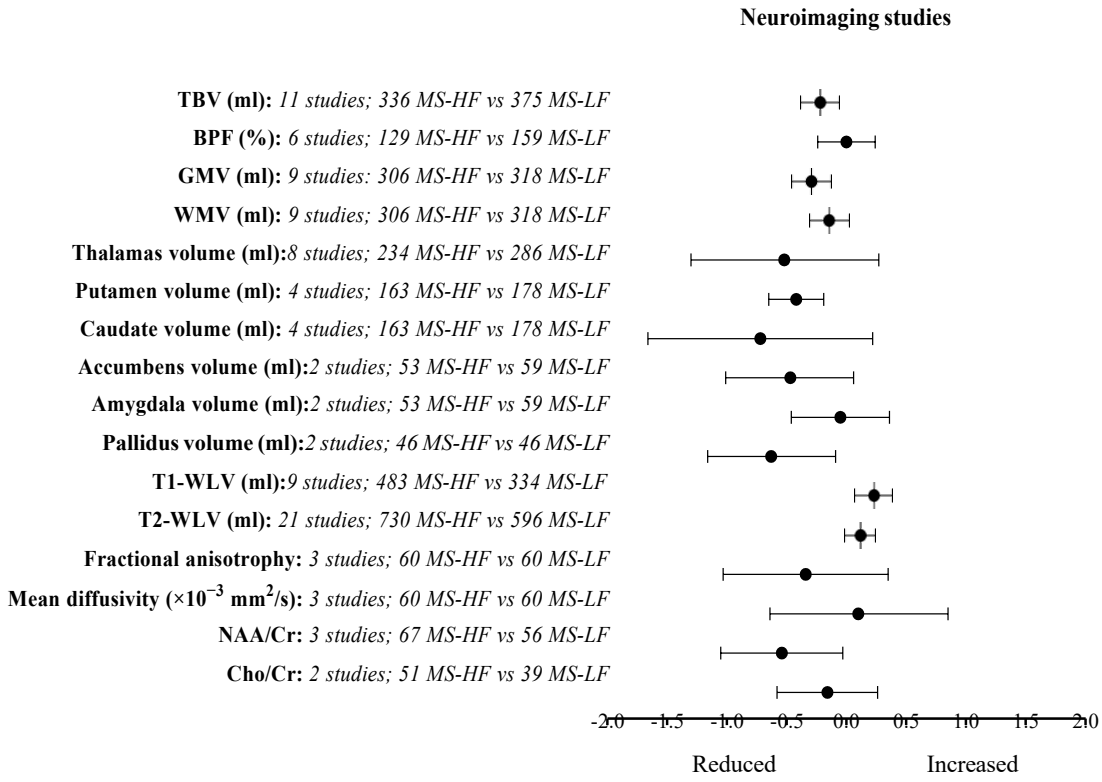

Figure 4.3. Summary of results of meta-analyses comparing neuroimaging and neurofunctional data for MS-HF versus MS-LF. Data are presented as standardised mean difference and 95% confidence intervals. The figure presents summary data for neuroimaging variables, with the abscissas representing a decrease or increase for MS-HF in comparison with MS-LF. TBV, total brain volume; BPF, brain parenchymal fraction; GMV, grey matter volume, WMV, white matter volume, T1-WLV, T1-weighted lesion volume, T2-WLV, T2-weighted lesion volume, NAA/Cr, N-acetylaspartate to creatine ratio Cho/Cr, choline to creatine ratio, UL, upper-limb; LL, lower-limb.

4.5.2 Subcortical Grey Matter Structure Volumes

Where data for sub-cortical structures were reported for the left and right sides, data were summed to provide a single volumetric measure for comparison with studies in which a single volumetric measure was reported. Meta-analysis showed a reduction in putamen (-0.40 ml; 95% CI: -0.69 to -0.10 ml; p=0.008) and accumbens (-0.09 ml; 95% CI: -0.15 to -0.03 ml; p=0.003) volumes for MS-HF versus MS-LF. Larger effect-size reductions in thalamus and caudate volumes did not reach statistical significance because of wider confidence intervals and there were high levels of heterogeneity (I^2 ⟩89%; Figure 2). Volumetric reductions were apparent for the thalamus, putamen and caudate (p:;0.02) in MS-LF and MS-HF versus HC, and for the accumbens in MS-HF versus HC (p=0.04; Figure 4.3 and Appendix 18, 20 and 22).

4.5.3 Lesion Volume, White Matter and Axonal Integrity and Function

There was an increased volume of T1-weighted hypointense lesions in MS-HF versus MS-LF (1.10 ml; 95% CI: 0.47 to 1.73 ml; p<0.001) and for MS-LF and MS-HF versus HC (p<0.0001). However, there were no differences between MS-HF and MS-LF for T2-weighted lesion volume (1.19 ml; 95% CI: -0.43 to 2.80 ml; p=0.15), white matter microstructural integrity (diffusion tensor imaging indices of fractional anisotropy and mean diffusivity) or axonal integrity/function (NAA/Cr or Cho/Cr by MRS). There was an increase in diffusion tensor imaging mean diffusivity for MS-HF (0.02 $\times 10^{-3}$ mm^2/s; 95% CI: 0.01 to 0.03 $\times 10^{-3}$ mm^2/s; p<0.001) and MS-LF (0.03 $\times 10^{-3}$ mm^2/s; 95% CI: 0.00 to 0.06 $\times 10^{-3}$ mm^2/s; p=0.03) versus HC, and a reduction in the NAA/Cr ratio in MS-HF versus HC (-0.10; 95% CI: -0.18 to -0.01; p<0.03), indicating relative impairment of microstructural and axonal integrity/function (Figure 4.3 and Appendix 18, 20 and 22).

4.6 Neurophysiological Meta-Analyses

4.6.1 Corticospinal Integrity and Intra-Cortical Inhibition

There were no significant differences between MS-HF and MS-LF in MEP amplitude, latency, threshold, CMCT or SICI. However, higher MEP thresholds were apparent for MS-LF and MS-HF versus HC (p :; 0.02; Figure 4.4 and Appendix 19, 21 and 23).

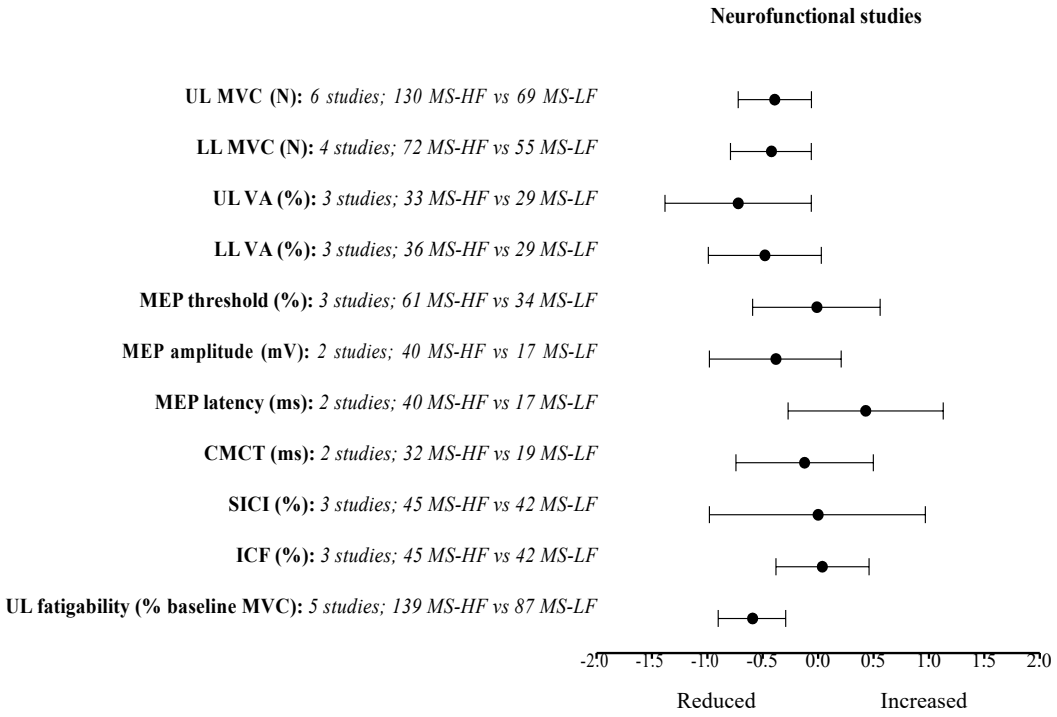

Figure 4.4. Summary of results of meta-analyses comparing neurofunctional data for MS-HF versus MS-LF. Data are presented as standardised mean difference and 95% confidence intervals. The figure presents summary data for neurofunctional variables, with the abscissas representing a decrease or increase for MS-HF in comparison with MS-LF. UL, upper-limb; LL, lower-limb; MEP, motor evoked potential; CMCT, central motor conduction time; SICI, short-interval intracortical inhibition, ICF, intracortical facilitation; MVC, maximum voluntary contraction force.

4.6.2 Skeletal Muscle Maximum Voluntary Contraction Force and Voluntary Activation

There were reductions in lower-limb (-19.23 N; 95% CI: -35.93 to -2.53 N; p=0.02) and upper-limb MVC force (-3.55 N; 95% CI: -7.11 to 0.01 N; p=0.05) in MS-HF versus MS-LF, with the latter of borderline statistical significance. Reductions in upper-limb MVC force were also apparent in MS-LF and MS-HF versus HC (p:;0.03). Meta-analysis of studies which used the twitch-interpolation technique during a MVC showed reduced voluntary activation in MS-HF versus MS-LF for upper-limb (-5.77 %; 95% CI: -8.61 to -2.93%; p<0.0001) and lower-limb skeletal muscles (-2.16%; 95% CI: -4.24 to -0.07%; p=0.04). Upper-limb muscles included finger and thumb flexors/extensors and lower-limb muscles included the quadriceps and dorsiflexors (Figure 4.4 and Appendix 19, 21 and 23).

4.6.3 Fatigability

Meta-analysis of the percent decline in MVC from baseline after an upper-limb (finger or thumb flexor/extensor) skeletal muscle fatigue task (either sustained [N=3] or intermittent [N=2] isometric MVC) revealed greater fatigability for MS-HF versus MS-LF (-5.61%; 95% CI: -9.57 to -1.65%; p=0.006). A more pronounced level of upper-limb fatigability was also observed for MS-HF versus HC (-7.43%; 95% CI: -11.95 to -2.90%; p=0.001; Figure 4.4 and Appendix 19, 21 and 23).

4.7 Discussion

Using a dichotomised model (MS-HF versus MS-LF), this systematic review and accompanying meta-analyses aimed to provide an improved insight into structural and neurophysiological correlates of MS fatigue. By robustly consolidating an extensive and somewhat conflicting evidence-base, we demonstrate that higher levels of MS fatigue are characterised by greater cortico-subcortical atrophy, and with indications of greater neural damage, as evidenced by an increased volume of T1-weighted hypointense lesions (Napoli & Bakshi, 2005). These neurostructural impairments are accompanied by neurophysiological decrements, manifest as impaired MVC force and reduced skeletal muscle voluntary activation. The synthesis of cross-sectional data in published reports of included studies, together with published peer-reviewed data (acquired from senior authors) that were not originally presented by fatigue status of PwMS, means these results provide the most precise effect-size estimates of neurobiological differences between MS-HF and MS-LF to date.

Although the meta-analyses provided clear evidence of white matter atrophy in MS-HF and MS-LF versus HC, the smaller normalised brain volume in MS-HF versus MS-LF appears to be mainly attributable to a volumetric reduction in grey matter. Cortical regions with reduced volumes for MS-HF versus MS-LF in the included studies were the precentral gyrus, inferior and superior temporal gyrus, superior and inferior frontal gyrus, anterior cingulate gyrus, central sulcus, superior and inferior parietal lobules (Sepulcre et al., 2009; Andreasen et al., 2010a; Riccitelli et al., 2011; Rocca et al., 2014). This meta-analysis also consolidated the evidence for sub-cortical grey matter structures, revealing volumetric reductions in the putamen and accumbens for MS-HF versus MS-LF. Evidence suggests that putamen atrophy is present early in the MS disease cycle (Kramer et al., 2015) and many participants recruited to the

included studies are likely to have fallen into this category (EDSS :; 3.5 in over 80% of studies). Interestingly, larger effect size reductions in caudate and thalamus volumes were also observed in MS-HF versus MS-LF and HC but these only reached statistical significance for comparisons with the HC data. Other sub-cortical and basal ganglia structures reported to have reduced volumes in MS-HF versus MS-LF which were inversely correlated with perceived fatigue were the pallidum and superior cerebellar peduncle (Rocca et al., 2014; Damasceno et al., 2016; Bernitsas et al., 2017) but there were insufficient data for meta-analyses. In addition, studies reported microstructural changes within the basal ganglia, thalamus and frontal lobe and impaired functional connectivity between basal ganglia structures and the sensorimotor cortex, frontal, parietal and temporal lobes (Wilting et al., 2016; Jaeger et al., 2018). Impaired basal ganglia circuitry, including striatocortical and striatothalamic networks and potentially implicating regions that are heavily reliant on dopamine neurotransmission (e.g., ventral striatum), have been postulated to be important mechanistic factors underpinning perceived MS fatigue (Chaudhuri & Behan, 2000; Dobryakova et al., 2015). These regions are primarily responsible for motor control, motor planning, attentional control and the integration of afferent and efferent information.

MS-HF showed an increased number of T1-weighted hypointense lesions in comparison with MS-LF, a difference that was even more pronounced in comparison with HC. However, there was no difference in the number of T2-weighted lesions or diffusion tensor imaging indices of white matter microstructural integrity between MS-HF and MS-LF. The increased number of T1-weighted hypointense lesions could reflect associations between MS fatigue symptoms and recently activated immune inflammatory pathways or irreversible pathological changes which are features of the disease (Morris et al., 2016). Recently formed T1-weighted scan-identified hypointense lesions represent current disease activity, including reversible oedema, inflammation, demyelination and remyelination, whereas chronic T1-weighted hypointense lesions reflect irreversible demyelination and axonal loss (Napoli & Bakshi, 2005). In contrast, T2-weighted scan-identified lesions, which are non-specific for the underlying pathology, reflect the accumulated lesion load or “burden of disease” (Sinnecker et al., 2012) and occur throughout the brain and white matter,

but less commonly, the grey matter (Napoli & Bakshi, 2005). Nevertheless, the possibility that localised white matter atrophy and loss of white matter microstructural integrity within specific brain regions could influence MS fatigue symptoms should not be overlooked. Consistent with this observation, there is evidence that atrophy progression within the corpus callosum (largest collection of brain white matter) is implicated in the evolution of MS-related fatigue (Yaldizli et al., 2010). Furthermore, other studies have provided evidence of localised metabolic alterations or anisotropic changes in white matter adjacent to the lateral and medial pre-frontal cortex and in fibres connecting basal ganglia structures (Hanken et al., 2015).

Meta-analysis revealed a reduction in muscle strength (MVC) in MS-HF versus MS-LF, which consolidates a conflicting body of data on this measure from studies investigating PwMS (irrespective of fatigue status) versus HC (Zijdewind et al., 2016). Greater cortico-subcortical grey matter atrophy and/or structural damage in MS-HF versus MS-LF could have a more pronounced effect on neural transmission from the brain to active skeletal muscles, and this could account for the reduced MVC. (Rocca et al., 2012) reported a more diffuse pattern of spinal cord interneuron activation in the axial and longitudinal planes in MS-HF versus MS-LF, which they speculated could be attributable to abnormally functioning local circuits, altered modulation from supraspinal pathways and/or local and remote structural damage. However, findings from our meta-analyses suggest that the relative integrity of corticospinal motor pathways is similar in MS-HF and MS-LF, as there were no differences in MEP variables or central motor conduction time between the groups. In contrast, a significant increase in MEP threshold was apparent for MS-HF and MS-LF versus HC, consolidating inconsistent data from previous studies on this measure of corticospinal excitability (Zijdewind et al., 2016).

Our meta-analyses revealed clear evidence of impaired voluntary activation (central motor drive) in MS-HF versus MS-LF, suggesting MS-HF have a relatively impaired ability to fully activate skeletal muscles in comparison with MS-LF. This may explain the observed reduction in MVC in MS-HF versus MS-LF, as previous studies have reported significant correlations between the decline in MVC and voluntary activation during sustained muscular contractions in PwMS (Zijdewind et al., 2016; Mamoei et al., 2020). Although females are reported to record lower MVC and voluntary

activation values than males (Solianik et al., 2017), the higher female to male ratio in the included studies is unlikely to account for these findings, as MS-HF and MS-LF comparison groups tended to be well-balanced for sex. An alternative explanation for the lower MVC and voluntary activation scores in MS-HF could be the deconditioning effects of relative physical inactivity after an MS diagnosis, which may be further compounded by the experience of severe MS fatigue (Sebastiao et al., 2017). Relative inactivity leads to disuse atrophy and neurophysiological changes affecting skeletal muscle activation, leading to impaired muscular strength and function (Rice et al., 1992). In turn, this could increase the amount of effort required for everyday tasks, thus exacerbating perceived fatigue and fatigability.

Current data provides no clear evidence of a link between MS fatigue and altered intracortical inhibition (SICI) or intracortical facilitation (ICF), despite reports of altered functional connectivity and hyperactivation in fronto-parietal cortical regions, sensorimotor network and subcortical areas important for motor, sensory and cognitive processing in MS-HF (Tartaglia et al., 2008; Specogna et al., 2012; Rocca et al., 2016; Bisecco et al., 2017; Jaeger et al., 2018). Evidence from functional magnetic resonance imagery and electroencephalogram studies suggests that functional reorganisation within cortico-subcortical networks as a compensatory response to MS brain lesions could account for an increased energy demand for neural processing within certain networks (Filippi & Rocca, 2004; Kos et al., 2008). This could at least partially explain increased perceptions of fatigue in PwMS because of an elevated demand on functioning neural circuits. However, at present very few studies have compared SICI or ICF variables between MS-HF and MS-LF, making it difficult to draw conclusions about the extent to which modulation of intracortical inhibitory or facilitatory networks could be implicated in MS fatigue. The limited conflicting data that is currently available for SICI may be a reflection of different MS populations studied, as two of the published studies were focused on people with relapsing-remitting MS (Liepert et al., 2005; Morgante et al., 2011), whereas a third was focused on progressive MS (Chalah et al., 2019).

Meta-analysis of five studies revealed an increased level of upper-limb fatigability for MS-HF versus MS-LF, showing a more pronounced decline in force production. In contrast, only one of the included studies with a small sample size (N=9) compared

lower-limb fatigability between MS-HF and MS-LF (Ng *et al*. 2000) using a sustained 30% MVC dorsi-flexor protocol. There is no standardised method for assessing fatigability (Severijns et al., 2017) and this is reflected in the broad range of protocols used in comparisons of PwMS versus HC. It is also acknowledged that fatigability is task specific, being influenced by task complexity (Wolkorte et al., 2015b), and that heterogeneity between patients (attributable to MS-specific functional impairments and differences in motor control) can confound fatigability measures (Severijns et al., 2017). However, aside from measurement of force decline over time, consistent fatigability data for MS-HF versus MS-LF have been reported in studies that have used exercise duration and number of muscular contractions before reaching a fatigue criterion (Perretti et al., 2004; Liepert et al., 2005). Evidence suggests that fatigability resulting from a sustained voluntary muscle contraction in PwMS mainly results from a decline in voluntary activation, whereas in healthy controls fatigability seems to be mainly of peripheral origin at the level of skeletal muscle (Sheean et al., 1997; Steens et al., 2012c; Severijns et al., 2017). An elegant study that combined imaging and electrophysiological techniques showed that in PwMS there was an inability to increase cortical activation in response to fatigability-related changes downstream of the motor cortex, which was at odds with the increase in cortical activation observed in HC (Steens et al., 2012c). Our meta-analysis of upper-limb data suggests that MS-HF may have less ability than MS-LF to increase cortical activation as a compensatory response to peripheral fatigue and this warrants further study. In addition, the relative paucity of lower-limb studies needs to be addressed, as PwMS more commonly report issues of fatigability in relation to lower-limb activities such as walking (Severijns et al., 2017).

4.8 Limitations

Key limitations of this meta-analysis include the diversity of magnetic resonance imagery techniques used for neuroimaging studies and heterogeneity of methods used to assess self-reported perceived fatigue and fatigability. Furthermore, many studies collected either neuroimaging or neurophysiological data, which prevented an exploration of relationships between neuroanatomical and neurophysiological impairments (including the impact on fatigability measures) within the same participants. The broad-ranging patient characteristics and lack of participant ethnicity data across different studies may also be considered as a limitation, although

confounders such as disease severity, level of disability, sex and age were minimised in the larger data-set meta-analyses. Nevertheless, some of the meta-analyses included a small number of studies and as the overall quality rating of included studies was 'moderate', as such, caution is needed when interpreting these results. In addition, although the Agency for Healthcare Research and Quality (Zeng et al., 2015) is suitable for use in systematic reviews of cross-sectional studies, there is no obvious candidate tool for assessing the quality of observational/cross-sectional studies, which may be considered a study limitation. Finally, the method used to differentiate MS-HF and MS-LF in the included studies was based on previously published cut-points for the FSS and MFIS that rely on recollections of fatigue experiences over the previous 1 - 4 weeks. Fatigue can be sporadic and the intensity of fatigue symptoms amongst PwMS at the time of testing was not well-documented in many studies.

4.9 Conclusion

In conclusion, this is the first meta-analysis to synthesise published cross-sectional data on structural and neurophysiological measures between MS-HF and MS-LF. The results indicate that higher levels of MS fatigue are characterised by greater cortico-subcortical grey matter atrophy and brain lesions, reduced muscular strength, reduced central drive (voluntary activation), and increased upper-limb fatigability. By consolidating an extensive and somewhat conflicting evidence-base, the meta-analysis provides new insights into neurobiological differences that exist between MS-HF and MS-LF. This is an important step in delineating key homeostatic and psychophysiological pathways underpinning perceived fatigue and fatigability in PwMS.

CHAPTER 5 – Test-Retest Reliability of Neurophysiological Measures in People Experiencing High and Low Levels of MS-Fatigue

5.1 Introduction

Neurofunctional deficiencies are associated with perceived fatigue in MS, often experienced as extreme tiredness or exhaustion (unrelated to recent physical exertion) and an increased sense of effort for everyday tasks, frequently accompanied by mood changes, poor sleeping patterns and pain (Kluger et al., 2013a). Neurophysiological correlates of perceived MS-fatigue can be assessed using techniques that evaluate cortical function, the integrity of the corticospinal pathway and performance of motor behaviours (Anand & Hotson, 2002; Rocca et al., 2009). Previous work has reported impairments in muscle strength (Ng et al., 2004; Liepert et al., 2005; Wolkorte et al., 2016; Jørgensen et al., 2017), increased skeletal muscle fatigability (Sheean et al., 1997; Liepert et al., 2005; Wolkorte et al., 2016) and reductions in voluntary muscle activation (Wolkorte et al., 2016) in MS patients. On the basis of current evidence, it is unclear whether there are alterations in corticospinal excitability or intracortical inhibition (Perretti et al., 2004; Todd et al., 2004; Liepert et al., 2005) in people experiencing high levels of perceived MS-fatigue, in comparison with healthy adults., To date, no studies have investigated the test-retest reliability and measurement error of such neuromuscular measures in people experiencing high (clinically important) and low levels of perceived MS-fatigue.

For the useful application of neuromuscular and transcranial magnetic stimulation measures, they must be able to yield reproducible data over repeated assessment sessions and/or multiple muscle representations (Malcolm et al., 2006; Furlan & Sterr, 2018) with low measurement error. Test-retest reliability has been shown to vary widely across different neurophysiological measures in upper-limb studies of healthy individuals (Cicinelli et al., 1997; Fritz et al., 1997; Carroll et al., 2001; Wassermann, 2002; De Gennaro et al., 2003b; Orth & Rothwell, 2004; Wolf et al., 2004; Koski et al., 2005; Nuzzo et al., 2019). Furthermore, limited evidence exists informing the reliability of these measurements in lower limb muscles (Frontera et al., 1993; Cacchio et al., 2009; Wheaton et al., 2009; Jørgensen et al., 2017). Moreover, very few neurophysiological studies have assessed variability of measurement and test-retest reliability in PwMS (Schwid et al., 2002; Surakka et al., 2004b; Sehle et al., 2014) and none have compared the test-retest reliability of neurophysiological correlates in people experiencing high and low levels of perceived MS-fatigue. Approximately 75% of PwMS are affected by lower-limb sensorimotor impairment (Johansson et

al., 2007) and the majority of experimental studies have focused on the lower-limbs (Dalgas et al., 2008; de Souza-Teixeira et al., 2009). Nonetheless, 66% of the PwMS experience upper-limb motor impairment (Spooren et al., 2012). These studies highlight the high level of lower- and upper-limb neuro-dysfunctional heterogeneity amongst PwMS, which has important consequences for studies of neurophysiological function and the temporal stability of neurophysiological measures. For example, the degree of neuromuscular impairment in a particular limb could influence the test-retest reliability of related neurophysiological measurements.

The most commonly reported measure of test re-test reliability is intraclass correlation coefficients (ICC). Test-retest measurements using ICC of muscle strength in PwMS vary between 0.46 and 0.96 (Djaldetti et al., 1996; Schwid et al., 1999; Surakka et al., 2004b). One study by Surakka et al. (2004b) used a sample size of 28 and reported excellent day-to-day reliability using the ICC = 0.97 for maximal isometric torque of the knee flexors and extensors using a knee dynamometer in PwMS. Another study reported larger variability for motor fatigability measures for muscles of the lower- and upper-limbs in PwMS, but showed that elbow extensor fatigability correlated with hand grip fatigability (Schwid et al., 1999), supporting a probable central underlying mechanism of performance fatigability in PwMS (Schwid et al., 2002).

To date, no studies have reported on the reliability of neurophysiological correlates of MS perceived fatigue or fatigability in upper- and lower-limb muscle groups in well-characterised PwMS on the basis of fatigue status (i.e., MS-HF versus MS-LF). Understanding the repeatability and measurement error measures are fundamental to our understanding of the neurophysiology of perceived MS-fatigue and performance fatigability and will provide guidance for the design of experimental protocols used in subsequent Chapters of this Thesis. Test-retest reliability data of neurophysiological fatigue correlates in people experiencing high levels of perceived MS-fatigue is also a fundamental step in understanding how exercise-induced improvements in these measures are associated with the magnitude of MS-fatigue symptoms. The aim of this study was to establish the test-retest reliability, variability and measurement error of a comprehensive set of upper- and lower-limb neuromuscular and transcranial magnetic stimulation measures (knee-extensors and wrist-flexors, respectively) in people experiencing higher and lower levels of perceived MS-fatigue and healthy controls.

5.2 Methods

5.2.1 Participants

Following ethical approval (3.2.1 Ethical Approval), 40 PwMS from the Department of Neurology at the Royal Victoria Infirmary Hospital, Newcastle upon Tyne national health service Foundation Trust volunteered to partake in the study. The 40 relapsing-remitting MS patients (EDSS <5) met all criteria for participation (3.3.1 Inclusion and Exclusion Criteria) and were recruited as follows; patient referral at clinic (n=23), advertising flyers (n=11), and postal letters (n=6) (3.3.1 Recruitment). Additionally, twenty right-handed healthy volunteers (HC) without a history of neurological illness, were matched on a participant-to-participant basis for gender and age (Table 5.1).

Table 5.1 Participant Characteristics.

	HC	**MS-LF**	**MS-HF**
N	20	20	20
Age (years)	44.8 ± 15.1	45.9 ± 9.0	43.6 ± 10.2
Gender (F/M)	13/7	15/5	15/5
EDSS (arbitrary units)	-	2.1 ± 1.2	2.4 ± 1.4
Disease Duration (years)	-	9.8 ± 3.8	9.9 ± 5.5
Disease modification Therapy (Y/N)	-	17/3	14/6
Other comorbidities (Y/N)	4/16	6/14	9/11
FSS	2.2 ± 1.0	3.5 ± 1.1	6.0 ± 0.6
HADS	6.8 ± 5.6	9.0 ± 5.4	13.7 ± 4.8

FSS: Fatigue Severity Scale; HADS: Hospital and Anxiety Depression Scale; HC: Healthy Control; MS-LF: Less-Fatigued People with Multiple Sclerosis; MS-HF: Highly-Fatigued People with Multiple Sclerosis N: Numbers; F: Females; M: Males; EDSS: Extended Disability Status Scale; Y: Yes; N: No, Data reported as Mean ± SD.

5.2.2 Experimental Protocol

Prior to engaging in studies of neurophysiological function, participants attended the laboratory where their perceived symptoms of fatigue were measured (3.9.1 Fatigue Severity Scale). Mood was also determined (3.9.2 Anxiety and Depression) (Bakshi et al., 2000), and contraindications to the experimental procedures were assessed with a study-specific health questionnaire. Eligible participants then provided written

informed consent (3.3.2 Informed Consent) before undergoing a 60 min familiarisation of the entire neuromuscular protocol (see 3.4 Familiarisation and 3.6 Neuromuscular Assessment), with experimental controls being implemented as previously described (3.5 Experimental Criterion). Participants visited the laboratory on four separate occasions, comprising of two visits for the neuromuscular assessment of the knee-extensors, and two visits for the wrist-flexor muscles. The order of experimental visits was randomised and separated by 2-14 days. Each experimental visit involved approximately 35 minutes of neuromuscular data collection at rest, followed by a submaximal intermittent exercise task to task failure, as previously described (3.7.2 Submaximal Test Protocol). All neuromuscular measures were then repeated.

5.2.3 Neuromuscular Assessment

Neuromuscular assessments were performed according to Figure 5.1. Following determination of supramaximal motor nerve stimulation intensity (3.7 Percutaneous Stimulation), the participant performed MVCs (3.6.1 Force and Electromyography Recordings). The twitch interpolation technique (Allen et al. 1995b) was used for the measurement of voluntary activation (3.7.1 Voluntary Activation) and to record the potentiated resting twitch (3.7 Percutaneous Stimulation). EMG was recorded during voluntary and evoked contractions at rest (3.6.1 Force and Electromyography Recordings). Determination of active motor threshold for transcranial magnetic stimulation-related measurements, corticospinal excitability and inhibition were recorded (3.8 Transcranial Magnetic Stimulation and 3.8.1 Short Interval Intracortical Inhibition) as well as CSP (3.8.2 Corticospinal Silent Period). During each experimental visit, the participant performed a submaximal intermittent exercise task to task failure for the wrist flexor and the knee extensor, defined as previously described (3.7.2 Submaximal Test Protocol).

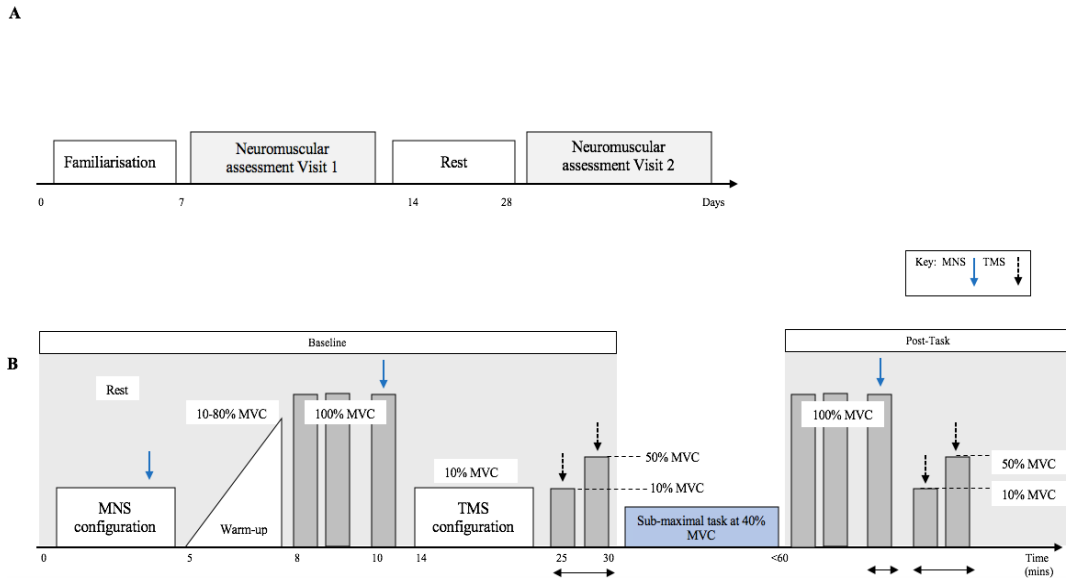

Figure 5.1 Schematic of test re-test neuromuscular protocol, **(A)** test re-test neuromuscular intervals of 2-14 days between knee-extensors and wrist-flexors, **(B)** Neuromuscular assessment including, percutaneous nerve stimulation, transcranial magnetic stimulation and submaximal task to failure.

5.2.4 Perceived Fatigue

To assess subjective fatigue and determine two fatigue groups, PwMS completed the nine-item self-report FSS questionnaire developed and validated by Krupp et al. (1989). High-fatigue was defined as FSS>5 and low-fatigue as FSS<4. The FSS has a high internal consistency was demonstrated by a Cronbach's alpha of 0.88. Test-retest analysis between two time points, separated by 5 to 33 weeks, have shown no statistically significant differences in a group of clinically stable patients with MS or systemic lupus erythematosus (Krupp et al., 1989). Additionally, to measure symptomatic fatigue, a small number of scales were completed at the beginning of two separate experimental visits with severity, frequency and impact of fatigue in everyday life recorded (Fatigue Severity Scale; Modified Fatigue Impact Scale and Chalder Fatigue Scale).

5.2.5 Patient Reported Outcomes

Mood (3.9.2 Anxiety and Depression), sleep quality (3.9.3 Sleep Quality) and pain experienced (3.9.4 Pain) were also measured by means of perceptual scales at the beginning of two separate experimental visits.

5.2.6 Data Analysis

Voluntary activation using motor nerve stimulation was determined using the interpolation twitch technique (Allen et al., 1998) by comparing the amplitude of the superimposed twitch with the amplitude of the potentiated resting twitch ($Q_{tw,pot}$) using the formula: VA (%) = (1 – [superimposed twitch ÷ $Q_{tw,\ pot}$]) × 100]. SICI was quantified as the ratio between the amplitude of conditioned MEPs to the amplitude of unconditioned MEPs. Corticospinal excitability was inferred from the AMT and expressed as the mean MEP amplitude during the 10% MVC as a percentage of Mmax. The root-mean-square of EMG activity (RMS_{EMG}) was also recorded during the middle 500 ms epoch of a 3 s maximal contraction. All data analysis was performed offline using Spike 2 (v6, CED, UK).

5.2.7 Statistical Analysis

Data are presented as group mean ± SD within the text and figures and the level of statistical significance was set at $P \leq 0.05$. Normal Gaussian distribution of data was confirmed using the Kolmogorov–Smirnov test. If a violation was detected, the data were logarithmically transformed. For between-session test-retest reliability, multiple indices were calculated: paired samples t-tests, intraclass correlation coefficient (ICC; Atkinson and Nevill (1998) and Hopkins (2000)) between the two time points (2-14 days) and typical error. Within-subjects variation was calculated as the standard deviation of the mean differences divided by the square root of 2 and termed typical error. The intra-subject coefficient of variation was the typical error expressed as a percentage of the mean. The ICC was used to assess the relationship of each measure across the two experiential visits days and was defined as: <0.5 = poor, 0.5-0.75 = moderate, 0.75-0.9 = good, >0.9 = excellent, in accordance with Koo and Li (2016). All statistical calculations were performed using SPSS (Version 18.0, Chicago, IL, US).

5.3 Results

5.3.1 Measurement Completion

All participants completed neuromuscular assessments of the knee-extensors and wrist-flexors, except two PwMS who could not attend the last session for health reasons. There were incomplete transcranial magnetic stimulation measures in six PwMS. These MS participants were unable to complete all measurements due to

inadequate muscle force/inability to activate the muscle group sufficiently (n=2), being unable to obtain accurate MEP responses because of uncomfortableness (n=2) and injury (n=2).

5.3.2 Reliability of Neuromuscular Measures of the Knee-Extensors

Data for the knee extensor force variables are presented in Table 5.2. There were no between-day differences for MVC, $Q_{tw,\,pot}$, TFF or VA (p >0.05) in any of the groups. Data for the neuromuscular variables showed good to excellent test-retest reliability ($Q_{tw,\,pot}$, MVC), as evidenced by low coefficient of variation for these measures (2.6 to 8.0%). The measure of VA also displayed good to excellent test-retest reliability for HC and MS-HF (ICC: 0.77 - 0.90), while for MS-LF reliability of VA was moderate (ICC = 0.58). VA for all groups showed a low degree of random error (coefficient of variation: 1.3 – 1.9%; typical error: 1.1 to 1.9%). Similarly, TTF showed excellent test-retest reliability for HC (ICC = 0.93), while for MS-LF and MS-HF test-retest TTF reliability was good (ICC ≥ 0.76) with relatively low typical error and coefficient of variation (3.0 to 4.3 min; 9.9 to 13.5%, Figure 5.2 respectively).

The test-retest reliability of surface electromyography variables of the knee-extensors are presented in Table 5.2. There were no between-day differences for any of the EMG variables (Mmax, AMT, MEP/Mmax, RMS_{EMG}, SICI or SP; p>0.05). Mmax demonstrated good test-retest reliability (ICC ≥ 0.84) for all the groups, with low typical error and coefficient of variation ranging from 0.39 to 0.97 mV and 7.2 to 12.3%, respectively. AMT demonstrated good test-retest reliability in HC (ICC = 0.87, Figure 5.2) and was moderately reliable in MS-LF and MS-HF (ICC: 0.67 to 0.72), with low typical error and coefficient of variation ranging from 3.4 to 5.7% and 4.9 to 8.3%, respectively. The measures of SICI and SP showed good to excellent day to day reliability for all groups (ICC: 0.79 to 0.92), with relatively low coefficient of variation ranging from 7.7 to 12.3%. Other surface EMG variables showed good to excellent reliability (MEP/Mmax, and RMS_{EMG}; ICC ≥ 0.80), with moderately larger test-retest coefficient of variations than the force variables (range: 15.8 – 19.3%).

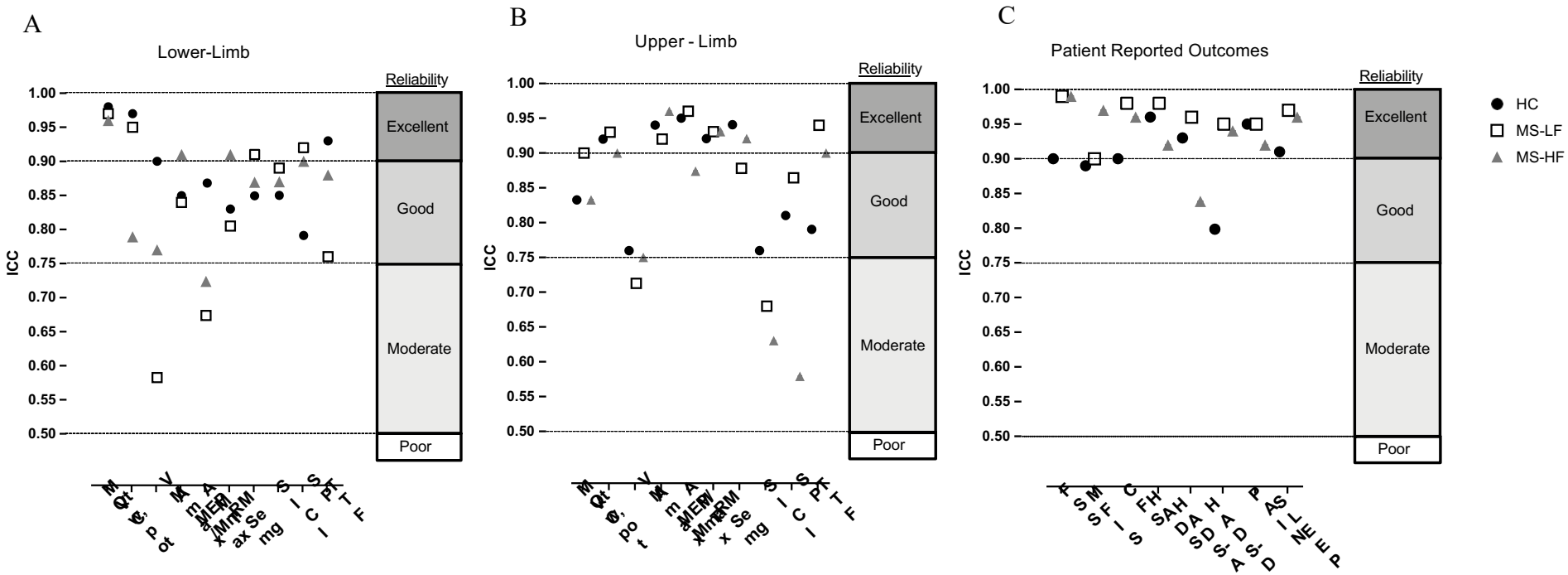

Figure 5.2 Scatter plot for test intraclass correlation (ICC) for test re-test of neurophysiological measurements, including **(A)** knee-extensors and **(B)** wrist-flexors, and **(C)** patient reported outcomes and fatigue scales in healthy control (HC), less-fatigued (MS-LF) and highly-fatigued (MS-HF) PwMS. The ICC was used to assess the relationship of each measure across the two experiential visits days and was defined as: <0.5 = poor, 0.5-0.75 = moderate, 0.75-0.9 = good, >0.9 = excellent, in accordance with Koo and Li (2016).

Table 5.2: Typical error expressed in raw units and coefficient of variation (%) for between-day measures of force and electromyography derived outcomes for the knee-extensor muscle (Mean ± SD).

	HC						MS-LF						MS-HF					
Measure	**N**	**Visit 1**	**Visit 2**	***P***	**TE**	**CV (%)**	**N**	**Visit 1**	**Visit 2**	***P***	**TE**	**CV (%)**	**N**	**Visit 1**	**Visit 2**	***P***	**TE**	**CV (%)**
Force Outcomes:																		
MVC (N)	20	412 ± 77	416 ± 80	0.281	12.4	2.6	19	393 ± 66	382 ± 73	0.082	12.2	3.5	19	335 ± 68	340 ± 74	0.345	14.4	2.9
$Q_{tw,\ pot}$ (N)	20	151 ± 48	152 ± 44	0.687	8.9	5.5	18	131 ± 38	125 ± 35	0.155	8.4	6.2	18	134 ± 21	136 ± 33	0.552	13.5	8.0
VA (%)	20	93.3 ± 3.4	92.2 ± 3.3	0.162	1.1	1.3	18	91.7 ± 2.4	91.6 ± 3.3	0.980	1.9	1.9	18	88.1 ± 4.1	88.9 ± 3.8	0.249	1.9	1.8
TTF (minutes)	20	25 ± 15	26 ± 13	0.810	4.0	9.9	18	16 ± 6	17 ± 10	0.403	4.3	14.4	19	13 ± 8	13 ± 9	0.916	3.0	13.5
Electromyography outcomes:																		
Mmax (mV)	20	7.29 ± 2.51	7.01 ± 2.23	0.369	0.97	12.3	18	5.08 ± 1.73	5.38 ± 1.80	0.126	0.48	9.2	18	4.71 ± 1.26	4.92 ± 1.16	0.133	0.39	7.2
MEP Threshold (AMT%)	20	49 ± 9	50 ± 9	0.528	3.4	4.9	20	55 ± 9	56 ± 10	0.586	5.7	8.3	20	58 ± 9	60 ± 9	0.334	4.8	6.8
MEP/Mmax (%)	20	16.8 ± 10.4	16.9 ± 10.3	0.925	4.5	18.9	15	10.9 ± 6.1	11.6 ± 5.4	0.492	2.7	18.2	17	12.6 ± 6.3	12.1 ± 6.4	0.581	2.5	16.9
RMS_{EMG} (mV)	20	0.69 ± 0.28	0.76 ± 0.29	0.080	0.13	15.8	19	0.40 ± 0.24	0.45 ± 0.26	0.075	0.08	19.3	18	0.40 ± 0.19	0.39 ± 0.22	0.672	0.08	19.3
SICI (ratio)	20	0.85 ± 0.24	0.90 ± 0.30	0.158	0.11	11.2	17	0.74 ± 0.26	0.77 ± 0.31	0.344	0.10	11.4	18	0.54 ± 0.18	0.56 ± 0.20	0.351	0.07	12.0
SP (ms)	18	153 ± 52	145 ± 45	0.313	23.5	11.7	17	170 ± 49	167 ± 45	0.202	16.3	7.7	18	189 ± 60	165 ± 54	0.065	19.5	12.3

CV: Coefficient of variation; HC, Healthy control, ICC: Intraclass correlation coefficient; MVC: maximum voluntary contraction, N, Number, MS-LF: Less-fatigued people with multiple sclerosis; MS-HF: Highly-fatigued people with multiple sclerosis, $Q_{tw,\ pot}$ potentiated twitch force, TE: Typical error, TTF: Time to task failure, VA: Voluntary activation**.** MEP: Motor evoked potential, N, Number, RMSEMG, Root mean squared electromyography, SICI: Short interval cortical inhibition, SP: Silent period, Mmax: maximum compound action potential, P: *p* value, TE: Typical error.

5.3.3 Reliability of Neuromuscular Measures of the Wrist-Flexors

Data for wrist extensor force variables are presented in Table 5.3. MVC, $Q_{tw, pot}$, VA and TTF were not different between experimental visits (p >0.05) in any of the groups. Force variables (MVC, and $Q_{tw, pot}$) showed good to excellent reliability (ICC ≥ 0.83), with the typical error and coefficient of variation being relatively low, ranging from 2.6 to 14.6 N and CV from 5.9 - 10.9%, respectively. Measures of VA demonstrated moderate to good test-retest reliability in all groups (ICC: 0.71 - 0.76, Figure 5.2) and there was a relatively low degree of random error (coefficient of variation: 1.8 – 2.9%) and typical error (2.2 - 2.7%). Similarly, TTF showed good to excellent reliability (ICC: 0.79 - 0.94), with low typical error and moderate coefficient of variation ranging from 1.6 to 5.6 min and 14.5 to 15.8%, respectively.

Test-retest reliability analysis of surface electromyography variables for the wrist-flexors are presented in Table 5.3. There were no between-day (visit 1 and 2) differences in any of the transcranial magnetic stimulation measurements for all groups (Mmax, AMT, MEP/Mmax, RMS_{EMG}, SICI or SP; p>0.05). Furthermore, data for Mmax, AMT, MEP/Mmax and RMS_{EMG} showed excellent test-retest reliability (ICC ≥ 0.87), while the typical error and coefficient of variation ranged from 0.08 to 3.8, with a moderately larger coefficient of variation ranging from 4.6 to 18.7%. Between-day measures of SICI and SP were moderate to good (ICC: 0.58 to 0.86) but demonstrated larger test-retest coefficient of variations than force variables (range: 5.5 – 16.7%).

5.3.4 Reliability of Perceived Fatigue and Patient Reported Outcomes

Perceived fatigue data are presented in Table 5.4. There were no between-day differences for any of the self-reported fatigue scales (FSS, MFIS, and CFS; p >0.05), with all measures demonstrating excellent test-retest reliability (ICC ≤ 0.89, Figure 5.2). The typical error (≤ 2.4) and coefficient of variation (≤ 10.4%) were also relatively low. Test-retest reliability for patient-reported scales can be viewed in Table 5.4. There were no between-day differences for the co-existing symptom scales (HADS, HADS-Anxiety, HADS-Depression, NARCOMS Pain or PSQI) (p >0.05) and excellent reliability (ICC ≤ 0.80) for all groups. The typical error was low (≤ 1.3) but with larger test-retest coefficient of variations than the self-reported fatigue scales (≤ 15.4%).

Table 5.3: Typical error expressed in raw units and coefficient of variation (%) for between-day measures of force and electromyography derived outcomes for the wrist-flexors muscle (Mean ± SD).

	HC						MS-LF						MS-HF					
Measure	**N**	**Visit 1**	**Visit 2**	***P***	**TE**	**CV (%)**	**N**	**Visit 1**	**Visit 2**	***P***	**TE**	**CV (%)**	**N**	**Visit 1**	**Visit 2**	***P***	**TE**	**CV (%)**
Force Outcomes:																		
MVC (N)	20	136 ± 28	130 ± 39	0.209	14.6	9.7	16	125 ± 24	128 ± 22	0.217	7.8	5.9	17	98 ± 21	104 ± 30	0.201	11.2	8.2
$Q_{tw,\,pot}$ (N)	20	31 ± 16	32 ± 15	0.324	3.3	9.8	16	23 ± 9	25 ± 9	0.158	2.6	10.4	20	26 ± 10	25 ± 9	0.650	3.3	10.9
VA (%)	20	91.5 ± 4.7	90.9 ± 4.2	0.397	2.2	1.8	16	90.0 ± 4.3	89.2 ± 4.6	0.830	2.5	2.0	17	84.5 ± 5.8	84.5 ± 4.5	0.966	2.7	2.9
TTF (minutes)	20	22 ± 13	20 ± 11	0.535	5.6	15.8	16	14 ± 8	15 ± 8	0.529	2.1	14.6	17	11 ± 5	12 ± 5	0.159	1.6	14.5
Electromyography Outcomes:																		
Mmax (mV)	20	10.39 ± 3.98	10.11 ± 3.60	0.362	1.0	6.7	17	9.17 ± 9.21	9.21 ± 4.24	0.466	1.2	8.3	17	8.11 ± 4.23	8.43 ±4.15	0.302	0.39	7.2
MEP Threshold (AMT%)	20	45 ± 10	44 ± 9	0.057	2.3	4.8	16	52 ± 12	53 ± 11	0.227	2.5	4.6	17	54 ± 10	54 ± 10	0.661	4.8	6.8
MEP/Mmax (%)	20	11.9 ± 8.1	12.8 ± 8.1	0.251	2.4	14.0	14	8.8 ± 5.0	9.4 ± 6.8	0.642	1.6	14.4	14	12.2 ± 8.2	11.2 ± 8.2	0.280	2.5	16.9
RMS_{EMG} (mV)	20	0.58 ± 0.35	0.62 ± 0.35	0.203	0.09	16.2	17	0.47 ± 0.21	0.48 ± 0.20	0.658	0.08	18.3	17	0.42 ± 0.24	0.47 ± 0.26	0.065	0.08	19.3
SICI (ratio)	20	0.86 ± 0.23	0.89 ± 0.20	0.318	0.11	9.8	17	0.72 ± 0.21	0.76 ± 0.19	0.398	0.12	15.6	17	0.71 ± 0.27	0.70 ± 0.22	0.802	0.07	12.0
SP (ms)	20	133 ± 22	139 ± 22	0.062	10.1	7.0	16	142 ± 20	147 ± 21	0.113	8.2	5.5	17	155 ± 28	162 ± 26	0.287	19.5	12.3

CV: Coefficient of variation; HC, Healthy control, ICC: Intraclass correlation coefficient; MVC: maximum voluntary contraction, N, Number, MS-LF: Less-fatigued people with multiple sclerosis; MS-HF: Highly-fatigued people with multiple sclerosis, $Q_{tw,\,pot}$ potentiated twitch force, TE: Typical error, TTF: Time to task failure, VA: Voluntary activation. MEP: Motor evoked potential, N, Number, RMSEMG, Root mean squared electromyography, SICI: Short interval cortical inhibition, SP: Silent period, Mmax: maximum compound action potential, P: p value, TE: Typical error.

Table 5.4: Typical error expressed in raw units and coefficient of variation (%) for between-day measures of self-reported fatigue and patient-reported outcome variables (Mean ± SD).

	HC						MS-LF						MS-HF					
Measure	**N**	**Visit 1**	**Visit 2**	***P***	**TE**	**CV (%)**	**N**	**Visit 1**	**Visit 2**	***P***	**TE**	**CV (%)**	**N**	**Visit 1**	**Visit 2**	***P***	**TE**	**CV (%)**
Self-Reported Fatigue Outcomes:																		
FSS	20	2.2 ± 1.0	2.1 ± 0.8	0.198	0.3	6.8	20	3.5 ± 1.1	3.5 ± 1.1	0.232	0.1	2.0	20	6.0 ± 0.6	6.1 ± 0.6	0.088	0.1	0.6
MFIS	20	10.8 ± 3.7	11.3 ± 3.1	0.157	1.2	9.8	20	22.7 ± 6.0	23.0 ± 6.3	0.543	2.0	6.8	20	47.0 ± 14.1	46.2 ± 13.8	0.343	2.4	3.5
CFS	20	1.9 ± 1.4	2.0 ± 1.4	0.494	0.5	10.4	20	4.0 ± 2.9	3.9 ± 2.8	0.494	0.5	7.8	20	5.9 ± 2.8	6.2 ± 2.7	0.171	0.6	8.3
Patient-Reported Outcome																		
HADS	20	7.6 ± 3.8	7.7 ± 3.7	0.853	0.8	9.6	20	9.0 ± 5.4	8.7 ± 4.9	0.185	0.8	5.7	20	13.2 ± 4.5	12.9 ± 4.3	0.399	0.39	7.2
HADS-Anxiety	20	5.1 ± 2.8	5.3 ± 2.8	0.545	0.8	14.9	20	5.8 ± 3.2	5.6 ± 3.2	0.330	0.6	12.0	20	9.0 ± 3.2	8.8 ± 2.9	0.711	4.8	6.8
HADS-Depression	20	2.6 ± 1.7	2.4 ± 1.5	0.545	0.9	11.4	20	3.3 ± 2.8	3.3 ± 2.3	0.804	0.6	15.4	20	4.6 ± 2.5	4.8 ± 2.5	0.330	2.5	16.9
NARCOMS Pain	20	1.2 ± 1.0	1.2 ± 1.0	1.000	0.2	3.8	20	1.5 ± 1.2	1.6 ± 1.2	0.577	0.3	5.2	20	2.1 ± 1.3	1.9 ± 1.3	0.104	0.08	19.3
PSQI	20	6.9 ± 2.9	7.3 ± 3.1	0.246	0.9	11.9	20	7.9 ± 3.6	8.2 ± 3.2	0.262	0.7	6.2	20	9.6 ± 4.9	9.2 ± 4.2	0.273	0.07	12.0

CV: Coefficient of variation; HC, Healthy control, ICC: Intraclass correlation coefficient; MVC: maximum voluntary contraction, N, Number, MS-LF: Less-fatigued people with multiple sclerosis; MS-HF: Highly-fatigued people with multiple sclerosis, $Q_{tw,\ pot}$ potentiated twitch force, TE: Typical error, TTF: Time to task failure, VA: Voluntary activation. MEP: Motor evoked potential, N, Number, RMSEMG, Root mean squared electromyography, SICI: Short interval cortical inhibition, SP: Silent period, Mmax: maximum compound action potential, P: p value, TE: Typical error.

5.4 Discussion

The aim of the present study was to establish the test-retest reliability, variability and measurement error of a comprehensive set of upper- and lower-limb neuromuscular and transcranial magnetic stimulation measures (knee-extensor and wrist-flexor, respectively) in people experiencing high and low levels of MS-fatigue, and to compare data from PwMS with healthy age and sex-matched controls.

To date, no studies have reported the reliability of neurophysiological correlates of MS-fatigue in upper- and lower-limb muscle groups in PwMS experiencing very different levels of fatigue (i.e., MS-HF versus MS-LF). This study demonstrates that a broad selection of neuromuscular and transcranial magnetic stimulation measurements have good to excellent ICC values (Figure 5.2) that are in accordance with Koo and Li (2016), but with the exception of moderate test re-test reliability of VA, SICI and SP. Moreover, ICC values were generally greater and demonstrated better day-to-day reliability in the lower limb compared with the upper limb muscles in PwMS. This study also demonstrates that patient-reported outcomes such as, fatigue, mood and sleep quality are highly reproducible in PwMS experiencing different levels of fatigue. This is the first study to provide data on the repeatability of neuromuscular and transcranial magnetic stimulation measures for lower-limb (knee-extensors) and upper-limb (i.e., wrist-flexors) muscle groups for a homogenous group of people experiencing high (clinically important) and low levels of MS-fatigue. The good to excellent test-retest reliability for many of the measures provides support for their utility in studies of MS-fatigue, including therapeutic interventions.

Maximum strength and voluntary activation across people experiencing different levels of MS-fatigue.

Manual muscle testing, hand-held dynamometry and isometric or isokinetic dynamometer recordings have been used in previous studies in PwMS to assess muscular strength but published reliability data for such measures in well-characterised PwMS on the basis of fatigue status is limited. Nevertheless, results for maximal muscle force (MVC) were highly reproducible and corroborate previously published research on the reliability of force measures for the knee extensors (Surakka et al., 2004b) and for grip strength (Schwid et al., 1999) in PwMS not characterised by fatigue status. Reliability data were also similar to previous work in the elbow flexors (Meeteren et al., 2002) and knee extensors (Frontera et al., 1993; Dvir, 2004) for healthy individuals. However, the results indicate that in comparison with healthy

controls, PwMS were found to be weaker in upper extremity muscles, whereas lower extremity strength is relatively preserved. In the present study, the MVC yielded a low measurement error at the group level for the knee-extensors compared to the wrist-flexors, which might suggest poorer reliability in muscle groups that are more severely affected by MS (see Tables 5.2 and 5.3).

Voluntary activation was measured using the interpolated twitch technique method and showed moderate to good reliability in MS-HF and further moderate to excellent in MS-LF. Data from this reliability analysis corroborates previous findings in PwMS whereby consistency in measurement and evidence of good reliability but with lower voluntary activation in PwMS reveals a central underlying mechanism at least partly explaining the inability to produce higher force, as reported elsewhere (Ng et al., 2000b; Ng et al., 2004; Andreasen et al., 2009; Steens et al., 2012b; Severijns et al., 2017). The reported low typical error and coefficient of variations, particularly for the knee-extensors compared to the wrist flexors, suggests smaller intra-subject variation in fatigued PwMS for the lower-limb, which means that the ability to reproduce fine motor skills in the wrist might be more compromised by impaired strength and more gross motor ability. Additionally, it might also be partly due to the difference in corticospinal projections between upper and lower limb, suggesting greater central neural drive. Therefore, the larger variability in the upper limb brings to light the possibility that impaired neural drive from the motor cortex has a more profound effect on the consistency of upper limb movements in fatigued PwMS (Amato et al., 2001). Further exploration of this phenomenon is warranted to better understand the differences between people experiencing higher and lower levels of MS-fatigue.

However, the technical challenges of measuring voluntary activation in PwMS need to be considered. Firstly, it was not possible to measure voluntary activation in four participants because of an inability to electrically stimulate sufficient muscle mass, and this might have been caused by the presence of greater subcutaneous and intramuscular fat (Ivanyi et al., 1998; Tolback et al., 1996). Secondly, voluntary activation was measured during maximal isometric contractions performed on a custom-made, adjustable dynamometer. In particular, the wrist extensors assessment required the arm and wrist angle to be individually adjusted to optimal muscle length, which differed between participants. Previous studies indicate that the force-activation relationship is influenced by muscle length in voluntary activation measurements (Bülow et al., 1993; Becker & Awiszus, 2001) and the ability to achieve optimal muscle length

in all participants is unclear. Nevertheless, the levels of test-retest reliability observed in this study support the use of these muscle strength measures and the twitch interpolation technique for measuring VA in upper and lower limb muscle groups, consistent with evidence from previous studies in healthy individuals and PwMS not partitioned on the basis of fatigue status (Merton, 1954b; Strojnik & Komi, 2000; Hartman et al., 2011; Gandevia et al., 2013; Thomas et al., 2017).

Fatigability across people experiencing different levels of MS-fatigue

Using the time to task failure design as a measure of performance fatigability, reliability analyses reveal time to task failure can be measured with good to excellent test-retest reliability in both the lower limb and the upper limb. The time to task failure was highly reproducible, corroborating findings from previous studies in PwMS not characterised by fatigue status (ICC: 0.71- 0.96, respectively, Schwid et al. (2002)). In fact, the test re-test reliability was higher than previously reported by Lambert et al. (2001) who showed poor to moderate reliability. However, their study investigated an isokinetic task of dynamic knee extension and flexion, rather than a single muscle group contracting isometrically to task failure, as used in the present study. Nevertheless, the data reported by Lambert et al. (2001) are important because the measures were based on dynamic muscle actions which may be more representative of everyday movements than isometric muscle actions. Differences between the time to task failure tasks may be an explanation for these discrepant results as sustained muscle actions are not synonymous with intermittent muscle actions. Muscle activation (Vøllestad, 1997) and brain activation patterns (Liu et al., 2005) differ between sustained and intermittent muscle action protocols, which should be taken onto account when quantifying performance fatiguability and assessing reliability of the measure.

Corticospinal and Intracortical Properties across people experiencing different levels of MS-fatigue

Corticospinal measures evoked using transcranial magnetic stimulation were highly reliable, notwithstanding poorer reliability for active motor threshold in both MS groups. The level of test re-test reliability of corticospinal properties corroborated the findings of Meaney et al. (2015; >0.80). However, their study explored the within session and test–retest consistency of MEP elicited by transcranial magnetic stimulation from the resting tibialis anterior muscle in a smaller cohort of PwMS not characterised by fatigue status (N=10; two men, eight women). Despite small intra-subject variability, the results were limited by the small number of PwMS

taking part, and further studies were recommended (Meaney et al., 2015). Healthy individuals demonstrated good to excellent reliability in all transcranial magnetic stimulation -related measurements in the present study, consistent with data reported for the upper-limb muscles by others (Mortifee et al., 1994; Carroll et al., 2001; Malcolm et al., 2006). In terms of reliability, corticospinal excitability (MEP/Mmax) in PwMS was moderate to good, consistent with previous research. Furthermore, the greater coefficient of variation for this measure in the present study (>10%), signifies a higher intra-subject variability. Overall, average responses to transcranial magnetic stimulation measurements were lower in PwMS due to uncomfortable nature of the tests, which should be taken into account when taking multiple measures of MEP throughout an intervention.

Abnormalities of corticospinal silent periods including lengthening of silent period (SP) have previously been reported in various neurological disease states, including stroke (Kukowski & Haug, 1992; Braune & Fritz, 1995), Parkinson's Disease (Priori et al., 1994a) and motor neurone disease (Triggs et al., 1992). This study showed that SP measurements are highly reliable in PwMS experiencing high (clinically important) and low levels of fatigue, despite lower reliability for MS-HF in the wrist flexor muscles. Our results, for SP are consistent with those of Reid and colleagues (2002), who reported a high intra-examiner reliability, but poor inter-examiner reliability. However, in the present study, a greater intra-subject variability was shown, consistent with findings from previous studies that reported across sessions SP variations ranging from <5 to 15% in healthy individuals (Orth & Rothwell, 2004; Koski et al., 2005). One possible influence on SP variability is the high transcranial magnetic stimulation intensity required for AMT (Wolf et al., 2004), as observed in the present study for PwMS compared to HC, and with the higher intensity comes an increased risk of saturation. Additionally, the proposed method of choice for measurement of SP duration has been the focus of some discussion (Škarabot et al., 2020). There is evidence that computer automated analysis can yield more reliable data that manual analysis (Daskalakis et al., 2003). Despite this, previous research by (Hermsen et al., 2016a) compared both methods regarding test–retest reliability and demonstrated similar, moderate reliability for visual (manual) and automated analysis of SP durations ($r = 0.466$, $r = 0.486$, respectively). These latter results support the utility of both methodological approaches for deriving this corticospinal measure of inhibition, and the results of the present study suggest that the manual method is sufficiently reliable for use in studies of PwMS.

Evidence for the reliability of SICI in healthy controls is inconclusive (Boroojerdi et al., 2000; Maeda et al., 2002; Wassermann, 2002). In the present study, reliability analysis demonstrated that SICI in MS-HF and in MS-LF was highly reliable, and with slightly lower test re-test reliability for HC (ICC: 0.76-0.85). However, the reported higher coefficient of variation (<16%) for SICI could reflect inherent differences between participants, including EDSS, disability duration and age (Cahn et al., 2003; McGregor et al., 2012). The strong reliability of MVC and Mmax in fatigued PwMS suggests that the greater level of variability for SICI and SP was not a result of changes in contraction strength or neuromuscular transmission at the level of skeletal muscle, but the impairment of central neural drive.

Due to the large number of women in this study (reflecting the higher prevalence of MS amongst females), the effect of menstrual cycle phase on cortical excitability and inhibition should be considered a potential confounding factor for neurophysiological measurements, and should be taken into account when undertaking repeated measures throughout an intervention (Smith et al., 2000; Cahn et al., 2003; Hattemer et al., 2007; Ansdell et al., 2019). Only a few transcranial magnetic stimulation reliability studies have included women (Maeda et al., 2002; De Gennaro et al., 2003a; Christie et al., 2007; Siniatchkin et al., 2011; Ansdell et al., 2019), and few have specified the phase of the menstrual cycle in which transcranial magnetic stimulation was performed and the impact on cortical excitability (De Gennaro et al., 2003a; Siniatchkin et al., 2011; Ansdell et al., 2019). Hence, the variability of measuring corticospinal excitability could be influenced by the timing of assessment sessions in relation to the phase of the menstrual cycle in female participants recruited to the present study, as well as pre- and peri-menopausal effects. However, the high levels of reliability observed in the present study suggest that corticospinal and inhibitory measurements could be useful for studies of neuromuscular function in people with MS-fatigue.

Patient reported outcomes across people experiencing different levels of MS-fatigue.

Self-reported fatigue showed high reliability for all measures and for all groups, consistent with previously published studies of PwMS (ICCs of 0.80-0.94; Feng and Rensel (2019)). Fatigue might be secondary to sleep and mood problems, which are frequently present in MS and, in turn, may result from urinary problems, spasms, pain, or anxiety (Kos et al., 2008). Thus, multidimensional approaches to symptom research are important and for the present study we included patient-reported scales for co-existing symptoms (HADS, HADS-Anxiety, HADS-Depression, NARCOMS Pain or PSQI). The present data demonstrated good to excellent

reliability for these measures in all groups, with low typical error (≤ 1.3) but larger test-retest coefficient of variations than the fatigue scales (≤ 15.4%). Nevertheless, this study has some advantages over previous studies. The gender mix and wide spectrum of disease duration and range of EDSS scores (0 to 5.0) in this test–retest reliability study means there was good representation of the mild-to-moderate PwMS population. Also, adoption of a longer inter-session time interval of 7-14 days could be considered a more useful analysis of the temporal stability of neurophysiological measures in comparison to previous studies that investigated transcranial magnetic stimulation -related and neuromuscular-related measures within hours or a few days. Furthermore, a longer time period between repeated measurements allows a sufficient period of recovery between sessions and, by conducting the measures at the same time of the day, minimises errors caused by diurnal variability. The high test-retest reliability of fatigue scale scores over this 7-14-day period is particularly reassuring, as the occurrence of severe MS-fatigue can be sporadic, and scores may be influenced by recent symptoms.

5.5 Limitations

While the present study provides important methodological information, which can be used to guide future investigations employing neuromuscular and transcranial magnetic stimulation-related measurements in the knee extensors and wrist flexors, the study is not without limitations. Specifically, motivation to participate in the research amongst PwMS was low, which could have implications for the generalisability of the results to the broader MS population, particularly PwMS who are less willing volunteer for research studies. The PwMS occasionally gave subjective feedback, such as feeling they would not do well that day due to a poor night's sleep, or because the previous day had been a tiring one. These potential confounders cannot be well-controlled, since they are likely to be present whenever a clinical measurement in PwMS is attempted, and especially in MS-HF. Nevertheless, participant welfare was checked in the lead-up to their assessment visit and re-scheduled if participants were experiencing undue levels of MS-fatigue or other debilitating MS symptoms. Lastly, the present study extends reliability data through including both on test -re-test reliability (ICC) and measurement error, as Schambra et al. (2015) suggest ICC is not suffice to measuring reliability as it only looks at agreement between sessions (absolute reliability) and that other measures of measurement error (such as, 95% limits of agreement, smallest detectable change or minimal detectable change, (Jørgensen et al., 2017)) are also important.

5.6 Future Directions

Moving forward, although the use of single investigator (intra-reliability) is common in small-scale experimental studies, to evolve to larger multi-site randomised trials additional research is needed to examine the inter-rater reliability of transcranial magnetic stimulation and neuromuscular measurements in PwMS classified by fatigue status. Moreover, future studies would benefit from the inclusion of both neuroimaging and neurophysiological measures, which would provide a more thorough picture of the reliability of neural correlates of perceived MS-fatigue and which measures have most potential to improve our understanding of therapeutic adaptations underpinning improvements in this debilitating symptom. The latter includes exercise studies with regular follow-up assessments.

5.7 Conclusion

The present study yields novel information on the reliability of neuromuscular- and transcranial magnetic stimulation -related measurements of the upper limb and lower-limb in PwMS experiencing high and low levels of fatigue. Neuromuscular measurements were generally reliable, with several transcranial magnetic stimulation measures displaying high reliability, particularly cortical excitability measures, which were found to be the most reliable. The application of transcranial magnetic stimulation and neuromuscular assessments in the MS setting has potential to provide further insight into the role of corticospinal and intracortical excitability in perceived MS-fatigue and performance fatigability. This study included a direct comparison of upper and lower limb muscles in contrast to many previous studies which focused on studies of single limb reliability. The results suggest that the reproducibility of most measures is adequate to support their use in future therapeutic studies aimed at evaluating underpinning neurobiological adaptations accounting for changes in perceived fatigue amongst PwMS, including those experiencing high (clinically important) levels of fatigue. As such, this Chapter presents data on the rigour of the methodological approach used in the next chapter, which examines neurophysiological differences at rest and in response to a fatiguing exercise task between PwMS experiencing high and low levels of fatigue.

CHAPTER 6- NEUROPHYSIOLOGICAL DIFFERENCES BETWEEN PEOPLE EXPERIENCING HIGH AND LOW LEVELS OF MS FATIGUE: A CROSS-SECTIONAL STUDY

6.1 Introduction

Highly fatigued MS patients (MS-HF) have shown an increase in the pattern of cortical brain activation and changes in central-peripheral neural communication in comparison with MS-LF (Perretti et al., 2004; Tomasevic et al., 2013). This adaptive cortical brain reorganisation could be a compensatory adaptation resulting from the physiological consequences of MS (i.e., impaired conduction in central motor pathways). It might affect the ability of PwMS to maintain sufficient central drive in everyday whole-body activities, thus influencing perceived MS fatigue. An improved understanding of how perceived MS fatigue is linked to neural control and motor function (as important contributing factors to whole body exercise) could have significant implications for rehabilitation and therapeutic interventions.

Differences in neurophysiological measures associated with perceived fatigue are shown in PwMS. For example, reductions in MVC strength (Rice et al., 1992; Sheean et al., 1997; Perretti et al., 2004; Zijdewind et al., 2016; Jørgensen et al., 2017), motor function (Ng et al., 2004) and performance fatigability during a motor task (Sheean et al., 1997; Liepert et al., 2005; Steens et al., 2012b; Wolkorte et al., 2016), have all been reported. Furthermore, several studies have identified neurophysiological differences between PwMS experiencing high and low levels of perceived MS fatigue. The decrements in strength and force production (performance fatigability) in MS-HF versus MS-LF (Ng et al., 2000b; Greim et al., 2007; Andreasen et al., 2009) are greatest during sustained voluntary muscle actions, suggestive of a centrally driven decline in VA. For this reason, impairments in neuromuscular function in fatigued PwMS appear to be, at least in part, attributable to sub-optimal insufficient central nervous system activation of skeletal muscle (i.e., impaired VA) during fatiguing exercise (Zwarts et al., 2008; Steens et al., 2012b).

The important role of central factors in the more pronounced level of performance fatigability observed in fatigued PwMS, is further supported by recent studies showing no differences in the relative integrity of corticospinal motor pathways (MEP variables and central motor conduction time) between MS-HF and MS-LF (Colombo et al., 2000; Perretti et al., 2004; Liepert et al., 2005; Steens et al., 2012c) . A significant lack of MEP facilitation in the pre-movement phase, has been previously reported after a sustained motor task in MS-HF compared to HC and MS-LF (Morgante et al., 2011;

Russo et al., 2015). As such, it is possible, disruption of brain networks involved in motor preparation, which has been correlated to structural and functional changes in frontal-thalamic pathways (Russo et al., 2015), which could partially explain increased perceptions of fatigue in PwMS due to an elevated demand on functioning neural circuits. However, few studies have compared intracortical facilitation (ICF) or intracortical inhibition (SICI) variables between MS-HF and MS-LF. Thus making it difficult to understand, whether modulation of the ICF and SICI networks are implicated in perceived MS fatigue, and data are further compounded by studies of people with relapsing-remitting MS (Liepert et al., 2005; Morgante et al., 2011) and progressive MS (Chalah et al., 2019). It remains unclear whether differences in the demands of a sub-maximal intermittent task, in homogenous groups of PwMS categorised by fatigue status (MS-HF and MS-LF) influence these variables. Thus, the role of corticospinal excitability and SICI are not assessed at rest and after a sub-maximal fatiguing exercise task warrants further investigation.

In contrast to PwMS, performance fatigability in HC seems to be mainly of peripheral origin, i.e., at the level of skeletal muscle (Sheean et al., 1997; Steens et al., 2012c; Wolkorte et al., 2015a, 2015b, 2016; Severijns et al., 2017). However, no current standardised method is available for assessing performance fatigability and comparing it between PwMS experiencing different levels of perceived MS fatigue and HC. Performance fatigability has been most commonly assessed in the upper-limb and the relative paucity of lower-limb studies needs to be addressed. Especially as PwMS commonly report issues of fatigability in relation to lower-limb activities such as walking (Severijns et al., 2017). In turn, this could increase the amount of effort required for everyday tasks, thus exacerbating perceived fatigue and fatigability. In addition, there is a lack of studies that have investigated both upper- and lower-limb neurophysiological differences in the same participants, likely due to the physical demand and resources available.

The underlying neurophysiological mechanisms contributing to MS fatigue warrant further investigation because many previous studies have recruited heterogenous groups of PwMS (including, all MS types, single limb, all disabilities levels) and have partitioned participants on the basis of one global fatigue score. As such, further research in more homogenous groups of PwMS with clearly characterised fatigue

status (highly-fatigued; MS-HF and less-fatigued; MS-LF) could improve the understanding of neurophysiological differences that are associated with high and low levels of perceived MS fatigue. Based on these considerations, the aim of this Chapter was to investigate an established battery of neuromuscular measures and performance fatigability from Chapter 5 in the upper- and lower-limbs of PwMS experiencing high and low levels of perceived MS fatigue, and to compare their responses with age-matched HC.

6.2 Methods

6.2.1 Participants

Following ethical approval (3.2.1 Ethical Approval: Institution: HLSPE111114 and national health service: 14/LO/2290) and informed consent (3.3.2 Informed Consent), forty relapsing-remitting MS participants and twenty healthy controls volunteered to participate in this study. Based on previous cross-sectional studies in PwMS and HC twenty participants per group was deemed sufficient to observe differences in measures of central and peripheral neurophysiological function (e.g., Chalder et al., 1993; Greim et al., 2007). The experimental groups consisted of the same participants from Chapter 5 (see 5.3.1 Participants) and complied with the criteria for participation (see3.3 Participants). See Table 6.1 Participant Characteristics.

6.2.2 Preliminary Visit

Prior to the experimental trials of the study, symptoms of fatigue (3.9.1 Fatigue Severity Scale), mood (3.9.2 Anxiety and Depression) and contraindications to experimental procedures (Rossini et al. 2009) were assessed. A 60-minute familiarisation of the entire neuromuscular protocol was performed (see 3.4 Familiarisation and 3.6 Neuromuscular Assessment) and experimental controls were implemented (3.5 Experimental Criterion).

6.2.3 Experimental Protocol

In this cross-sectional study, participants visited the laboratory on two separate occasions for the neuromuscular assessment of the right lower- and upper- extremity, according to limb dominance (Oldfield, 1971). Neuromuscular assessments were conducted at the same time of day, separated by 2-14 days. Reliability indices of the main variables of interest are presented in Chapter 5 (see Tables 5.2 to 5.4). The main

neuromuscular variables reported moderate to excellent test-retest reliability for all groups in both the upper and lower-limb, with ICC ranging from 0.58 - 0.98. In addition, patient reported psychometric outcomes reported good to excellent test-retest reliability, with ICCs ranging from 0.84 - 0.98 (See Figure 5.2).

6.2.4 Neuromuscular Assessment

Each experimental visit involved neuromuscular data collection (refer to 3.6 Neuromuscular Assessment and Figure 6.1) before and immediately after a sub-maximal intermittent task on the limb that was exercised to task failure, described in section 3.7.2 Sub-maximal Test Protocol. For detailed procedures of the dynamometer and isometric measurements recorded during isometric MVC and corticospinal assessments with transcranial magnetic stimulation during 10% of isometric MVC (Brownstein et al., 2018), refer to section 3.6.1 and 3.8. The set-up followed Chapter 5 using custom-made adjustable isometric dynamometers. Electromyography (EMG) activity was also recorded from the knee-extensors and wrist flexors during these visits, as described previously (3.6.1 Force and Electromyography Recordings).

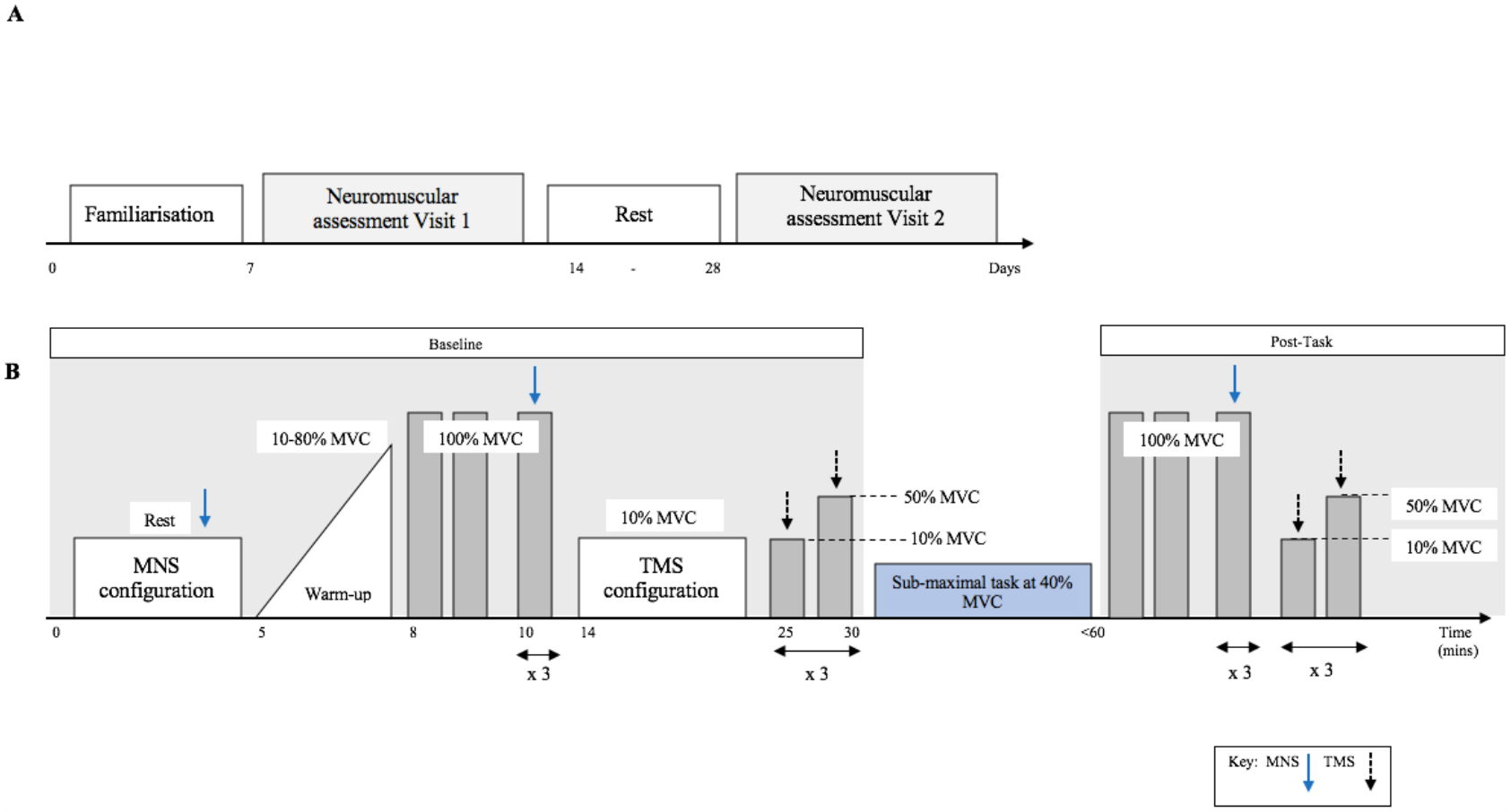

Figure 6.1 Schematic of neuromuscular protocol, **(A)** Neuromuscular assessment intervals of 2-14 days between knee-extensors and wrist-flexors, **(B)** Neuromuscular assessment including, motor nerve stimulation, transcranial magnetic stimulation and sub-maximal, intermittent task at 40% MVC to task failure.

Percutaneous Nerve Stimulation

Percutaneous nerve stimulation was delivered to evoke M-wave in the knee extensors and wrist flexors (see section 3.6.3). The intensity required to elicit M_{max} did not differ between groups (HC: 273 ± 137 mA, MS-LF: 300 ± 105 mA and MS-HF: 322 ± 108 mA, $P = 0.417$).

Transcranial Magnetic Stimulation

Single and paired-pulse transcranial magnetic stimulation were delivered to assess corticospinal excitability, CSP, and SICI, see section 3.8. AMT was determined at the beginning of the neuromuscular assessment. Motor threshold was different between groups (HC: 49 ± 9%, MS-LF: 55 ± 9% and MS-HF: 58 ± 9%, $P = 0.012$), with higher AMT intensity for MS-HF vs. HC ($P = 0.009$).

6.2.5 Perceived Fatigue and Patient Reported Psychometric Outcomes

Symptomatic fatigue scales were completed at the beginning of first experimental visit according to section 3.9.1. The severity, frequency and impact of fatigue in everyday life was recorded using different scales. Mood including, anxiety and depression, sleep quality and pain experienced were measured at the beginning of first experimental visit. For further details, see sections 3.92 – 3.9.4.

6.2.5 Data Analysis

Voluntary activation was determined using the formula: VA (%) = (1 – [SIT ÷ $Q_{tw,pot}$]) × 100), see section 3.6.3.2. EMG activity was quantified as RMSemg and recorded during the middle 500 ms epoch of a 3 s maximal contraction. EMG responses recorded from transcranial magnetic stimulation (e.g., MEPs) that were contaminated by artefact were excluded from analysis (<2% of trials per session). All data analysis was performed offline using Spike 2 (version 6.0, CED, UK). RMSemg of *rectus fermoris* and *flexor carpi radialis* was normalised to M_{max} (RMSemg/M_{max}) in order to remove the confounding effect of electrode location and body fat, and account for changes at the skin-electrode interface and differences in propagation along the sarcolemma (Wells & Fewtrell, 2006).

6.2.7 Statistical Analysis

All data are reported as means ± SD in Tables and Figures. Normality of the data was assessed using the Shapiro-Wilks test. If the assumption of normality was violated, appropriate transformations were performed, with common logarithm used for strongly positively skewed ICF and SICI data in Experiments 1 and 2, respectively, and reciprocal transformation used for extremely positively skewed ICF data in Experiment 2 (Bulmer, 1979). Sphericity was assessed using Mauchly's test and if necessary, controlled using the Greenhouse-Geisser correction. One-way repeated measures ANOVA were run for all pre-exercise dependent variables to assess group (fatigue severity) changes in neuromuscular function and psychometric reported measures. A two-way (2×3) ANOVA was used to assess whether acute mechanical (MVC, $Q_{tw,pot}$) and neural changes (VA, M_{max}, RMSemg, MEP/M_{max}, SICI, and SP) associated with fatigue severity group specific. The independent variables were time (PRE and POST) and group (HC, MS-LF and MS-HF). If significant interactions or main effects were found, analyses were continued using pairwise comparisons using the Bonferroni correction. Upper- versus lower- limb comparison performed by paired samples t-test & 95% Cis. Statistical significance was determined as an alpha of 0.05.

6.3 Results

Participant characteristics and psychometric measurements were gathered in all 60 participants (Table 6.1). Two participants withdrew from the study because one person with MS relapsed from the MS-HF group and was referred back to the consultant and one person with MS from MS-LF group could not perform muscle contractions. The lower- and upper-limb neuromuscular assessments described here had completion rates of 97% and 90%. In seven PwMS, one of the following indicators were incomplete due to failure to respond to transcranial magnetic stimulation and motor nerve stimulation for the following reasons: 1) in two MS participants inadequate muscle force or inability to generate sufficient muscle force, 2) in three MS participants we were unable to obtain accurate MEP or M_{max} responses, and 3) two MS participants had unrelated existing injuries. There were no statistically significant differences between the MS groups (MS-HF and MS-LF) and the control group in age, gender, disease duration and EDSS scores *(P* > 0.05). There were no observed group differences for age, gender, MS type, or duration of disease. Details of participant characteristics are presented in Table 6.1.

Table 6.1 Participant characteristics (Mean ± SD).

	HC	MS-LF	MS-HF
N	20	20	20
Age (years)	44.8 ± 15.1	45.9 ± 9.0	43.6 ± 10.2
Sex (F/M)	13/7	15/5	15/5
EDSS (arbitrary units)	-	2.1 ± 1.2	2.4 ± 1.4
Disease Duration (years)	-	9.3 ± 3.8	9.9 ± 5.5
Disease Modification Therapy (Y/N)	-	17/3	14/6
- Tecfidera		7	2
- Copazone		5	2
- Tysabri		-	3
- Gilenya		-	4
- Avonex		3	-
- Lemtrada		1	2
- Rebrif		1	-
- Aubagio		-	-
-Betaferon		-	1
Other comorbidities (Y/N)	4/16	6/14	9/11
- Osteoporosis	-	1	1
- Arthritis	1	1	-
- Trigeminal neuralgia	-	-	-
- Fibromyalgia	-	1	2
- Underactive thyroid	1	2	2
-Overactive bladder	2	1	2
-Type I diabetes	-	-	1
- Type II diabetes	-	-	1

FSS: Fatigue Severity Scale; HADS: Hospital and Anxiety Depression Scale; HC: HC; MS-LF: MS-LF People with Multiple Sclerosis; MS-HF: Highly-MS-HF People with Multiple Sclerosis N: Numbers; F: Females; M: Males; EDSS: Extended Disability Status Scale; Y: Yes; N: No. *One-way ANOVA significant group effect $p< 0.05$.

6.3.1 Baseline Patient Reported Outcomes

Perceptual responses for patient report outcomes can be viewed in Figure 6.2.

Perceived Fatigue

The mean FSS score was higher in MS-HF ($F_{2,57} = 82.64$, $P < 0.001$) in comparison with MS-LF ($P < 0.001$) and HC ($P < 0.001$), showing higher levels of fatigue interfere with daily activities in MS-HF. Other indices of fatigue severity were also higher in MS-HF. Mean CFS scores were higher in the extent and severity of fatigue in MS-HF ($F_{2,57} = 19.33$, $P < 0.001$), compared with MS-LF ($P = 0.021$) and HC ($P = 0.004$). Additionally, compared with MS-LF, MS-HF had higher mean MFIS scores ($F_{2,57} =$

84.07, $P < 0.001$), testifying to the continuing impact of fatigue on daily life when compared to MS-LF ($P < 0.001$) and HC ($P < 0.001$).

Mood (Depression and Anxiety), Pain and Sleep Quality

As shown in Figure 6.2, HADSglobal was higher in MS-HF ($F_{2,57} = 9.15$, $P < 0.001$), compared with MS-LF ($P = 0.008$), and versus HC ($P < 0.001$). There was no difference between MS-LF and HC ($P > 0.05$). Compared with MS-LF, MS-HF also had higher HADSanxiety and HADSdepression scores (anxiety: MS-HF: 9.2 ± 3.3 vs. MS-LF: 6.1 ± 4.1, $P = 0.006$ and depression: MS-HF: 5.0 ± 2.8 vs. MS-LF: 3.4 ± 3.0, $P = 0.039$). There was no difference between MS-LF and HC. Regarding pain, there was a group difference, with slightly higher scores among MS-HF and HC (MS-HF: 2.3 ± 1.2 vs HC: 1.3 ± 1.0, $P = 0.032$), but with no difference between MS-LF and HC. Conversely, PSQI was similar between MS-HF and MS-LF versus HC (9.6 ± 4.9 vs 7.6 ± 3.5 and 6.7 ± 4.1, $P = 0.097$), and with >75% of participants reporting poor sleep quality within the last month (established cut off > 5; Buysse, Reynolds, & Monk, 1989). Details of participant psychometric parameters are presented in Figure 6.2.

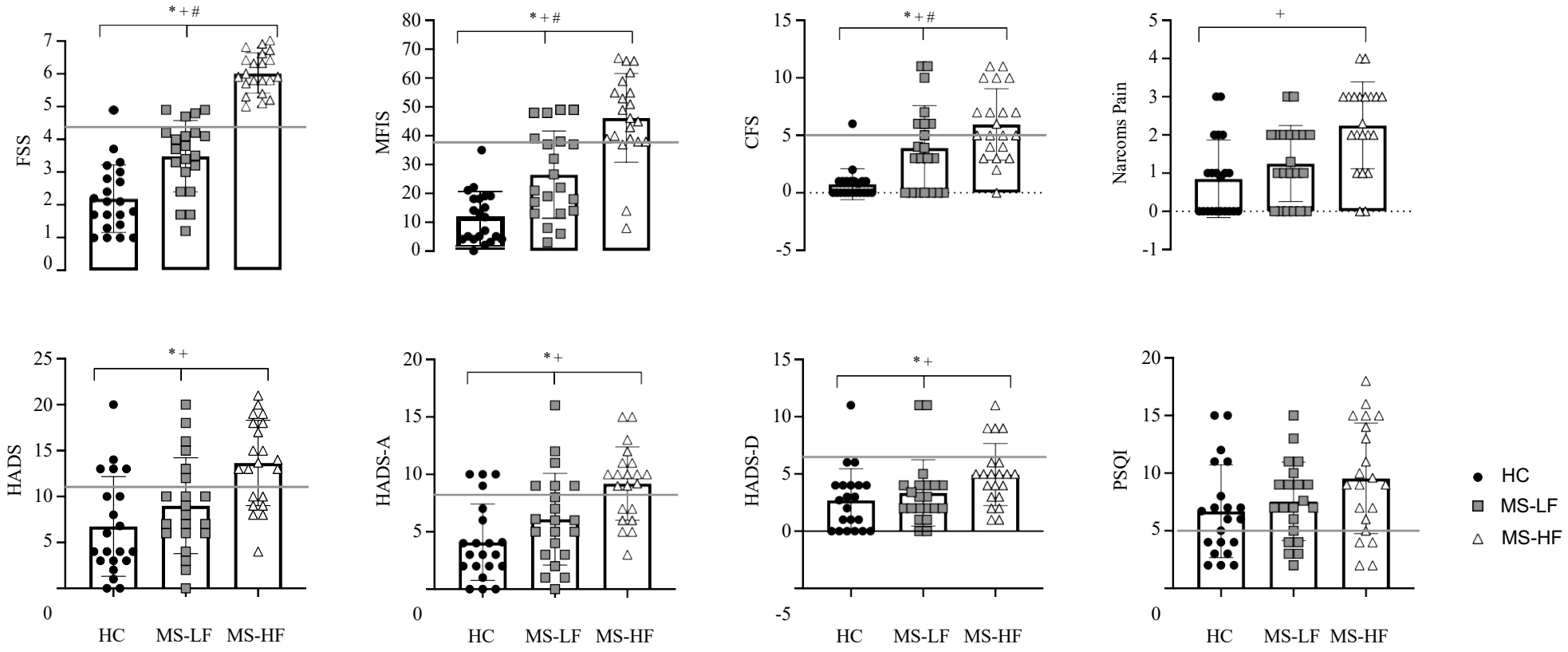

Figure 6.2 Differences between groups for patient reported outcomes, with ——indicating clinically important cut off levels of symptom scores. When a significant effect of symptom exacerbation was found, * MS-HF vs MS-LF; + MS-HF vs HC; # MS-LF vs HC (p <0.05

6.3.2 Baseline Neuromuscular Function

Lower-Limb

In Table 6.2. MVC force was different between groups ($F_{2, 55} = 6.15$, $P = 0.004$), with *post-hoc* tests showing reduced MVC in MS-HF compared to MS-LF (−58.3 N; $P = 0.044$) as well as HC (−77.1 N; $P = 0.004$). Potentiated twitch force was not different between the MS groups and HC (pooled average = 138.5 N, $F_{2, 53} = 1.49$, $P = 0.233$). However, VA elicited by motor nerve stimulation was different between groups ($F_{2, 53} = 11.59$, $P < 0.001$), with greater VA impairment in MS-HF compared to MS-LF (−3.6%; $P = 0.007$) and HC (−5.2%; $P < 0.001$).

As shown in Table 6.2, corticospinal excitability (MEP/M_{max}) did not differ between groups ($F_{2, 49} = 2.28$, $P = 0.113$), neither did SP (pooled average = 171.9 ms, $F_{2, 50} = 2.69$, $P = 0.078$). However, M_{max} was different between the groups ($F_{2, 53} = 10.06$, $P < 0.001$), with *post-hoc* tests showing reduced M_{max} in MS-HF versus HC (−2.6 mV, $P < 0.001$) and MS-LF compared with HC (−2.2 mV, $P = 0.003$). SICI was also different between the groups ($F_{2, 49} = 2.28$, $P = 0.113$), with *post-hoc* tests showing greater inhibition in MS-HF compared to HC (−0.2, $P = 0.04$). Finally, the pre-stimulus normalized RMSemg activity was also different between the groups ($F_{2, 54} = 8.56$, $P = 0.001$), with *post-hoc* tests showing less neural drive in MS-HF and MS-LF (−0.3 mV, $P = 0.002$) compared to HC (−0.3 mV, $P = 0.003$).

Table 6.2 Differences in knee-extensor outcomes between groups' pre -and post- exercise task. When a significant effect of exercise was found, the Δ in a variable from pre-post exercise was reported. * MS-HF vs. MS-LF; + MS-HF vs. HC; # MS-LF vs. HC (P <0.05).

Measures		HC	MS-LF	MS-HF	Group effect 1 × 3 ANOVA	Pre-post exercise 2 × 3 ANOVA
MVC (N)	Pre	412.0 ± 77.1	393.2 ± 67.9	334.9 ± 67.8 *+	**0.004**	**0.007**
	Post	241.4 ± 70.9	248.3 ± 52.0	217.6 ± 55.2		
$Q_{tw,\ pot}$ (N)	Pre	150.6 ± 48.1	131.2 ± 38.5	133.6 ± 20.6	0.233	**<0.001**
	Post	91.7 ± 31.8	87.0 ± 28.4	92.7 ± 29.0		
VA (%)	Pre	93.3 ± 3.4	91.7 ± 2.4	88.1 ± 4.1 *+	**0.001**	**<0.001**
	Post	79.4 ± 9.7	74.7 ± 12.2	76.3 ± 8.0		
Mmax (mV)	Pre	7.3 ± 2.5	5.1 ± 1.7 #	4.7 ± 1.3 #+	**<0.001**	**0.001**
	Post	6.8 ± 2.5	4.5 ± 1.5 #	4.4 ± 1.3		
MEP/Mmax (%)	Pre	16.8 ± 10.4	10.9 ± 6.1	13.0 ± 7.1	0.113	0.480
	Post	16.4 ± 10.0	10.3 ± 14.6	10.0 ± 7.9		
MEP amplitude (mV)	Pre	1.0 ± 0.4	0.5 ± 0.2	0.6 ± 0.3 #+	**<0.001**	0.313
	Post	1.0 ± 0.7	0.5 ± 0.2	0.4 ± 0.2		
RMSemg (mV)	Pre	0.7 ± 0.3	0.4 ± 0.2 #	0.4 ± 0.2 #+	**0.001**	**0.005**
	Post	0.7 ± 0.2	0.5 ± 0.2 #	0.5 ± 0.2		
SICI (ratio)	Pre	0.8 ± 0.2	0.7 ± 0.3	0.6 ± 0.2 +	**0.004**	**0.019**
	Post	0.8 ± 0.3	0.7 ± 0.3	0.5 ± 0.2		
SP (ms)	Pre	153.3 ± 52.2	172.8 ± 47.4	189.5 ± 59.9	0.078	**<0.001**
	Post	181.6 ± 61.8	218.9 ± 55.1	234.9 ± 53.7		

HC, HC; MEP: Motor evoked potential, N, Number, RMSemg, Root mean squared electromyography, SICI: Short interval cortical inhibition, SP: Silent period, M_{max}: maximum compound action potential, MS-LF: MS-LF people with multiple sclerosis; MS-HF: Highly-MS-HF people with multiple sclerosis. Data are presented as Mean ± SD.

Upper-Limb

Shown in Table 6.3, MVC force was different between the groups ($F_{2, 50} = 11.71$, $P < 0.001$), with *post-hoc* tests showing reduced MVC in MS-HF versus HC (−37.6 N, $P < 0.001$) and MS-LF compared with HC (−30.0 N, $P = 0.002$). There was no difference in MVC between the MS groups. Potentiated twitch force was not significantly different between MS groups and the HC (pooled average = 26.9 N, $F_{2, 50} = 1.85$, $P = 0.168$). However, there was a difference in VA between the groups ($F_{2, 50} = 9.32$, $P < 0.001$), with post-hoc tests showing an impairment for MS-HF compared with MS-LF (−4.5%; $P = 0.037$) and MS-HF versus HC (−7.0%; $P < 0.001$).

M_{max} did not differ between the groups (pooled average = 9.2 mV, $F_{2, 51} = 1.46$, $P = 0.241$), nor did corticospinal excitability (MEP/M_{max}) (pooled average = 10.9 %, $F_{2, 46} = 0.858$, $P = 0.431$) or SICI (pooled average = 0.76, $F_{2, 50} = 2.14$, $P = 0.129$). However, the length of SP was significantly different between the groups ($F_{2, 50} = 4.91$, $P = 0.011$), with post-hoc tests showing a more prolonged SP in MS-HF compared with HC (28.9 ms, $P = 0.009$) but there was no difference between MS-LF and HC ($P = 0.367$) or between the MS groups ($P = 0.460$). Pre-stimulus normalized RMSemg activity was not different between the groups ($F_{2, 51} = 1.07$, $P = 0.349$).

Table 6.3 Differences in wrist-flexors outcomes between groups' pre -and post- exercise task. When a significant effect of exercise was found, the Δ in a variable from pre-post exercise was reported. * MS-HF vs MS-LF; + MS-HF vs HC; # MS-LF vs HC (All P <0.05).

Measures		HC	MS-LF	MS-HF	Group effect 1 × 3 ANOVA	Pre-post exercise 2 × 3 ANOVA
MVC (N)	Pre	136.1 ± 28.1	105.1 ± 25.6	98.5 ± 21.3 #+	**0.001**	**0.002**
	Post	80.5 ± 30.2	71.1 ± 18.9	63.9 ± 27.9		
$Q_{tw,\,pot}$ (N)	Pre	31.2 ± 16.0	23.5 ± 8.6	26.0 ± 10.3	0.168	**0.023**
	Post	22.5 ± 10.8	19.0 ± 7.5	21.4 ± 9.6		
VA (%)	Pre	91.5 ± 4.7	89.0 ± 4.3	84.5 ± 5.8 *+	**0.001**	**0.001**
	Post	71.9 ± 12.1	76.2 ± 12.1	73.1 ± 11.2		
Mmax (mV)	Pre	10.4 ± 4.0	9.2 ± 3.9	8.1 ± 4.2	0.241	**0.001**
	Post	9.4 ± 3.7	8.3 ± 4.1	6.9 ± 3.7		
MEP/Mmax (%)	Pre	11.8 ± 8.1	8.8 ± 5.0	12.0 ± 8.3	0.431	0.503
	Post	10.6 ± 6.8	8.3 ± 6.1	9.3 ± 5.8		
MEP amplitude (mV)	Pre	1.0 ± 0.5	0.7 ± 0.3	0.7 ± 0.2 +	**0.019**	**0.001**
	Post	0.8 ± 0.3	0.6 ± 0.2	0.5 ± 0.2		
RMSemg (mV)	Pre	0.6 ± 0.3	0.5 ± 0.2	0.5 ± 0.3	0.349	**0.001**
	Post	0.7 ± 0.4	0.5 ± 0.2	0.6 ± 0.3		
SICI (ratio)	Pre	0.9 ± 0.2	0.7 ± 0.2	0.7 ± 0.3	0.129	**0.010**
	Post	0.8 ± 0.3	0.6 ± 0.2	0.6 ± 0.2		
SP (ms)	Pre	124.5 ± 29.7	139.1 ± 22.3	153.4 ± 30.5 +	**0.011**	**0.001**
	Post	134.1 ± 33.6	171.7 ± 36.4	206.6 ± 40.6		

HC, HC; MEP: Motor evoked potential, N, Number, RMSemg, Root mean squared electromyography, SICI: Short interval cortical inhibition, SP: Silent period, M_{max}: maximum compound action potential, MS-LF: MS-LF people with multiple sclerosis; MS-HF: Highly-MS-HF people with multiple sclerosis. Data are presented as Mean ± SD.

6.3.3 Fatigability and Neuromuscular Function (baseline versus post-fatigue task changes)

Nineteen MS participants cited muscle pain/tingle, muscle weakness, or an inability to maintain concentration as the reason for terminating the sub-maximal isometric, fatiguing task. The remaining MS participants and all HC cited non-specific reasons such as 'had enough' or 'unable to continue' for terminating the sub-maximal task.

Lower-Limb

As shown in Figure 6.5(A), MVC force decreased after the fatigue task ($F_{1,55} = 481.894$, $P < 0.001$). Specifically, a group × time interaction was found for MVC force of the knee-extensors ($F_{2,55} = 5.513$ $P = 0.007$), with *post-hoc* analysis displaying a larger reduction in MVC after the fatigue task in HC (mean difference: 170.6 N, $P < 0.001$), compared with less change in MVC for MS-LF and MS-HF (mean difference: 145.0 N and 117.4 N, both $P < 0.001$). TTF during the sub-maximal isometric task was also different between the groups (Figure 6.5(C), HC: 24.6 ± 14.9 vs. MS-LF: 15.8 ± 6.3 vs. MS-HF: 13.2 ± 8.1 mins $P = 0.005$), with *post-hoc* tests showing shorter TTF in MS-HF and MS-LF MS patients compared with HC ($P = 0.005$ and $P = 0.048$). However, there was no difference between the MS groups ($P > 0.05$). Also, no difference in the rate of force decline (N·s) was observed between the groups ($F_{2, 54} = 5.958$, $P = 0.400$).

Performance fatigability (ΔMVC) was similar in all groups (Figure 6.3 (B), HC: 58.2 ± 13.5 vs. MS-LF: 63.5 ± 9.7 vs. MS-HF: 65.0 ± 11.3%, respectively, $P = 0.174$). The two-way ANOVA (group × time effect) showed that $Q_{tw,pot}$ decreased pre-post exercise ($F_{1,53} = 140.778$, $P < 0.001$), as did M_{max} ($F_{1,53} = 13.087$, $P = 0.001$), VA ($F_{1,53} = 144.400$, $P < 0.001$), and RMSemg ($F_{1,52} = 8.620$, $P = 0.005$). SP also increased after the fatigue task ($F_{1,50} = 37.904$, $P < 0.001$), and there was a decrease in SICI after the fatigue task ($F_{1,51} = 5.896$, $P = 0.019$). No differences between the groups in corticospinal excitability (MEP and MEP/M_{max}) were found after the fatigue task (see Table 6.2).

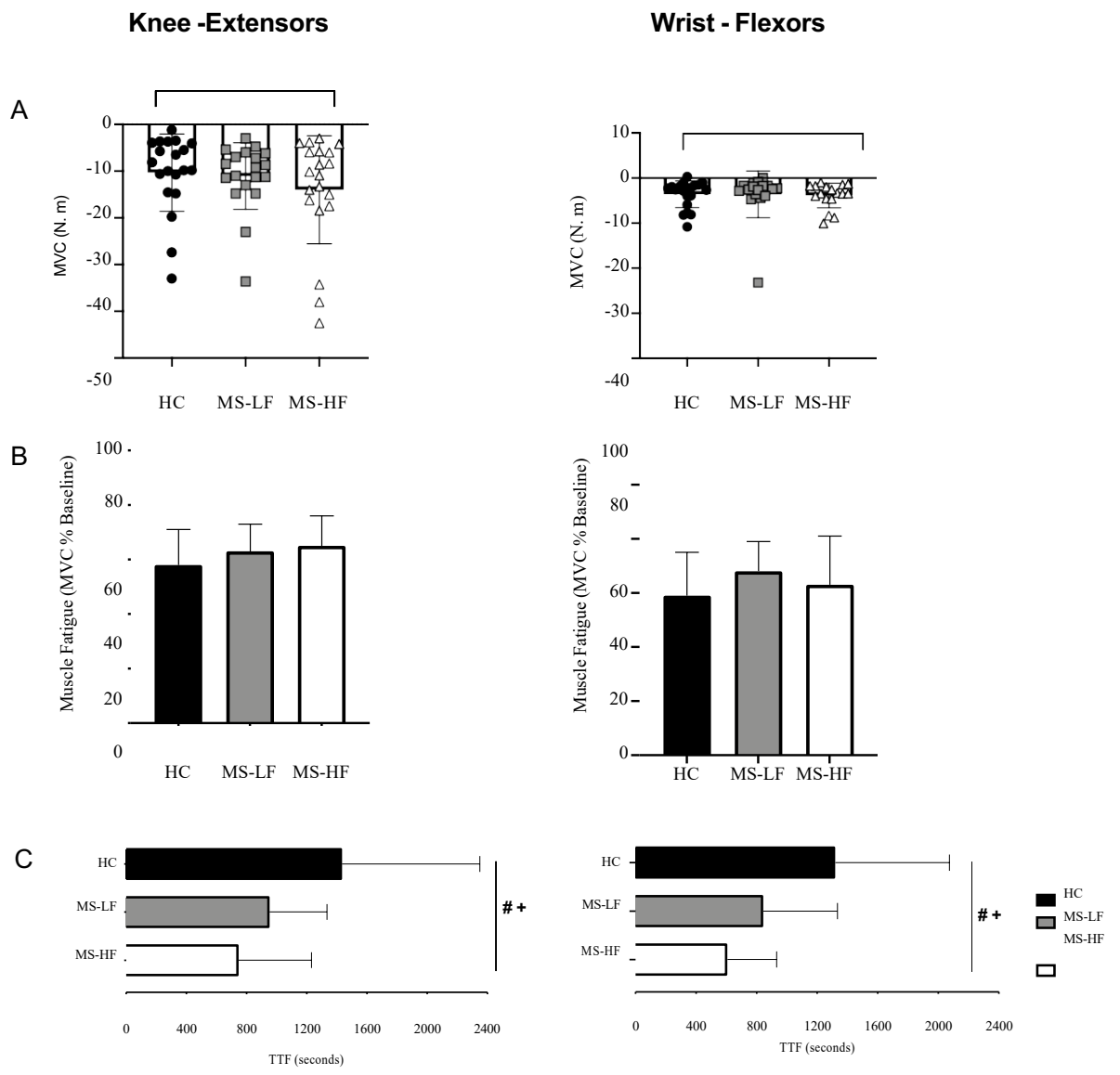

Figure 6.3 Performance fatigability measures: (A) Rate of Force Decline as MVC (N. s), (B) Performance Fatigability (MVC as % of baseline) and (C) Time to Task Failure (TTF, minutes). Significant effect between groups was shown as * MS-HF vs MS-LF; + MS-HF vs HC; # MS-LF vs HC. Significance set at P <0.05.

Upper Limb

As shown in Figure 6.5, MVC force decreased after the fatigue task ($F_{1,50} = 225.163$, $P < 0.001$). Specifically, a group × time interaction was found for MVC force of the wrist-flexors ($F_{2,50} = 7.066$ $P = 0.002$), with *post-hoc* analysis displaying a larger reduction in MVC after the fatigue task in HC (mean difference: 55.6 N, $P < 0.001$), and with less change in MVC for MS-LF and MS-HF (mean difference: 34.0 N, $P < 0.001$ and 34.5 N, $P < 0.001$). Likewise, TTF during sub-maximal isometric task for the upper-limb was different between the groups (Figure 6.5C), HC: 22.5 ± 12.2 vs. MS-LF: 14.2 ± 8.2 vs. MS-HF: 11.1 ± 4.9 minutes respectively, $P = 0.001$), with both MS-HF and MS-LF MS groups performing for less time compared with HC (P =

0.002 and $P = 0.025$). No difference existed between the MS groups ($P > 0.05$). In addition, there was no difference in the rate of force decline (N·s) between the groups ($F_{2, 52} = 7.465$, P

= 0.952). Performance fatigability (ΔMVC) did not significantly differ between the groups (HC: 58.5 ± 16.5 vs. MS-LF: 68.3 ± 11.0 vs. MS-HF: 63.3 ± 18.4%, respectively, $P = 0.177$). The two-way ANOVA (group × time) showed that M_{max} decreased after the fatigue task ($F_{1,50} = 28.847$, $P < 0.001$), as did VA ($F_{1,50} = 88.267$, $P < 0.001$), RMSemg ($F_{1,51} = 12.870$, $P = 0.001$) and SICI ($F_{1,50} = 7.103$, $P = 0.010$).

$Q_{tw,\,pot}$ decreased after the fatigue task ($F_{1,50} = 70.132$, $P < 0.001$). Specifically, a group × time interaction was found ($F_{2,50} = 4.085$ $P = 0.023$). *Post-hoc* analysis showed a larger reduction in $Q_{tw,pot}$ after the fatigue task in HC (mean difference: 8.7 N, P < 0.001), and with less change in $Q_{tw,pot}$ for MS-LF and MS-HF (mean difference: 4.4 N, P = 0.001 and 4.6 N, $P = 0.001$). Additionally, SP increased after the fatigue task ($F_{1,50} = 71.071$, $P < 0.001$). Specifically, a group × time interaction was found ($F_{2,50} = 11.808$ $P < 0.001$). Post-hoc analysis showed a more prolonged SP after the fatigue task in MS-HF (mean difference: 53.2 ms, $P < 0.001$) andMS-LF, with no change in HC (mean difference: 32.6 ms, $P < 0.001$ and 9.6 ms, $P = 0.124$). There was a trend for an increase in corticospinal excitability (MEP/M_{max}) after the fatigue task($F_{1,45} = 3.819$, $P = 0.057$) but there was no significant group × time interaction ($F_{2,45} = 0.697$, $P = 0.503$).

Lower Limb versus Upper-Limb Changes

A greater reduction in $Q_{tw,\,pot}$ after the fatigue task was observed in the upper-limb compared with the lower-limb in HC (−10.9 [−19.7 to −2.08], $P = 0.018$), as for MS-LF (−17.6 [−30.7 to −4.5], $P = 0.018$). Additionally, VA (−6.4 [1.04 to 11.85], $P = 0.022$), and SP (-10.9% [−19.7 to −2.08, $P = 0.018$) were reduced in the upper-limb compared with the lower-limb in HC. Similarly changes after the fatigue task were observed between upper- and lower-limb for MS-HF and for the remaining neurophysiological outcomes in MS-HF and HC.

6.4 Discussion

This is the first study to compare neurophysiological correlates of perceived MS fatigue, in the upper- and lower-limbs of a homogenous group of relapsing-remitting PwMS partitioned on the basis of fatigue status (i.e., experiencing high or low levels of perceived MS fatigue). The data for values of central drive and modulation of neural drive after a fatigue task (i.e., VA and SICI), points to the suggestion that PwMS suffering from high levels of fatigue, require a greater demand on central components and less peripheral disturbance. These key findings are consistent with simple tasks being perceived as effortful and are further substantiated by the

accompanying post-exercise fatigue data. Furthermore, these data add weight to the argument that MS-HF have neurophysiological responses that differ from their MS-LF counterparts and healthy individuals.

Neurophysiological Differences at Baseline

A number of potential factors might have contributed towards the reduced MVC in both muscles in MS-HF versus MS-LF and HC. Psychosocial issues, including depression and poor sleep may have been key factors, and may have caused a relative lack of motivation during the voluntary contractions. Additionally, VA measured through motor nerve stimulation was significantly reduced in MS-HF (lower-limb: 88 and upper-limb: 85). The magnitude of impaired VA was similar (85) to that reported by Wolkorte et al. (2016), but lower (95-98). than that reported by Andreasen et al. (2009) Methodological differences between the studies (i.e., use of an isometric force rig versus isokinetic dynamometry) might explain the different results. Interestingly, the results of the present study reported no difference in $Q_{tw,pot}$ at baseline, indicating that the intramuscular muscle contractile properties ($Q_{tw,pot}$) was similar between PwMS with high and low levels of fatigue and HC. Accordingly, results from the present study suggest that any higher levels of perceived MS-fatigue are likely associated with decrements in central nervous system function rather than skeletal muscle (peripheral) impairments in the resting, unfatigued state, which concurs with previous studies (Liepert et al., 2005; Conte et al., 2009; Morgante et al., 2011; Chalah et al., 2019).

Performance Fatigability

For both muscle groups, the time to task failure was significantly shorter for both MS groups compared to HC. There is evidence that PwMS, are less able to increase cortical drive to maintain force during sustained contractions (Post et al., 2009; Steens et al., 2012c). As a consequence, the inability to increase central activation results in a decline in voluntary drive and subsequent force production at the level of skeletal muscle (Andreasen et al., 2009; Skurvydas et al., 2011; Steens et al., 2012b; Steens et al., 2012c). There has been little reported evidence of an association between performance fatigability and perceived MS fatigue (assessed using self-reported fatigue scales: (Sharma et al., 1995; Iriarte & de Castro, 1998; Ng et al., 2004; Enoka & Duchateau, 2016), suggesting that these two fatigue constructs are independent. However, a study by Wolkorte et al. (2015a) demonstrated a regression model that included performance fatigability, depression and MVC explained 48% of the variance in MFIS-physical scores. In addition, Steens et al. (2012b) found that an association between

performance fatigability and perceived MS fatigue was related to central fatigue (VA) but not to peripheral fatigue ($Q_{tw, pot}$). However, this might only be true for relapsing remitting MS, as performance fatigability did not correlate with perceived fatigue for secondary progressive MS using the same model (Wolkorte et al., 2015b).

Post Task Neurophysiological Differences

A greater decline in MVC force was observed in HC after the fatigue task compared to the MS groups, and this is likely attributable to the increased level of effort needed to elicit a higher MVC force at baseline. This finding is consistent with previous work showing lower MVC force in PwMS compared with HC (Liepert et al., 2005). Although the lower force decline in PwMS is likely explained by neuropathic changes, that characterise MS. Some of the force decrement could be attributable to deconditioning effects on skeletal muscle (Sharma et al., 1995; Kent-Braun et al., 1997; de Haan et al., 2000; Skurvydas et al., 2011), as PwMS are generally less physically active than healthy populations (Motl et al., 2005). Importantly, previous studies have observed anatomical changes within skeletal muscle groups of PwMS; specifically, the tibialis anterior has reduced muscle fibre size, fewer Type I fibers and more Type II fibers, as compared with healthy controls (Sharma et al., 1995; Kent-Braun et al., 1997) These changes, which have the potential to impair MVC and ability to sustain a submaximal level of force in PwMS, could be accentuated in MS-HF.

A larger decline in $Q_{tw, pot}$, showed greater peripheral fatigue in HC, and this is likely to reflect the underpinning cause of fatigability in this group (i.e., peripheral skeletal muscle fatigue associated with the generation of higher muscle forces). In contrast, the inability to generate high MVC force in MS-HF (and hence lower level of overall metabolic effort) could explain why MS-HF show less evidence of peripheral fatigue after a fatiguing task. This result is consistent with the findings of Skurvydas et al. (2011), who showed that while peripheral fatigue in PwMS exists after a fatigability task, it is to a lesser extent than in HC. Therefore, the primary source of MS fatigue is likely to be deficits in central activation (Danion et al., 2000). As VA was similar after the fatiguing task across the groups, this greater relative decline from baseline in HC also suggests they experienced some level of central fatigue despite the greater level of peripheral fatigue observed. The present study also demonstrated reductions in post-fatigue variables (MVC, VA and $Q_{tw,pot}$) in both muscle groups studied (Table 6.2 and 6.3) that were two-fold greater than the TE values reported in the previous Chapter. Therefore,

it can be concluded that such neuromuscular measures are sensitive to detecting changes induced by task-related fatigue in the populations investigated.

The results of the present study extend current knowledge on MS fatigue, suggesting it mainly originates from dysfunction of central nervous system neuronal circuits (i.e., reduced excitability [evidenced by a higher AMT] and increased inhibition). PwMS have several corticospinal abnormalities in comparison to the general population, including higher motor thresholds (Liepert et al., 2005; Morgante et al., 2011; Neva et al., 2016), delayed MEP latencies (Neva et al., 2016), and longer CSP (Tataroglu et al., 2003), which supports the usefulness of transcranial magnetic stimulation as a biomarker of brain functioning in PwMS. However, in the context of MS fatigue, the current knowledge on corticospinal excitability derived from only a few studies have yielded inconsistent outcomes, including the lack of a causal link between intracortical function and voluntary activation (Perretti et al., 2004; Liepert et al., 2005; Morgante et al., 2011). The present chapter builds upon this through a more robustly executed method, suggesting more research is warrants in larger sample sizes. MS-related corticospinal dysfunction mainly suggests a reduction or failure of central inhibitory mechanisms leading to facilitation of MEP amplitude following a fatiguing exercise task (Leocani et al., 2001; Perretti et al., 2004; Thickbroom et al., 2006; Thickbroom et al., 2008). Such adjustments of intracortical circuitry might be linked to the severity of perceived MS fatigue.

In the present study, SICI was reduced in MS-HF in comparison with MS-LF, which was consistent with data from Liepert et al. (2005) but differed from those obtained in two other studies. Morgante et al. (2011) reported no difference in SICI between two groups of patients; and Chalah et al. (2019) found increases in SICI in MS-HF compared with MS-LF. This observed increase in SICI could be due to MS type, as the study groups were primary progressive MS type, in which the likelihood of neuronal damage is significant greater. This study's findings suggest an increased involvement of gamma-aminobutyric acid -inhibitory neurotransmission (Rossini et al., 2015), referred to as gamma-aminobutyric $acid_A$ mechanisms in the processes of cerebral plasticity, and/or the existence of an improper balance between cortical gamma-aminobutyric $acid_A$ inhibitory mechanisms and glutamatergic facilitatory mechanisms as a potential underlying mechanism of perceived MS fatigue (Ayache& Chalah, 2017). It is important to note, that the sample size was relatively smaller in the

above-mentioned studies (n = 16,Liepert et al. (2005); n =21, Morgante et al. (2011), but similar to Chalah et al. (2019), n = 38).

The present study identified a prolonged duration of SP in MS-HF at rest and after the fatigue task. These findings are in accordance with those of Russo et al. (2017), demonstrating greater intracortical inhibition and suggesting the presence of possible motor dysfunction (Tataroglu et al., 2003) and reflect spinal contributions (Yacyshyn et al., 2016). In PwMS, modulation of gamma-aminobutyric acid -ergic activity (more inhibition) has been associated with greater disability (Cawley et al., 2015), though it is unknown whether this phenomenon contributes to MS progression or is a compensatory mechanism to protect the brain and maintain optimal brain function (Stampanoni Bassi et al., 2017; Chaves et al., 2019). Interestingly, longer SPs are indicative of increased intracortical inhibition, greater disability and poorer motor function in other clinical populations, such as Huntington's (Priori et al., 1994b) and stroke (Classen et al., 1997). Therefore, future research into the SP and the relationship with SICI in MS-HF is warranted. Finally, similar to the fatigue related variables, the changes observed in the present Chapter concerning corticospinal excitability and inhibition (see Table 6.2 and 6.3) were greater than the typical error presented in Chapter 5. Therefore, it can be concluded that these measures are sensitive to detecting changes induced by task-related fatigue in the populations investigated.

Differences in Patient-Reported Outcomes Between the Groups

In the present study, MS-HF exhibited worse symptoms of fatigue, mood (anxiety and depression) and pain. These abnormalities may play a role in the pathophysiology of fatigue perception and development, particularly high levels of clinical anxiety and depression (HADS scores) in MS-HF compared to the other groups. This is consistent with a bi-directional causal interaction with fatigue symptoms i.e. fatigue and depression present and effect together (Gobbi et al., 2014a; Finke et al., 2015; Chalah et al., 2019); and resonates with recent work by Chalah et al. (2019) which reported high scores in MS-HF for depression, anxiety and alexithymia. It is possible that MS-HF feel demotivated and melancholic, which might contribute to the accentuation of fatigue and faster fatiguability via the manifestation of new fears and negative thoughts. Additionally, pain was greater in MS-HF compared with HC, despite being similar between the MS groups. Sensory disturbances such as neuralgia, dysesthesia, and painful muscle spasms may be experienced by PwMS and often interfere with sleep, contribute to physical deconditioning and worsen depression (MacAllister et al., 2005;

Krupp et al., 2010). In this way, pain maybe indirectly related to perceived MS fatigue. Sleep quality was also assessed via the PSQI and was presented in all groups. Sleep quality data were similar to previous studies, which used correlation analysis and did not find a significant correlation between measures of sleep quality using the Epworth Sleepiness Scale and total MFIS fatigue scores (Nociti et al., 2017; Chalah et al., 2019). The similarities in sleep quality between the groups could be further explained by multiple overlapping factors such as pain, spasticity, anxiety, depression, bladder dysfunction and medications in PwMS (Kaminska et al., 2012). The lack of difference might also be due to multiple underlying sleep disorders, particular as sleep disorders such as restless legs syndrome, periodic limb movement disorder, and obstructive sleep apnea, are more common in PwMS (Tachibana et al., 1994). Therefore, further investigation into additional measures of sleep quality, such as all-night polysomnograms and daytime multiple sleep latency tests, are warranted to gain further insights into sleep disturbances and fatigue relationships.

6.5 Limitations

Firstly, the majority of PwMS were only mildly affected with relapsing remitting MS, as measured by the EDSS. It is unclear whether in more severely affected PwMS, neurophysiological correlates of perceived MS fatigue show the same patterns of response. In addition, the existence of anxiety and mood reflects more pronounced somatic disturbances in PwMS experiencing high levels of fatigue and this may have affected motivation, thereby influencing the reduced neurophysiological performance and level of exerted effort. Lastly, the cross-sectional design of this study does not allow causal relationships to be drawn from differences in neurophysiological measures and level of MS fatigue being experienced.

6.6 Future Directions

Future research would benefit from the inclusion of neuroimaging techniques, notably magnetic resonance imaging, as identified in Chapter 4, as such techniques can provide more detailed insights into the brain regions and sites of dysfunctional connectivity that may differentiate MS-HF from MS-LF. In respect of the latter, further work into motor tasks which recruit multiple brain areas and muscle groups could provide greater insight in neuromuscular function during more complex tasks that are more characteristic of everyday activities in PwMS and how this is altered in MS-HF. As highly fatigued PwMS appear to demonstrate a greater demand on central components and less peripheral disturbances, research aimed at designing and testing the efficacy of therapeutic interventions (including exercise) that could

optimise corticocortical neuroplastic adaptations may prove to have the greatest impact on perceived MS symptoms and this also warrants further consideration.

6.7 Conclusion

The present study demonstrated that in the resting state and following exercise, MS-HF experience reduced MVC, VA and impaired cortical inhibition. This is likely to result from central nervous system insufficiencies linked to a reduced central motor drive and spinal contributions over peripheral disturbances. In line with the thesis aims, a multidimensional approach using an array of functional neurophysiological measures proved to be a valuable method for investigating the neurobiology of perceived MS fatigue and identifying processes that may contribute to the subjective experience of this debilitating symptom and impaired motor task performance (fatigability). The next Chapter will explore progressive resistance exercise as a potential therapeutic exercise modality for ameliorating perceived MS fatigue and modulating neurophysiological pathways that differentiated MS-HF from MS-LF in the present study.

CHAPTER 7–Progressive Resistance Exercise in Fatigued People with Multiple Sclerosis: A Randomised Controlled Feasibility Study

7.1 Introduction

Around ~78% of PwMS do not participate in minimum recommended guidelines for meaningful physical activity (Marrie et al., 2009). However, Somerset et al. (2001) reported that exercise advice is one of the most common unmet needs of PwMS. Exercise is a safe, non-pharmacological treatment strategy for improving health and wellbeing in PwMS, with recent systematic reviews highlighting many health benefits, including improvements in muscle power, physical and psychosocial functioning, as well as health-related quality of life (Rietberg et al., 2005b; Motl et al., 2008; Asano et al., 2009). Other positive effects include mood/depression (Ahmadi et al., 2013; Briken et al., 2014) and cognitive disturbances (Sangelaji et al., 2016). Exercise has also been shown to mitigate fatigue and be an effective strategy for managing symptoms of MS fatigue (Ahmadi et al., 2013; Schmidt & Wonneberger, 2013; Learmonth et al., 2014), which has been shown to be a problem for PwMS in the previous Chapter. Conversely, MS fatigue symptoms may be exacerbated by lower physical activity levels (Motl et al., 2008; Motl & Gosney, 2008).

A review of the literature by Andreasen et al. (2011) suggested that progressive resistance exercise (PRE) might have more consistent fatigue-reducing effects than aerobic exercise, although fewer well controlled trials had studied this exercise modality (Andreasen et al., 2011). For example, studies have reported improvements in fatigue and physical capacity following 8-12 week programmes of twice-weekly PRE (White et al., 2004; Gutierrez et al., 2005; Dalgas et al., 2010; Dodd et al., 2011), whereas in some studies, higher volumes of aerobic exercise (e.g. thrice-weekly aerobic exercise for 12-15 weeks) showed no effect (Petajan et al., 1996; Geddes et al., 2009). Furthermore, aerobic exercise can present problems for PwMS with ambulatory difficulties and can raise the body's core temperature to levels that may exacerbate MS symptoms in thermosensitive individuals (Davis et al., 2010). PRE can overcome both these problems, as exercises can be performed in fully supported (or seated) positions and core temperature does not increase to the same extent (Gutierrez et al., 2005). Limited evidence of adverse events or symptom exacerbations in studies of PRE have been reported in PwMS (Dalgas et al., 2010).

PwMS face distinctive barriers to participation in physical activity, including lack of confidence, anxiety, and embarrassment (Becker & Stuifbergen, 2004; Yorkston et al., 2005; Borkoles et al., 2008; Brown et al., 2012; Klaren et al., 2013), physical (fatigue, pain, overheating, muscle weakness, poor mobility, see review by Halabchi et al. (2017)) and

environmental factors (lack of facilities, transport and costs (Becker & Stuifbergen, 2004; Rimmer et al., 2004; Sim & Lewis, 2012). Thus, accessible forms of exercise and maintenance of exercise-induced fatigue reduction are other important considerations and strategies that can facilitate regular long-term participation in exercise are clearly warranted. Home-based PRE may a good therapeutic strategy to this end, as it is easily transferrable to the home environment (Normandin et al., 2018). One study reported excellent adherence to home-based PRE and flexibility exercises with subsequent improvements in activities of daily living in patients with knee osteoarthritis, reinforcing the notion that patients with long-term conditions proactively engage in home-based PRE (Suzuki et al., 2019). In addition, a study that encouraged PwMS to continue PRE after a 12-week period of supervision, reported a sustained improvement in fatigue, though this was not statistically significant (Dalgas et al., 2010). More research is clearly needed to expand current knowledge and studies focused exclusively on PRE in PwMS reporting high levels of self-reported fatigue are clearly warranted.

To date, no studies have focused exclusively on PRE in PwMS reporting high levels of perceived fatigue. The significance of investigating the effects of exercise and other therapeutic interventions on MS fatigue in a heterogeneous sample of PwMS experiencing high and low levels of this debilitating symptom is questionable, and might explain the lack of effect of exercise on self-reported fatigue in previous studies (Petajan et al., 1996; DeBolt & McCubbin, 2004; Schulz et al., 2004; van den Berg et al., 2006; Newman et al., 2007; Geddes et al., 2009). In addition, only three previous exercise intervention studies have investigated MS fatigue as a primary outcome measure: two short duration aerobic exercise studies in fatigued PwMS reporting that the exercise intervention had no effect (Mostert & Kesselring, 2002; Surakka et al., 2004a), and a third study by Rasova et al. (2006) that included a non-fatigued control group in a comparison of intervention groups, compromising the validity of their positive findings. This lack of evidence supports the requirement for more high-quality randomised control trials to assess the potential fatigue-reducing effects of PRE in PwMS, and with a secondary aim of incorporating skills into long-term self-management strategies.

As a first step, there is a need for feasibility studies to address a series of questions surrounding issues of acceptability, adherence to PRE and attrition in PwMS experiencing clinically important levels of MS fatigue. Thus, the primary aim of this study was to evaluate the feasibility of undertaking a randomised controlled trial aimed at investigating the effectiveness of PRE (part supervised, part home-based) in relation to perceived fatigue and other important

health outcome in people experiencing high levels of MS fatigue.

7.2 Methods

7.2.1 Participants

Following ethical approval (3.2.1 Ethical Approval: Institution: HLSPE010216 and National Health Service: 16/SS/0142) and informed consent (3.3.2 Informed Consent), 33 highly fatigued PwMS (MS-HF) were recruited over a 12-month period from MS clinics at the Newcastle University Teaching Hospitals National Health Service Foundation Trust (Royal Victoria Infirmary). This conforms to guidance on feasibility and pilot studies, with justification that a sample size of 24 – 50, with 10 to 20 participants per group is recommended as sufficient and appropriate for determining variability data for key outcome measures to be used in sample size calculations for a larger trial (Dobkin, 2009; Sim & Lewis, 2012; Plow et al., 2013). All participants met the criteria for participation (see 3.3 Participants); aged over 18 years, fulfilled the McDonald criteria (Poser et al., 1983; McDonald et al., 2001), had an EDSS score (Kurtzke, 1983) of <4.5 and clinically-important levels of fatigue defined by a fatigue severity score (FSS) cut-off score ≥5 (Krupp et al., 1989). Participants were also stable on disease modification therapy for ≥3 months prior to recruitment. All were right-handed and had normal function of the right limbs (Oldfield, 1971). Participants were excluded if they experienced relapses within the preceding 3 months, had other illnesses substantially affecting their ability to exercise (confirmed by consultant physician) or who were already physically active (≥2 × per week of ≥30 min of moderate to vigorous exercise during the previous 3 months) and left-handed. Of the thirty-three participants, 16 were randomised to the PRE group and 17 to the control group. Table 7.1 presents the participant characteristics.

Table 7.1 Characteristics of the resistance PRE and usual care control group.

	PRE	**Control**
N	16	17
Age (years)	51.7 ± 9.3	48.2 ± 7.7
Gender (F/M)	12/4	11/6
EDSS (arbitrary units)	2.7 ± 1.4	3.3 ± 5.3
Disease Duration (years)	10.8 ± 4.5	8.8 ± 4.4
Fatigue Severity Scale	6.1 ± 0.6	5.7 ± 0.6
Disease modification	13/3	15/2
Therapy (Y/N)		
- *Tecfidera*	5	3
- *Copazone*	3	5
- *Tysabri*	1	1
- *GiLenya*	1	4
- *Avonex*	1	-
- *Lemtrada*	2	-
- *Rebrif*	-	1
- *Aubagio*	-	1
Other comorbidities (Y/N)	6/10	5/12
- *Osteoporosis*	1	1
- *Arthritis*	2	-
- *Trigeminal neuralgia*	-	1
- *Fibromyalgia*	1	2
- *Underactive thyroid*	2	1

*Data are presented as Mean ± SD. * Significance p value <0.05. HC: Healthy Control; MS-LF: Less-Fatigued People with Multiple Sclerosis; MS-HF: Highly Fatigued People with Multiple Sclerosis N: Numbers; F: Females; M: Males; EDSS: Extended Disability Status Scale; Y: Yes; N: No.*

7.2.2 Experimental Protocol

This feasibility study was a parallel randomised controlled trial and it was not possible to blind the research team or the participant to group assignment. Participants were randomised on a 1:1 basis (random selection without replacement) using a computer programme (nQuery Advisor 6.0, Statistical Solutions, Ireland) to either a PRE group or a usual-care control group (CG). Consistent with CONSORT guidelines (Schulz et al., 2010), this was performed by an external researcher not involved in the team and treatment allocation was not disclosed to the lead researcher responsible for the day to day supervision of the trial, until all baseline measures had been recorded. Participants visited the laboratory on three separate occasions for each assessment point (baseline, 6-week follow-up 1 and 12-week follow-up 2). Each assessment point involved two separate visits to record neuromuscular assessments of the lower-limb (knee-extensor) and upper-limb (wrist-flexor) muscles as well as patient reported outcomes, conducted at the same time of day within a time period of 2-14 days. Participants randomised to PRE, engaged in 6-weeks of supervised PRE, followed by 6-weeks of home-based PRE. The

control group received no external advice or support and both groups received normal clinical care. Figure 7.1 presents a schematic of the study design.

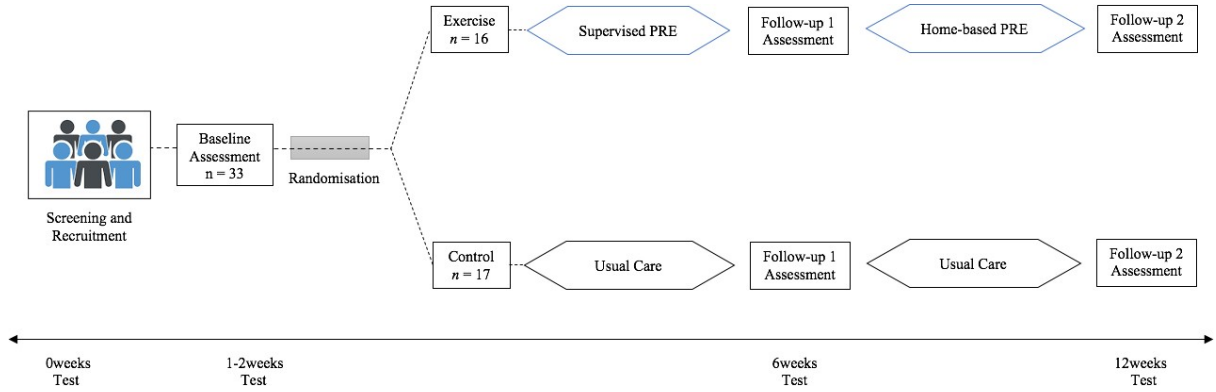

Figure 7.1. Schematic of study design, illustrating screening and recruitment through to follow up assessments.

7.2.2 PRE-Intervention

Supervised PRE

The PRE intervention consisted of 6-weeks of supervised whole body PRE, performed twice weekly and consistent with the ACSM guidelines for prescription of PRE training ("American College of Sports Medicine position stand. Progression models in resistance training for healthy adults," 2009). Training sessions were organised for Mondays and Fridays, allowing participants time to recover between sessions (Carroll et al., 2017) with alternative training sessions offered if needed, to maintain twice-weekly attendance. The training sessions were arranged so that participants could exercise together in small groups (maximum of 6), as participant enjoyment after exercise sessions has been shown as an important determinant of physical activity behaviour and associated with greater adherence to exercise prescription in PwMS (McAuley et al., 2007). Each session comprised of warm-up mobility exercises, followed by 10 PREs (of 1–3 sets of 10–15 repetitions) targeting large skeletal muscle groups of the upper and lower extremities using bodyweight and coloured elastic *Therabands*, and a cool-down of stretching exercises (see review by Aboodarda et al. (2016) and "American College of Sports Medicine position stand. Progression models in resistance training for healthy adults" 2009) The prescribed whole-body exercises incorporated balance tasks (e.g. hip flexion, hip extension, hip abduction and hip adduction), knee extension and flexion, bicep

curls, and wrist flexion and wall/chair supported squat. Exercises were designed to mimic functional everyday activities such as, wrist flexion (grip capabilities and carrying an object movement (Jarque-Bou et al., 2020)) and standing supported squats (i.e. standing and sitting movement (Lubans et al., 2010; Lloyd et al., 2014)). Figure 7.2 below presents some of the resistance training theraband exercises.

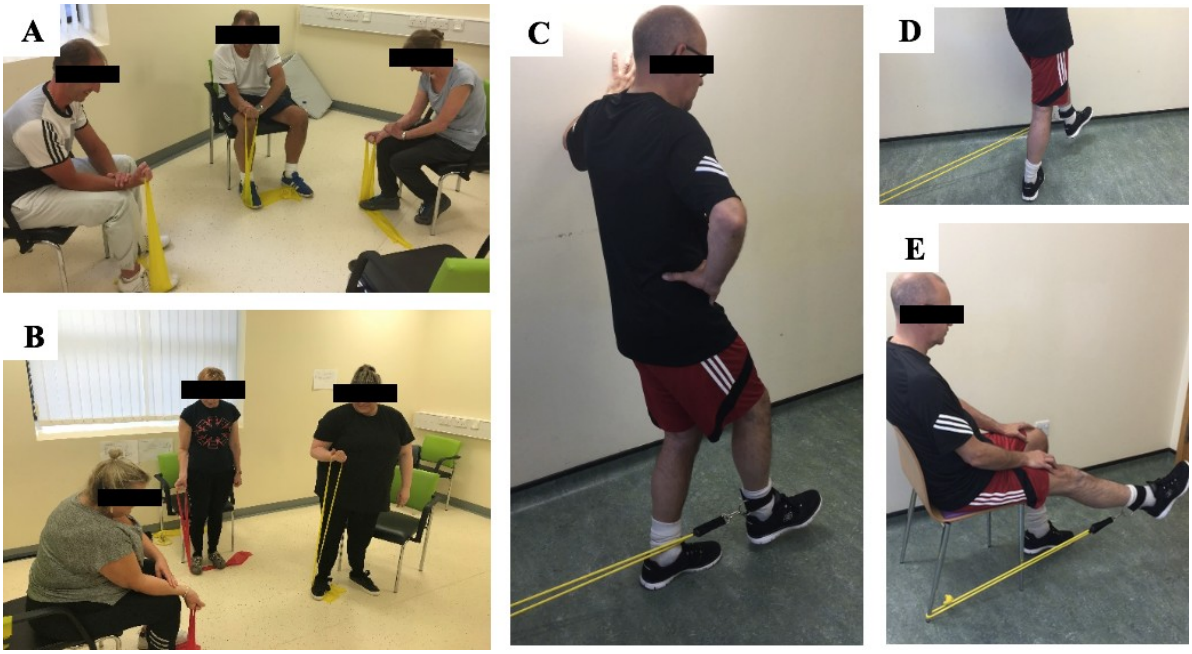

Figure 7.2 Participants in the PRE group demonstrating some of the upper- and lower- limb theraband resistance exercises, **(A)** seated wrist-flexion, **(B)** standing and seated bicep curl, **(C)** hip- flexion, **(D)** hip -abduction and **(E)** seated knee-extension.

A controlled progression of the applied load, range of motion and angular velocity in a progressive manner to a muscle group has shown to improve muscle strength (Matheson et al., 2001). Progression of resistance training was determined on the basis of individual capability and facilitated by the lead researcher by changing the level of resistance/difficulty (i.e., colour) of elastic band, the amount of tension to each band, increasing the number of sets and repetitions and level of difficulty (e.g., changing exercise position from sitting to standing). Using the rating of perceived exertion (rating perceived exertion; Borg (1982)), beginning at "very light" (9/20) and progressing to "somewhat hard" (13/10) during weeks 1-3, and continuing to increase the Theraband tension and colour to maintain the rating perceived exertion "somewhat hard". This progression method allowed participants to train to the

requisite rating perceived exertion to improve motor performance (used to the movement) by building a better tolerance to a greater stimulus.

Audible cueing

A metronome (MetroTimer) was used to pace each muscle action, with the speed of each repetition paced at a cadence of 60 beats·min^{-1}. Each repetition was performed for a total of 7 s (3 s concentric phase and 4 s eccentric phase). As co-ordinated movements and rhythmic perception are intuitively connected, with a connection between the cerebral auditory and motor system (Grahn & Brett, 2007; Chen et al., 2008), this suggests that movements synchronised to sound might improve connectivity between motor and auditory areas with increased rhythmic complexity (Thaut & Thaut, 2005; Thaut et al., 2009; Leung et al., 2017)

Home-based PRE

The home-based component of the intervention consisted of 6-weeks of PRE, two self-directed home-based exercise sessions per week. Home-based exercise sessions mirrored the supervised-based sessions in terms of the skeletal muscle groups targeted, intensity and duration. Fortnightly telephone contacts from the lead researcher during this period ensured that support was maintained, and that PRE programme was properly progressed with completion of an exercise logbook and diary. Participants had the opportunity to discuss any issues/questions arising from home-based exercises, with the aim of helping promote independent exercise participation following the intervention.

7.2.4 Usual Care Control Group

Participants in the control group were advised to maintain usual national health service care. At the end of the study, a one-on-one exercise consultation was offered, along with supporting exercise goals and objectives and two further sessions were arranged to run through their PRE programme with a *Theraband* demonstration.

7.2.5 Assessment of Outcomes

7.2.5.1 Primary Outcomes

Feasibility

Feasibility was assessed via recruitment rate to the study, acceptability of the intervention, adherence to PRE, attrition, and appropriateness/acceptability of the outcome measures. Figure 7.3 presents the feasibility outcomes and methods of measurement. Adverse events were also

monitored throughout the study.

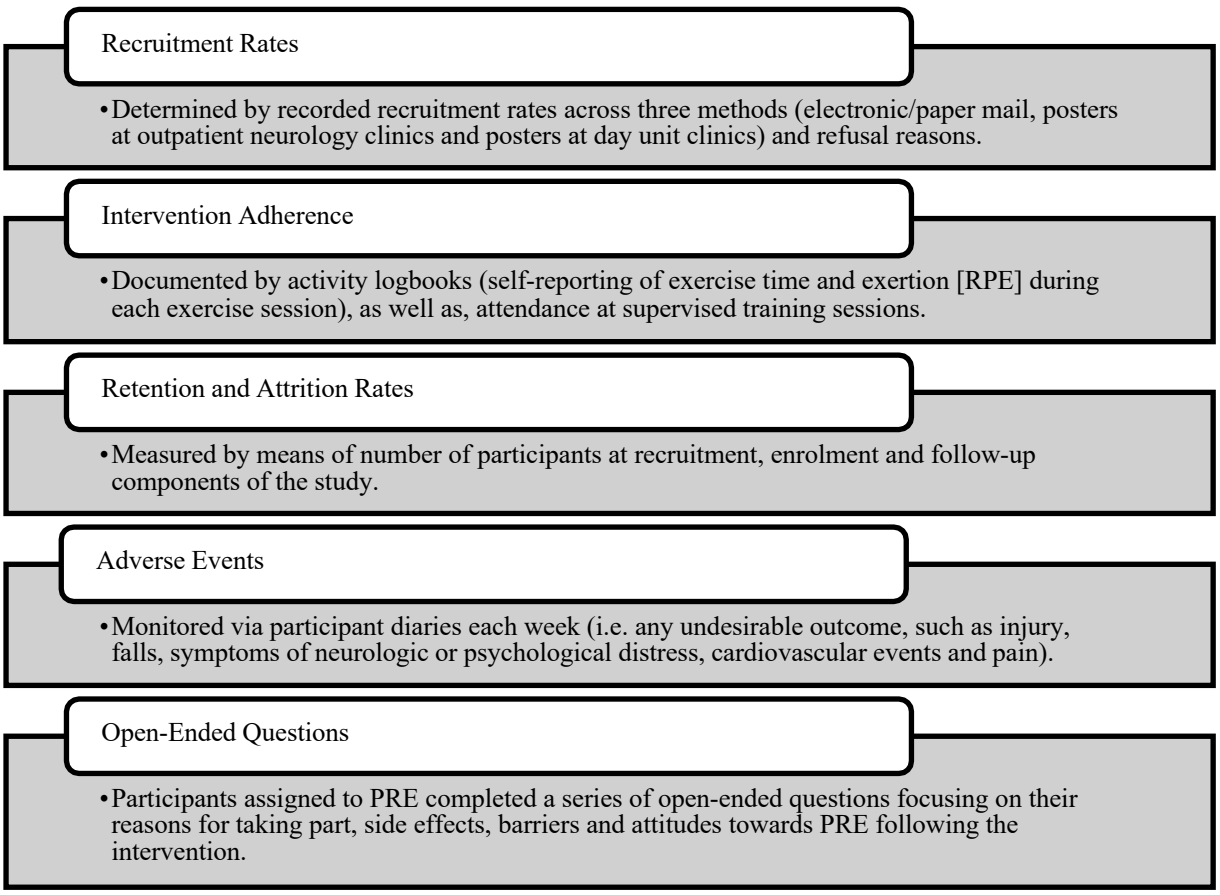

Figure 7.3 Feasibility was measured by recruitment rates, acceptability of the intervention, compliance and attrition, and appropriateness of outcome measures.

Perceptual Measures and Patient Reported Outcomes

Self-reported fatigue scales recorded severity, frequency and impact of fatigue in everyday life and were completed at the beginning of each follow up assessment (3.9.1 Fatigue Severity Scale, Modified Fatigue Impact Scale, and Chalder Fatigue Scale). Depression and anxiety scores using the Hospital Anxiety and Depression Scale (HADS, refer to 3.9.2 Anxiety and Depression), sleep quality using the Pittsburgh Sleep Quality Index (PSQI, refer to 3.9.3 Sleep Quality), and pain using NARCOMS scale (refer to 3.9.4 Pain), were also monitored with lower scores indicating better fatigue and health outcomes. Quality of life was assessed using the Multiple sclerosis Quality of Life-54 scale (refer to 3.9.5 Quality of Life), with higher scores reflecting a better QOL.

7.2.5.1 Secondary Outcomes

Neurophysiological Assessment

All participants attended one familiarisation session and two experimental visits (wrist flexor and knee extensor measures). Each visit involved 35 minutes of resting neuromuscular data collection and a sub-maximal intermittent exercise task to task failure (refer to 3.7.2 Sub-maximal Test Protocol). With regard to neuromuscular measurements, the set-up largely followed Chapters 5 and 6 with force of the right wrist flexor and knee extensor muscles recorded using a custom-made adjustable isometric dynamometer. Participants received continuous feedback of their force via a computer screen.

7.2.6 Data Analysis of Neurophysiological Data

As in previous Chapters, voluntary activation using motor nerve stimulation, was determined using the interpolation twitch technique (Allen et al., 1998) by comparing the amplitude of the SIT with the amplitude of the $Q_{tw.pot}$ using the formula: VA (%) = (1 – [SIT ÷ $Q_{tw, pot}$]) × 100) (See Chapter 3 = 3.7.1 Voluntary Activation). SICI was quantified as the ratio between the amplitude of conditioned MEPs to the amplitude of unconditioned MEPs. Corticospinal excitability was determined as the mean MEP amplitude during the 10% MVC as a percentage of M_{max}. Additionally, MEPs contaminated by artefact or showing evidence of voluntary activation during the pre-stimulus period were excluded. The root-mean-square of EMG activity (rmsEMG) was also recorded during the middle 500 ms epoch of a 3 s maximal contraction. All data analysis was performed offline using Spike 2 (v6, CED, UK).

7.2.7 Statistical Analysis

Data were analysed using SPSS for Windows version 18.0 (SPSS Inc., Chicago, Illinois, USA). Data were first checked for normality using Kolmogorov–Smirnov test and found to be normally distributed. Sphericity was assessed using Mauchly's test and if necessary, controlled using the Greenhouse-Geisser correction. To determine whether PRE group improved more than control group after 6-weeks and 12-weeks program, neurophysiological and patient report outcomes data were analysed by one-way (i.e., condition) analysis of covariance (ANCOVA), using baseline values as the covariate. Comparing differences between groups at each time point (baseline values at 6-weeks and 12- weeks), is a method that has been recommended for the analysis of continuous data measured at baseline and follow-up in randomised controlled trial (Vickers et al., 2001; 2005). Standardised mean differences and 95% confidence intervals (CI) were calculated from post intervention means and standardised deviation (SD; Hedges and

Olkin, 1985). If significant group (i.e., PRE vs Control group) effects were found, analyses were continued using pairwise comparisons using the Bonferroni correction. Intention to treat analysis was applied, with all participants who were allocated and commenced their program included in analysis. To interpret clinical significance of any statistically significant between group differences, typical error from Chapter 5 of this thesis were accepted as clinically important differences. Statistical significance was determined as an alpha of 0.05. Results are presented as mean (± SD) at each time point. As this was a feasibility study, changes in outcome data are considered to be preliminary, and a cautious approach to interpretation has been taken.

7.3 Results

7.3.1 Participants

Descriptive characteristics of the study participants are shown in Table 7.1. No significant differences in demographic or clinical characteristics were found between the PRE and control groups. Both groups were largely female (PRE: 75% and Control: 65%). Additionally, 38% of PRE group and 29% of control group reported other comorbidities including, osteoporosis, trigeminal neuralgia, fibromyalgia and underactive thyroid. Many were stable on disease modification treatments throughout the course of the study (PRE: 81% and Control: 88%; including, Tecfidera n = 8, Copazone n = 8, Tysabri n = 2, GiLenya n = 5, Avonex n = 1, Lemtrada n = 2, Rebrif n = 1 and Aubagio n = 1).

7.3.2 Primary Outcomes

Recruitment and Retention

336 PwMS were screened for study eligibility from one site, with 33 (10%) fulfilling the inclusion criteria. Most PwMS did not meet the rigorous inclusion criteria (n = 260), due to diagnosis of later MS stages (primary progressive or secondary progressive MS), reported by the consultant as patients having EDSS >4.5 (n = 212) or because of a recent relapse (n = 48). Other reasons included, lack of interest (N = 3), undergoing change to disease-modification treatment (N = 22) or lived too far away (N = 18). Between 2017 and 2019, 15 (94%) PRE and 15 (88%) control group patients completed the supervised phase of the study with reasons for premature discontinuation including, unable to contact (N=2), and one participant had a relapse and withdrew themselves. Fourteen (88%) PRE and 13 (77%) control group patients completed the home-based phase of the study with reasons for premature discontinuation including, unable to commit to the study (N=2) and with one participant having a relapse and withdrawing themselves (Refer to Appendix 24).

Intervention Adherence and Adverse Events

Mean adherence to the supervised PRE was good with 90 ± 7% (range 75-100%) of the 15 patients attending 9 ± 1 sessions' from a total of 12 planned sessions (range 9 – 12 sessions). Missed sessions were caused by overwhelming fatigue (n = 4), relapse (n = 1) and reported illness (n = 1). Adherence to the home-based PRE was good with the 14 patients attending 79 ± 10% (range 67-100%) of the 12 supervised sessions (range 8 – 12). Missed sessions were caused by overwhelming fatigue (n = 5), difficulty finding the time (3) and relapse (n = 1). No PRE-induced symptom exacerbations and/or adverse events such as falls resulted from the PRE programme.

Participant Feedback

Around 85% of participants felt confident they would continue with PRE after the intervention. When asked during the exist debrief questions about feelings during and after PRE, 93% (n = 13) gave positive comments, with remarks such as '*PRE made me feel less sluggish throughout the day'*, '*use my stairs with ease'*, and that '*my balance and walking ability had improved'*. Following PRE, 36% (n = 5) reported feeling '*happier and more self-confident'*, 50% (n = 7) reported that they '*felt tired at first, but this improved'* and 14% (n = 2) continued to feel occasional tiredness, but this was reported as manageable. All participants liked the session structure because it was tailored and progressed gradually, and that they enjoyed using the metro-timer and exercising as a group. However, 29% (n = 4) suggested that a wider variety of balance and/or yoga would have been suitable.

7.3.3 Secondary Outcomes

Overview

The outcome assessments provided robust measurements of participant's neurophysiological and self-reported measures. In the intervention group, patient reported measures and neurophysiological outcomes were obtained in 15 patients (94%) at 6-weeks follow-up due to inability to contact and 14 patients (88%) at 12-weeks follow-up because of time commitment. In the control group, patient reported measures and neurophysiological outcomes were obtained in 15 patients (94%) at 6-weeks follow-up due to relapse occurrence and inability to contact and 13 patients (77%) at 12-weeks follow-up because of relapse occurrence and time commitment (Appendix 6.7).

Effects of PRE on perceived fatigue differences between PRE and control groups

At 6- and 12-weeks of follow-up, differences between the exercise and control group were shown in MFIS, in favour of PRE (6-weeks: $F_{(1, 27)} = 19.612$, $p = 0.001$, $\eta_p^2 = 0.42$; 12-weeks: $F_{(1, 24)} = 10.122$, $p = 0.004$, $\eta_p^2 = 0.29$; Figure 7.4B). No differences were observed between the PRE and control groups post intervention for the FSS or CFS fatigue scales (Figure 7.4A, Table 7.2).

Effects of PRE on Depression, Anxiety, Sleep and Pain between PRE and control groups

At 6-weeks of follow-up, a difference between the exercise and control group was observed in HASDS ($F_{(1, 27)} = 11.759$, $p = 0.002$, $\eta_p^2 = 0.30$) and HADS-Anxiety ($F_{(1, 27)} = 12.726$, $p = 0.001$, $\eta_p^2 = 0.32$). This was also shown at 12-weeks of follow-up in HADS ($F_{(1, 24)} = 10.843$, $p = 0.003$, $\eta_p^2 = 0.31$) and HADS-Anxiety ($F_{(1, 24)} = 9.109$, $p = 0.006$, $\eta_p^2 = 0.28$). The PRE group had reduced symptoms of mood and anxiety versus the controls (Figures 7.4 D & E). Pain at 6- and 12-weeks of follow-up showed differences in favour of the PRE group (6-weeks: $F_{(1, 27)} = 7.679$, $p = 0.010$, $\eta_p^2 = 0.22$; 12-weeks: $F_{(1, 24)} = 6.283$, $p = 0.019$, $\eta_p^2 = 0.21$). Also, QOL-Physical ($F_{(1, 27)} = 4.985$, $p = 0.034$, $\eta_p^2 = 0.16$) and QOL-Mental ($F_{(1, 27)} = 6.571$, $p = 0.016$, $\eta_p^2 = 0.20$) at 6-weeks of follow-up showed differences in favour of the PRE group. This was also shown at 12-weeks follow up in QOL-Physical ($F_{(1, 24)} = 4.873$, $p = 0.037$, $\eta_p^2 = 0.17$) and QOL-Mental ($F_{(1, 24)} = 14.410$, $p = 0.001$, $\eta_p^2 = 0.38$; Figure 7.4 G , H & I). There were no differences between the PRE and control group post-intervention for sleep quality (PSQI) or HADS-Depression (Table 7.2).

Table 7.2 Self-reported fatigue and patient reported Outcomes Mean (SD) of groups, mean (SD) difference within groups, and mean difference (95%CI) between groups

Outcome	Groups						Difference within groups				Difference between groups	
	Baseline		6-Weeks Follow-Up		12-Weeks Follow-Up		6-Weeks Follow-Up - Baseline		12-Weeks Follow-Up - Baseline		6-Weeks Follow-Up - Baseline	12-Weeks Follow-Up - Baseline
	PRE (n =16)	CON (n =17)	PRE (n =15)	CON (n =15)	PRE (n =14)	CON (n =13)	PRE	CON	PRE	CON	PRE-CON	PRE-CON
Perceived Fatigue Outcomes												
FSS	6.1 (0.6)	5.7 (0.6)	5.9 (0.7)	5.7 (0.6)	5.8 (0.7)	5.6 (0.6)	-0.2 (0.2)	0.0 (0.2)	-0.3 (0.3)	-0.1 (0.3)	-0.1 (-0.3 – 0.2)	-0.2 (-0.4 – 0.1)
MFIS	47.0 (11.6)	49.9 (8.9)	41.9 (8.3)	50.1 (8.4)	42.9 (8.1)	47.9 (8.5)	-5.2 (7.2)	1.6 (2.6)	-4.4 (5.9)	-0.4 (3.3)	-7.2 ** (-10.6 – -3.9)	-4.3 ** (-7.1 – -1.5)
CFS	6.9 (2.3)	6.5 (2.5)	6.8 (2.5)	7.0 (2.3)	7.0 (2.3)	6.8 (2.2)	0.1 (1.3)	0.2 (1.9)	0.2 (1.5)	-0.3 (1.9)	-0.1 (-1.4 – 1.1)	0.4 (-0.9 – 1.7)
Patient Reported Outcomes												
HADS	14.1 (5.6)	12.5 (3.2)	12.1 (3.6)	13.5 (3.2)	11.7 (3.3)	13.7 (2.7)	-1.9 (3.1)	0.9 (2.1)	-2.3 (3.7)	0.9 (3.0)	-2.2 ** (-3.6 – -0.9)	-2.5 ** (-4.1 – -1.0)
HADS-Anxiety	8.1 (4.1)	7.5 (3.1)	7.0 (3.1)	8.1 (2.4)	7.3 (2.9)	8.0 (1.7)	-1.2 (1.9)	0.5 (1.4)	-1.2 (1.9)	0.5 (2.1)	-1.5 ** (-2.4 – -0.6)	-1.3 ** (-2.2 – -0.4)
HADS-Depression	6.0 (2.6)	5.0 (2.6)	5.1 (1.8)	5.3 (2.5)	4.4 (1.7)	5.7 (2.1)	-0.7 (2.1)	0.4 (1.7)	-1.1 (2.4)	0.4 (2.4)	-0.8 (-1.9 – 0.4)	-1.3 (-2.7 – 0.1)
NARCOMS Pain	2.2 (1.3)	1.6 (1.4)	1.7 (1.3)	1.7 (1.2)	1.8 (1.3)	1.8 (1.0)	-0.5 (0.5)	0.1 (0.5)	-0.4 (0.6)	0.2 (0.6)	-0.5 ** (-0.8 – -0.1)	-0.5 * (-0.9 – -0.1)
PSQI	9.4 (4.1)	8.6 (4.0)	8.2 (3.8)	9.1 (3.2)	8.2 (3.7)	8.7 (3.2)	-1.3 (1.0)	0.1 (2.8)	-1.3 (1.7)	0.3 (2.6)	-1.2 (-2.6 – 0.1)	-1.3 (-2.8 – 0.2)
MSQOL-Physical	57.9 (18.0)	53.7 (14.1)	65.6 (13.9)	55.8 (15.2)	64.9 (14.5)	55.9 (14.3)	6.5 (9.6)	0.2 (9.1)	6.3 (12.2)	-1.5 (8.1)	7.1 * (5.7 – 13.5)	7.9 * (0.5 – 15.3)
MSQOL-Mental	61.0 (18.0)	55.6 (13.1)	67.5 (16.1)	58.2 (14.5)	70.6 (16.1)	58.2 (14.1)	8.7 (6.0)	0.6 (10.9)	12.9 (7.6)	-0.4 (10.4)	8.2 * (1.6– 14.7)	13.0 ** (6.0 – 20.1)

PRE, progressive resistance exercise group; CON, control group; FSS, fatigue severity scale; MFIS, modified fatigue impact scale; CFS, chalder fatigue scale; HADS, hospital and depression scale; HADS-Anxiety; hospital and depression scale-anxiety, HADS-Depression ; hospital and depression scale-depression, PSQI; pittsburgh sleep quality index, MSQOL; multiple sclerosis quality of life. *$p < 0.05$, **$p < 0.01$

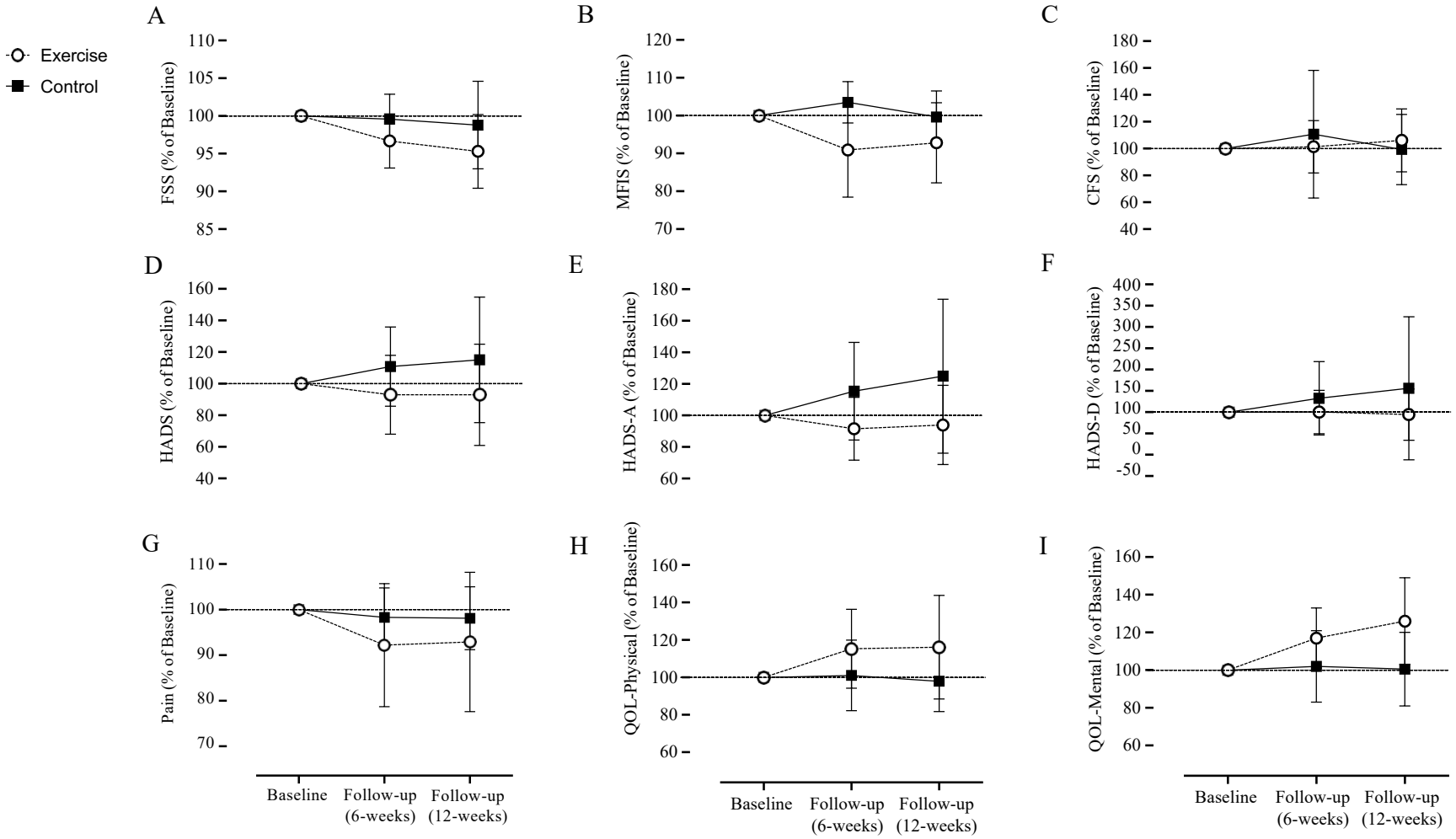

Figure 7.4 FSS (A), MFIS (B), CFS (C), HADS (D), HADS-Anxiety, (E), HADS-Depression (F), Pain (G), QOL-Physical (H), and QOL-Mental (I) all expressed as a percentage of baseline before and 6, 12-weeks follow-up in the exercise group (open circles) and control group (closed squares).

7.3.4 Effects of PRE on Lower-Limb Neurophysiological Measures between PRE and control groups

Neuromuscular measures

At 6-weeks of follow-up differences were shown between the PRE and control group in MVC $F_{(1, 27)} = 7.727$, $p = 0.010$, $\eta_p^2 = 0.22$ and VA $F_{(1, 27)} = 33.150$, $p < 0.001$, $\eta_p^2 = 0.55$. A greater increase in MVC and VA occurred in the PRE group (see Figure 7.5A & E). No differences were observed between the PRE and control groups for MVC or VA at 12-weeks of follow-up. Additionally, no difference in $Q_{tw, pot}$ was observed between the PRE and control group at any of the post-intervention follow-ups (see Table 7.3). However, M_{max} was different in favour of the PRE group at the 6-week follow-up ($F_{(1, 27)} = 5.647$, $p = 0.025$, $\eta_p^2 = 0.17$) and 12-week follow-up ($F_{(1, 24)} = 7.412$, $p = 0.012$, $\eta_p^2 = 0.24$).

Fatiguability

There was no difference in TTF between the PRE and control groups at 6-weeks of follow-up ($p = 0.113$) but a difference in favour of the PRE group was observed at 12-weeks of follow up ($F_{(1, 24)} = 7.865$, $p = 0.010$, $\eta_p^2 = 0.25$). There were no differences between the groups at any follow-up time-point in the rate of force decline (Table 7.3).

Corticospinal and Inhibitory measures

At 6-weeks of follow-up improvements in MEP amplitude and SP appeared to be greater in the PRE group versus control, but between-group differences were not observed (Figure 7.5H & I; MEP amplitude, $p = 0.055$ and SP duration, $p = 0.077$ and). Neither were there any differences between the PRE group and controls for SP at 12-weeks of follow-up, or for MEP/M_{max}, SICI and rmsEMG at any follow-up time-point (Table 7.3).

Table 7.3 Neurophysiological measures in lower-limb (knee-extensors). Mean (SD) of groups, mean (SD) difference within groups, and mean difference (95%CI) between groups

Outcome	Groups						Difference within groups				Difference between groups	
	Baseline		6-Weeks Follow-Up		12-Weeks Follow-Up		6-Weeks Follow-Up - Baseline		12-Weeks Follow-Up - Baseline		6-Weeks Follow-Up - Baseline	12-Weeks Follow-Up - Baseline
	PRE (n=16)	CON (n=17)	PRE (n=15)	CON (n=15)	PRE (n=14)	CON (n=13)	PRE	CON	PRE	CON	PRE-CON	PRE-CON
MVC (N)	336.4 (81.4)	352.7 (105.9)	403.3 (78.5)	352.4 (107.6)	398.7 (89.0)	344.1 (91.1)	64.1 (40.6)	9.7 (63.3)	54.9 (47.6)	21.4 (58.4)	54.0 * (14.2 – 93.9)	35.8 (-7.0 – 78.6)
$Q_{tw, pot}$ (N)	121.4 (23.6)	128.7 (43.5)	130.9 (25.7)	130.1 (40.6)	122.8 (25.6)	131.2 (43.5)	7.2 (9.4)	3.5 (18.6)	-2.0 (15.3)	8.1 (18.6)	3.4 (-7.7 – 14.5)	-9.8 (-23.3 – 3.8)
VA (%)	88.7 (3.6)	90.8 (3.3)	91.6 (2.2)	91.2 (2.7)	90.9 (2.7)	91.4 (3.1)	2.9 (1.9)	0.3 (1.1)	2.4 (2.4)	0.6 (1.4)	2.7 ** (1.8 – 3.7)	1.0 (-0.3 – 2.3)
TTF (mins)	10.3 (5.7)	12.7 (8.2)	12.7 (6.4)	13.5 (7.8)	13.2 (6.4)	11.9 (6.2)	2.1 (2.3)	0.0 (3.6)	2.5 (2.1)	-1.0 (3.9)	1.9 (-0.5 – 4.2)	3.1 * (0.8 – 5.3)
Rate of force decline (N·Min)	-17.0 (12.9)	-14.7 (9.5)	-13.8 (7.4)	-11.6 (5.8)	-13.1 (6.5)	-14.4 (13.8)	3.5 (9.8)	0.7 (6.3)	4.9 (11.9)	-2.5 (11.9)	-0.3 (-4.3 – 3.7)	3.7 (-4.6 – 12.1)
M_{max} (mV)	4.6 (1.5)	5.1 (1.3)	5.8 (1.7)	5.3 (1.0)	5.9 (1.5)	5.0 (0.9)	1.2 (1.1)	0.3 (0.9)	1.1 (1.1)	0.2 (0.9)	0.8 * (0.1 – 1.5)	0.9 * (0.2 – 1.8)
MEP Amplitude	0.6 (0.3)	0.6 (0.3)	0.9 (0.6)	0.7 (0.4)	0.9 (0.5)	0.7 (0.4)	0.3 (0.3)	0.1 (0.2)	0.3 (0.3)	0.1 (0.2)	0.17 (-0.04 – 0.4)	0.2 (-0.01 – 0.4)
MEP/Mmax (%)	14.3 (7.5)	12.7 (10.2)	15.3 (8.1)	13.5 (9.3)	16.0 (7.6)	13.2 (8.8)	0.5 (5.6)	0.0 (4.4)	1.4 (5.6)	-1.0 (5.9)	0.0 (-0.03 – 0.04)	0.0 (-0.03 – 0.05)
rmsEMG (mV)	0.6 (0.3)	0.6 (0.2)	0.7 (0.3)	0.6 (0.2)	0.7 (0.3)	0.6 (0.2)	0.2 (0.3)	0.0 (0.3)	0.1 (0.3)	0.0 (0.1)	0.1 (-0.05 – 0.32)	0.1 (-0.2 – 0.3)
SICI (ratio)	0.6 (0.2)	0.6 (0.2)	0.7 (0.2)	0.6 (0.2)	0.7 (0.2)	0.6 (0.2)	0.1 (0.2)	0.0 (0.10)	0.0 (0.2)	0.0 (0.2)	0.1 (-0.04 – 0.20)	0.1 (-0.06 – 0.28)
SP (ms)	193.5 (52.0)	149.1 (43.3)	165.1 (45.1)	151.4 (52.1)	184.0 (48.7)	168.3 (47.1)	-30.2 (49.0)	-3.3 (25.1)	-12.5 (26.4)	10.6 (45.7)	25.3 (-3.0 – 53.4)	24.9 (-12.0 – 61.7)

PRE, progressive resistance exercise group; CON, control group, MVC; maximal voluntary contraction, Qtw,pot; potentiated twitch, VA; voluntary activation, TTF; time to task failure, Mmax; maximal m-wave, MEP; motor evoked potential, rmsEMG; root mean squared electromyography, SICI; short intracortical inhibition and SP; silent period. *$p < 0.05$, **$p < 0.01$

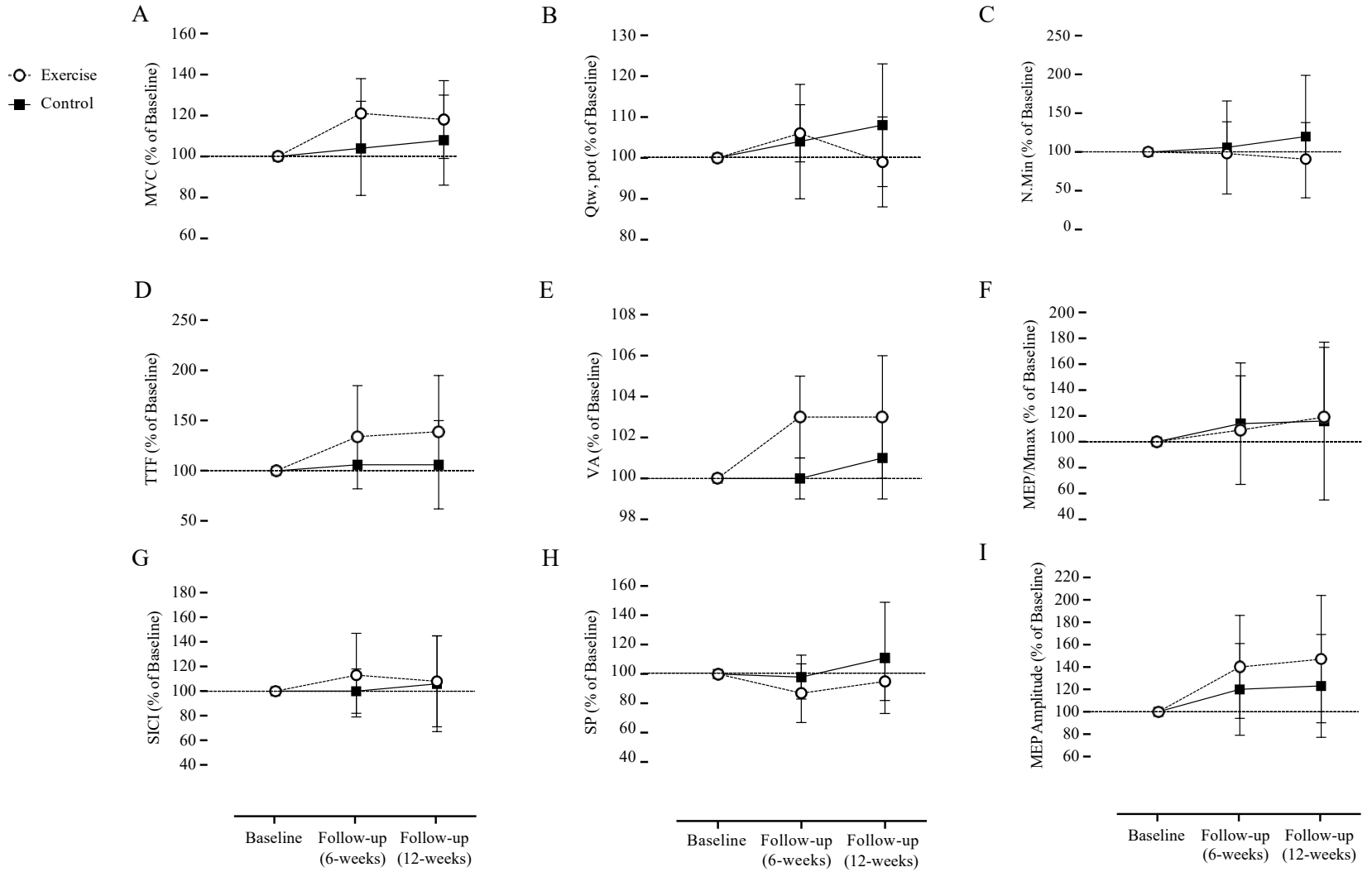

Figure 7.5 MVC (A), Qtw,pot (B), N.Min (C), TTF (D), VA, (E), MEP/Mmax (F), SICI (G), SP (H), and MEP Amplitude (I) of the lower-limb muscle, all expressed as a percentage of baseline before and 6, 12-weeks follow-up in the exercise group (open circles) and control group (closed squares).

7.3.5 Effects of PRE on Upper-Limb Neurophysiological Measures between PRE and control groups

Neuromuscular measures

At 6-weeks of follow-up, there was a difference in favour the PRE group in MVC ($F_{(1, 27)}$ = 7.482, p = 0.011, η_p^2 = 0.22) and $Q_{tw, pot}$ ($F_{(1, 27)}$ = 9.426, p = 0.005, η_p^2 = 0.26). At 12-weeks of follow-up, the difference between the PRE group and controls remained for $Q_{tw, pot}$ ($F_{(1, 24)}$ = 8.115, p = 0.009, η_p^2 = 0.25) but not for MVC (Figure 7.6 A & B). There were no differences between the groups at any follow-up time-point for VA or M_{max} (Table 7.4).

Fatiguability

At 6-weeks of follow-up, improvements in TTF and the rate of force decline (N·Min) were apparent for the PRE group versus controls, but none of the between-group differences were significant (Figure 7.6 D; TTF, p = 0.084 and N·Min, p = 0.147). However, at 12-weeks of follow-up, differences in favour of the PRE group were observed for TTF ($F_{(1, 24)}$ = 8.613, p = 0.007, η_p^2 = 0.26) and N·Min; ($F_{(1, 24)}$ = 4.590, p = 0.043 , η_p^2 = 0.161; Table 7.4).

Corticospinal and Inhibitory measures

There were no differences in MEP amplitude, MEP/M_{max}, SICI or SP between the PRE and control group at any of the follow-up time-points (Table 7.4).

Table 7.4 Neurophysiological measures in upper-limb (wrist-flexors). Mean (SD) of groups, mean (SD) difference within groups, and mean difference (95%CI) between groups

Outcome	Groups						Difference within groups				Difference between groups	
	Baseline		6-Weeks Follow-Up		12-Weeks Follow-Up		6-Weeks Follow-Up - Baseline		12-Weeks Follow-Up - Baseline		6-Weeks Follow-Up - Baseline	12-Weeks Follow-Up - Baseline
	PRE (n =16)	CON (n =17)	PRE (n =15)	CON (n =15)	PRE (n =14)	CON (n =13)	PRE	CON	PRE	CON	PRE-CON	PRE-CON
MVC (N)	103.8 (31.2)	114.1 (22.1)	131.8 (34.5)	111.3 (22.3)	133.6 (32.5)	119.0 (32.1)	27.0 (28.8)	-1.8 (26.2)	26.4 (27.7)	8.2 (32.6)	25.2 ** (6.3 – 44.1)	16.7 (-5.9 – 39.2)
$Q_{tw,\,pot}$ (N)	31.5 (12.2)	34.5 (12.4)	36.9 (13.1)	33.8 (10.8)	39.2 (13.2)	35.8 (11.1)	5.7 (5.1)	-1.1 (6.4)	7.9 (5.2)	1.5 (6.2)	6.2 ** (2.1 – 10.4)	5.8 ** (1.6 – 10.1)
VA (%)	87.3 (3.6)	88.8 (4.8)	90.5 (4.2)	90.5 (3.1)	90.1 (3.6)	88.8 (2.5)	3.4 (3.4)	2.2 (3.5)	2.8 (3.5)	1.6 (2.4)	0.7 (-1.5 -2.9)	1.2 (-0.7 – 3.2)
TTF (mins)	14.2 (6.0)	12.9 (7.3)	16.0 (5.3)	13.1 (7.5)	15.9 (5.1)	11.5 (5.9)	2.5 (3.2)	0.9 (2.0)	2.5 (3.6)	-0.2 (2.0)	1.7 (-0.3 – 3.7)	3.0 ** (0.9 – 5.2)
Rate of force decline (N·Min)	-3.3 (2.4)	-5.1 (4.4)	-2.6 (1.6)	-4.3 (2.2)	-2.5 (1.3)	-4.1 (1.7)	0.8 (2.2)	1.0 (3.2)	1.0 (2.0)	1.7 (3.8)	0.8 (-0.3 – 2.0)	-1.1 * (-2.2 – -0.4)
M_{max} (mV)	9.2 (4.4)	8.9 (4.2)	10.2 (4.4)	9.2 (4.1)	9.8 (4.0)	9.3 (4.1)	0.7 (1.4)	0.3 (0.9)	0.7 (1.1)	0.2 (1.6)	0.4 (-0.5 – 1.3)	0.4 (-0.6 – 1.4)
MEP Amplitude	0.7 (0.3)	0.7 (0.3)	0.8 (0.2)	0.8 (0.3)	0.8 (0.4)	0.8 (0.3)	0.1 (0.2)	0.0 (0.1)	0.1 (0.2)	0.0 (0.1)	0.1 (-0.03 – 0.2)	0.1 (– 0.1 – 0.2)
MEP/Mmax (%)	7.6 (2.4)	9.0 (4.6)	8.2 (2.6)	9.1 (4.5)	8.3 (3.1)	9.2 (4.0)	0.7 (1.8)	-0.3 (1.0)	0.6 (1.8)	-0.5 (1.7)	0.0 (-0.01 – 0.02)	0.0 (-0.01 – 0.02)
rmsEMG (mV)	0.6 (0.3)	0.6 (0.3)	0.7 (0.3)	0.6 (0.2)	0.7 (0.2)	0.6 (0.2)	0.1 (0.2)	0.0 (0.1)	0.2 (0.2)	0.1 (0.2)	0.1 (-0.01 – 0.2)	0.1 (-0.02 – 0.23)
SICI (ratio)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	0.6 (0.2)	0.8 (0.2)	0.6 (0.2)	0.0 (0.2)	0.0 (0.2)	0.1 (0.2)	0.0 (0.2)	0.1 (-0.04 – 0.2)	0.1 (-0.02 – 0.23)
SP (ms)	135.2 (39.4)	143.8 (47.1)	158.4 (54.5)	154.7 (44.9)	164.3 (49.7)	160.0 (37.0)	25.2 (29.9)	16.7 (25.2)	28.8 (29.9)	30.2 (33.5)	8.1 (-13.0 – 29.2)	-0.2 (-24.6 – 24.2)

PRE, progressive resistance exercise group; CON, control group, MVC; maximal voluntary contraction, Qtw,pot; potentiated twitch, VA; voluntary activation, TTF; time to task failure, Mmax; maximal m-wave, MEP; motor evoked potential, rmsEMG; root mean squared electromyography, SICI; short intracortical inhibition and SP; silent period. *$p < 0.05$, **$p < 0.01$.

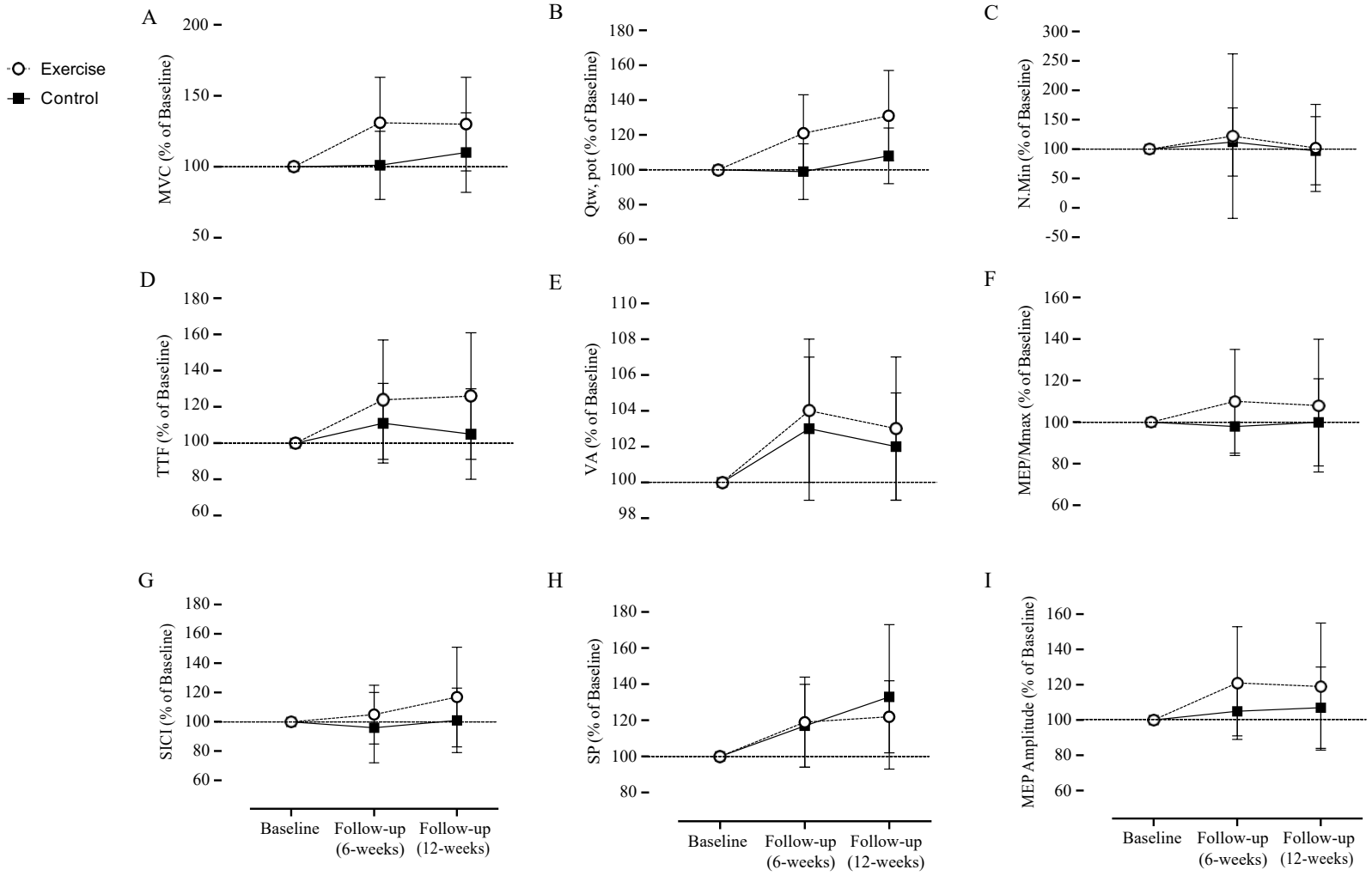

Figure 7.6 MVC (A), Qtw,pot (B), N.Min (C), TTF (D), VA, (E), MEP/Mmax (F), SICI (G), SP (H), and MEP Amplitude (I) of the upper-limb muscle, all expressed as a percentage of baseline before and 6, 12-weeks follow-up in the exercise group (open circles) and control group (closed squares).

7.3 Discussion

The main aim of the present study was to examine the feasibility of PRE (part supervised, part home-based) in highly fatigued PwMS. Compared to usual care alone, PRE was found to be feasible with excellent retention (6 weeks, 94%; 12 weeks, 88%) and high adherence (>75% of all sessions) in highly fatigued participants. The excellent level of adherence to the programme resulted in reductions in perceived fatigue (MFIS), mood, anxiety, pain and health-related quality of life following supervised PRE, which were maintained following home-based training. Neurophysiological data showed that 6-weeks of supervised PRE led to improved muscle strength and activation in the upper and lower extremities, and with an improvement in TTF also shown after additional 6 weeks of home-based PRE. This early evidence of efficacy shows that a blended programme of supervised and home-based PRE has potential to improve perceived fatigue, health and specific neuromuscular function outcomes in individuals with high levels of MS fatigue. The present study is an important addition to the evidence-base that illustrates the potential therapeutic benefits of PRE in PwMS and the role it could play in self-management of MS fatigue.

Feasibility of PRE in Fatigued PwMS

The evidence of feasibility is noteworthy, as this modality of exercise may represent a more accessible option for self-directed structured exercise versus other exercise modalities, such as aerobic exercise for some PwMS. Aerobic training via gym-based classes and/or expensive gym equipment, or exposure to adverse weather conditions may be less appealing than PRE performed in a home setting using resistance bands with lower financial cost and higher degree of control regarding safety and rest periods. The present study provides further evidence that PRE is an exercise modality is highly accessible and adoptable by PwMS, with much potential for excellent adherence and maintenance in non-supervised settings, in accordance with previous findings (DeBolt & McCubbin, 2004; McCullagh et al., 2008). Interestingly, there is also evidence from supervised progressive aerobic PRE studies in PwMS with similar session frequency, of slightly lower retention rates (73 to 85% at follow-up; (Petajan et al., 1996; Cakt et al., 2010). Therefore, PRE using therabands warrants further investigation to wider MS community uptake as an exercise modality that can feasibly be adopted as part of self-management strategies in people experiencing hight levels of perceived fatigue.

In the absence of any major injuries or adverse events, PRE was shown to be well-tolerated by all of the highly-fatigued PwMS recruited to this study. This is in agreement with previous studies, which reported no major problems or unpleasant experiences related to resistance training in more heterogeneous samples PwMS on the basis of fatigue status (DeBolt & McCubbin, 2004; White et al., 2004; Gutierrez et al., 2005). Although there was some evidence of mild muscle soreness in the latter studies, not all participants experienced muscle soreness, and this is likely to reflect physiological adjustment to a new exerciser training programme. The present study demonstrated a lack of PRE-induced severe symptom exacerbations in a cohort of participants that were all experiencing high levels of MS fatigue, which could reflect proper instruction and tailoring of PRE to specific capabilities (i.e., standing or seated PRE alternatives and use of fans during sessions to prevent heat sensitivities). In the present study, the PRE programme was also designed to incorporate regular breaks between upper- and lower-limb exercises that could be implemented without difficulty by highly-fatigued PwMS.

Changes in Fatigue following PRE

The results from this study also suggests that PRE can have a positive effect on the high levels of perceived fatigue experienced by some PwMS, as shown by the reductions in MFIS (7%) in the PRE group following 6-weeks of supervised PRE, and with this being maintained after 6-weeks of home-based PRE. These data support previous study findings (White et al., 2004; Dodd et al., 2006) but with White et al. (2004) reporting a reduction of 24% in MFIS, which is three-fold greater than the present study. This might have been due to the lower limb training approach that was used, in comparison to the whole-body approach used in the present study, although their participants were not recruited on the basis that they were experiencing high levels of MS fatigue at baseline. White et al. (2004) reported gradual progression of 2-5% resistance after completion of 15 repetitions, whereas the current study was adapted on the basis of the participant's own pace and fatigue sensation. Despite the reduction in MFIS score, no changes were observed for the FSS or CFS. A previous PRE intervention in fatigued PwMS reported a reduction in the FSS of −0.6 (−1.4 to −0.4) following 12-weeks of resistance PRE compared to the present study's small difference (−0.15, −0.29 to −0.01) after 6 weeks. A potential reason for this discrepancy could be a cut-off score of >4 used for the FSS. A cut-off score of >5 was used in the present study, suggesting

participants (as a whole) were experiencing higher levels of fatigue at baseline. Additionally, there was a longer training period of 12-weeks for single-limb training, as compared with whole body exercise for a shorter period in the present study. The one-dimensional FSS and CFS, versus the multi-dimensional MFIS might be less amenable to change following short-term programmes of PRE. Thus, the results of the present study suggest that the MFIS could be a more sensitive measure for exercise studies in PwMS, and particularly those investigating the impact of PRE in those with high levels of perceived fatigue. This being said, more research is warranted to evaluate the utility of single and multi-dimensional fatigue scales in large scale trials of exercise therapy for fatigue management in PwMS.

Changes in Health Outcomes following PRE

Mood and anxiety were improved in the PRE group, similar to previous exercise studies using different types of PRE in PwMS (Ahmadi et al., 2013; Briken et al., 2014), and these results are also consistent with studies showing the beneficial effects of PRE in individuals with major depression (Mota-Pereira et al., 2011; Trivedi et al., 2011; Silveira et al., 2013). However, the latter studies used different scales, such as the Beck Depression Inventory and Beck Anxiety Inventory (Ahmadi et al., 2013)and the Inventory of Depressive Symptoms self-report questionnaire (Briken et al., 2014). Therefore, future studies of PRE in highly fatigued PwMS would benefit from greater consistency in the use of depression and anxiety scales to strengthen the evidence base. Pain was also shown to be improved following supervised and home-based PRE (6 weeks, −28%; 12-weeks, −21%), consistent with previous data (Learmonth et al., 2014) which also showed that a 15-minute bout of moderate-intensity PRE had no adverse effect on pain or function in PwMS. However, the promising preliminary data from this feasibility study needs to be heeded with caution, as a larger scale trial with longer-term follow-up needs to be conducted before definite conclusions regarding these health outcomes can be drawn.

The PRE group experienced improvements in QOL-Mental and QOL-Physical after the supervised component of the programme and these health benefits were maintained after home-based PRE (Figure 7.4). This is an interesting finding because it is known that health-related quality of life is reduced in PwMS (Miller et al., 2006), and the changes observed in the present study were greater than previous work (Dodd et al.,

2006; Dalgas et al., 2010). Specifically, Dodd and colleagues (2006) used a qualitative approach, reporting a reduced QOL-physical component after 10 weeks of bi-weekly training. However, earlier research by Romberg et al. (2005) which examined home-based combined training found no improvement in health-related quality of life (HR-QOL). Reasons for the discrepant findings might be differences between the studies in the level of social isolation and support or contact provided to PwMS, as evidence from healthy older sedentary subjects supports this notion (Cox et al., 2003). Participant feedback from the present study supports this, with PwMS reporting enjoyment from the regular social interactions and saw this as a motivational feature, particularly during the supervised component of the PRE programme. This seems important because it is known that poor health-related quality of life is strongly influenced by loss of independency (Takemasa et al., 1998), which can adversely impact social connectedness.

Changes in Neuromuscular Function following PRE

An improvement in muscle strength was observed after 6-weeks of supervised PRE in both the upper- (31%) and lower- (21%) limbs in highly fatigued PwMS, suggesting the capacity to adapt over a shorter period of exercise time. The magnitude of muscle strength improvement was greater than the typical error reported in Chapter 5 (lower: 14.4, upper: 11.2), indicative of real clinically-important change. This supports previous resistance training studies in PwMS not categorised by fatigue status over a similar time period of 4-12-weeks (7 – 57%; Swensson et al., 1994; Kasser and Cubbin, 1996; Harvey et al., 1999; DeBolt & McCubbin, 2004; Taylor et al., 2006; Aimet et al., 2006). However, this was not in agreement with the non-fatigued findings of Harvey et al. (1999), despite similar improvements in quadriceps MVC (28–47%) being reported, likely because their study had a smaller sample size (n = 7).

It is also interesting to note that the present study identified a greater improvement in upper-limb strength versus lower-limb strength, similar to four previous studies reporting notable improvements (3–29%) in upper extremity muscle strength (Kasser & McCubbin, 1996; Kraft et al., 1996; Schwid et al., 1999; Taylor et al., 2006). This should be considered in the context of evidence of a more pronounced strength deficit in the lower extremities amongst PwMS and older people (Skelton et al., 1994; Bassey et al., 1992). The proposed greater strength increase recognises that training specificity

is important, i.e., in the present study, knee-extension and wrist flexion exercises were incorporated into the whole-body exercise programme. However, muscle strength was not maintained after the home-based PRE, with a possible explanation due to the limited tailoring of PRE over the phone in a home setting and less effective progression as strength improved, unlike the face-to-face supervised setting which allows adjustments to the training load consistent with individual responses and capabilities. Fatigability by way of time to task failure improved after supervised and home-based PRE, suggesting that along with an increase in strength, there was a tangible impact on the ability to sustain muscular work, and this is likely to be important for day-to-day functioning. This is further supported by participants anecdotally commenting on having greater energy to do more walking and house tasks with less frequent breaks and using walking aids less, supporting all-round functional improvements. Moreover, the present results corroborate reports regarding the effect of strength training in patients with neuromuscular disorders such as spinal muscular atrophy or facioscapulohumeral muscular dystrophy (McCartney et al, 1989; Spector et al. 1996).

Increased VA following 6-weeks of supervised PRE, in only the lower-limb, with no further increases after home-based PRE. These changes are greater than the typical error (1.9%) showing a real change outside the variability of the measure in highly fatigued PwMS. This change might be related to the more pronounced strength deficitobserved in the lower extremity in PwMS (Skelton et al., 1994; Bassey et al., 1992), suggesting more potential to enhance neural drive with lower-limb PRE. To date, no studies have reported neural drive changes using VA in PwMS after PRE. Previous studies in healthy individuals have reported changes in muscle strength (Moritani and de Vries, 1980) and neural drive (EMG based) to muscles in first 3-5 weeks (Aagaard et al., 2002; Tallent et al., 2017). In PwMS, Dalgas et al. (2013) reported EMG increasesof 36% after training 2 days a week for 12-weeks and Fimland et al. 2010 reported an increase of 40% after 3 weeks. The larger increase in EMG might be due to the highertraining frequency of 5 days a week in the latter study (Fimland et al., 2010), unlike the2 days a week protocol used in the present study, which was chosen to reduce risk of injury and allow appropriate recovery periods. While changes in MEP amplitude and inhibition (SP) were found after 6-weeks of supervised PRE, no differences were observed for the lower-limb (Table 7.3 & Figure 7.5) but suggest some possible early indicative signs of cortical plasticity accompanying the strength gains observed in the

present study. However, as longer-term structural plasticity occurs between sessions, not within sessions (Mednick et al., 2011), it might be that a twice-weekly PRE stimulus for 6-12-weeks is not optimal for such central nervous system adaptation (Kleim et al., 2004). Previous resistance exercise studies in PwMS have not explored corticospinal excitability and inhibitory responses, thus supporting the need for further research for greater exploration of these measures.

7.3 Limitations

The main limitation of this study was the lack of experimental control over the blinding of participants to the intervention and lack of blinding in the follow-up assessments. Another limitation of the present study could be restricting neurophysiological assessments to the right limb (identified using the Oldfield questionnaire). It can, therefore, not be stated whether the contralateral limb would have shown the same pattern of adaptations. Furthermore, compliance to home-based PRE was reportedly lower compared to the supervised PRE. Although, the participants benefited from fortnightly phone calls for support and the opportunities for advice and questions, superior support could have been provided to improve compliance. For example, remote use of online platforms for support, including fitness apps, real-time video conferencing, more regular phone calls/texts and "booster" face to face sessions are support mechanisms that could be used in future studies. Lastly, most relapsing-remitting PwMS are receiving a disease-modifying drug. Although, such information is described in the present study, it is poorly reported or not accounted for in previous trials of PRE training. This issue means that no clear understanding of the benefits of PRE in the context of disease-modifying drug use is available and this is an important issue when considering prescribing PRE to PwMS.

7.4 Future Directions

Based on the present study, representing a selected group of mildly affected PwMS (EDSS 0-5) with high fatigue, future directions could focus on PRE for more severely impaired PwMS (EDSS > 5.5) with high fatigue. Kraft et al. (1996a, 1996b) reported that resistance training was well tolerated and had beneficial effects in four PwMS having an EDSS greater than 6. Further research could also include assessment of both left and right extremities for neurophysiological measures, to explore whether the most affected limb might have a greater improved pattern of adaptations during whole body

PRE, particularly as more irreversible neuronal damage might be present, potentially limiting adaptability. Compliance to home-based PRE was good, yet additional work is still required to examine the efficacy and long-term compliance to PRE programmes within other supervised and community led settings such as local gymnasiums, community centres, aged residences, and a combined home/supervised center-based approach. Furthermore, little is known about PRE within the context of MS relapses (Maurer et al., 2018) and safety aspects must be considered, such as discontinuation of PRE during a relapse for safety. When and how PRE should be reinitiated after resolution of a relapse, and if PRE is only suitable after certain types of relapses might provide further insight into common causes of drop-out in PRE studies in PwMS. Lastly, patient feedback described improved balance and walking ability, however no gait, walking or balance assessments were included, which could provide further insight into falls reduction and increased independence. Thus, walking and balance measures might be considered, as there is incomplete evidence regarding the effects of resistance training on functional capacity. Previous studies reported no change in gait speed (Harvey et al. 1999, White et al. 2004), whereas some studies have shown significant improvements in functional capacity, including gait, stair climbing ability and 'timed up and go' (Kraft et al. 1996; Taylor et al. 2006). Further investigation into whether study participants reliably demonstrate placebo responses across different fatigue status groups (MS-HF vs MS-LF) could distinguish such individuals from non-responders to exercise interventions in the future and better understand psychological responses to exercise (Lindheimer et al., 2020).

7.5 Conclusion

The aim of this chapter was to establish whether progressive resistance exercise (supervised and home-based) is a feasible exercise modality for PwMS experiencing high levels of fatigue and explore health benefits via measures of neuromuscular function and patient reported outcomes. This Chapter demonstrated that a part supervised, part home-based PRE programme on 2 days per week was safe and well tolerated by fatigued PwMS. Additionally, home-based resistance training was effective for maintaining the supervised-based improvements in fatigue, mood, health-related quality of life and time to task failure. However, the improved muscle strength associated with supervised PRE, accompanied by enhanced muscle activation, was not maintained after the home-based exercise component. The apparent ineffectiveness of

home-based training to maintain the improvements in neuromuscular function was most likely due to the slight reduction in adherence and PRE training volume and intensity during the home-based training. Nevertheless, this study provides clearevidence that PRE has much potential to induce a positive effect on MS fatigue, whenevaluating MS fatigue as the primary outcome measure, emphasising the need for futurestudies within this field. This study also demonstrates the potential of PRE to improvemeasures of neuromuscular function over usual care in PwMS. Future studies should be designed as adequately powered randomised controlled trials, with fatigue as the primary endpoint, and using a multi-dimensional scale with well-validated cut-off values for classifying highly-fatigued PwMS.

CHAPTER 8- GENERAL DISCUSSION

8.1 Introduction

The primary aim of this thesis was to establish whether neurophysiological differences between highly-fatigued (MS-HF) and less-fatigued (MS-LF) could be reliably distinguished, and to investigate the feasibility and potential of PRE as a therapeutic exercise intervention for ameliorating perceived MS-fatigue. To meet this aim, four studies were conducted. The aim of Study 1 (Chapter 4) was to understand the current evidence-base regarding neurophysiological and neuro-structural differences between people experiencing high and low levels of fatigue via a systematic review of cross-section studies. The aim of Study 2 (Chapter 5) was to assess the test-retest reliability, measurement variability and measurement error of upper- and lower-limb neuromuscular and transcranial magnetic stimulation measures in MS-HF and HS-LF and healthy controls. Based on the findings of Study 2, Study 3 (Chapter 6) investigated differences between MS-HF, MS-LF and HC, for a range of neurophysiological measures, including an isometric fatiguing exercise task in the upper- and lower-limb (performance fatigability measure), with the aim of understanding which neurophysiological correlates best distinguish MS-HF from MS-LF. Finally, the aim of Study 4 (Chapter 7) was to evaluate the feasibility of (and glean preliminary evidence of efficacy for) PRE (part-supervised, part-home-based) as a therapeutic exercise intervention for ameliorating perceived MS-fatigue. This latter study was developed to address the relative paucity of studies that have recruited a homogenous sample of PwMS experiencing a high level of fatigue, and in which perceived fatigue is the primary outcome. This final chapter briefly summarises the main findings of this PhD programme and concludes with a brief discussion of the implications of this research and future directions for research in this area.

8.2 Principal Findings

Chapter 4 (Study 1) was the first systematic review and meta-analysis to synthesis the current evidence base comprising studies which used a dichotomised model (MS-HF versus MS-LF) to provide insights into structural and neurophysiological correlates of MS-fatigue. Synthesising and meta-analysing the current evidence base was a step towards overcoming some of the limitations of previous research (e.g., small sample sizes, conflicting evidence, unknown effect size estimates, etc.). This chapter shed some light on neuro-structural differences between MS-HF and MS-LF by means of

neuroimaging techniques and indicated greater cortico-subcortical atrophy (total brain loss -22.7 ml, mainly attributable to a volumetric reduction in grey matter -18.8 ml) in highly-fatigued PwMS. This chapter also helped to consolidate the evidence for the involvement of specific areas of localised damage and impaired connectivity in severe MS fatigue, for example, basal ganglia circuitry, including the striatocortical and striatothalamic networks, responsible for motor control, motor planning, attentional control and the integration of afferent and efferent information. The findings also suggested an increased volume of T1-weighted hypointense lesions in MS-HF, perhaps reflecting activated immune inflammatory pathways or irreversible pathological changes which are important features of the disease (Morris et al., 2016). These results concur with functional magnetic resonance imagery and electroencephalogram data suggesting functional reorganisation within cortico-subcortical networks as a compensatory response to MS brain lesions, and adaptative neural processing within certain networks resulting in an increase in energy demand (Filippi & Rocca, 2004; Kos et al., 2008). Therefore, the consolidated neuroimaging evidence-based was most useful for helping to discern key neurostructural differences in PwMS partitioned by fatigue status, implying that impairment (and/or atrophy) of specific brain structures and networks may place an elevated demand on functioning (non-pathological) neural circuits, and that this could be involved in increased perceptions of MS fatigue.

A synthesis of the evidence-base that used neuromuscular techniques identified peripheral and central correlates of MS fatigue via reduced muscle strength (MVC), impaired voluntary activation (central motor drive) and an increased level of upper-limb fatigability in MS-HF versus MS-LF and HC. This suggests an impaired ability to fully activate skeletal muscles during motor tasks in MS-HF (Zijdewind et al., 2016). The deconditioning effects of relative physical inactivity after an MS diagnosis, might further compound these underpinning issues and exacerbate MS-fatigue (Sebastiao et al., 2017), as inactivity can lead to disuse atrophy and neurophysiological changes affecting skeletal muscle activation, leading to impaired muscular strength and function (Rice et al., 1992). In turn, this could increase the amount of effort required for everyday tasks. No differences were shown in the relative integrity of corticospinal (MEP variables or central motor conduction time), intracortical inhibition (SICI) or intracortical facilitation (ICF) pathways between MS-HF and MS-LF. This may be at odds with evidence of altered functional connectivity and hyperactivation in fronto-

parietal cortical regions, sensorimotor network and subcortical areas important for motor, sensory and cognitive processing in MS-HF (Tartaglia et al., 2008; Specogna et al., 2012; Rocca et al., 2016; Bisecco et al., 2017; Jaeger et al., 2018). However, at present very few studies have compared SICI or ICF variables between MS-HF and MS-LF, making it difficult to draw definitive conclusions about the extent to which modulation of intracortical inhibitory or facilitatory networks could be implicated in MS-fatigue.

For some key variables, there is a small number of studies and the overall quality rating of included studies was 'moderate', as such, caution is needed when interpreting these results. Nevertheless, Chapter 4 robustly synthesises the existing evidence-base, and by consolidating available neuro-imaging and neurophysiological data, provides new insights into neurobiological differences that exist between MS-HF and MS-LF. This is an important step in delineating key homeostatic and psychophysiological pathways underpinning perceived fatigue and fatigability in PwMS. Although data from neuroimaging studies was needed to understand neurostructural correlates of MS fatigue, such techniques were beyond the scope of available resources for this PhD programme and could not be included in future chapters. In contrast to neuro-imaging techniques, neurophysiological measures are more accessible and are well-tolerated by PwMS and so were used for the experimental studies (Chapters 5-7) in this thesis.

Chapter 5 (Study 2) was an original study showing good to excellent test-retest reliability for a range of neuromuscular and transcranial magnetic stimulation measures assessed in the upper- and lower-limb muscles of people experiencing high and low levels of MS fatigue. The primary finding was that MVC, TFF, MEP amplitude, SP were highly reproducible in MS-HF, which extends current literature on the reliability of force measures for the knee extensors (Surakka et al., 2004b) and for grip strength (Schwid et al., 1999) in PwMS not characterised by fatigue status. There is similar evidence from previous work in the elbow flexors (Meeteren et al., 2002) and knee extensors (Frontera et al., 1993; Dvir, 2004) of healthy individuals. These findings suggest that these neurophysiological measures hold much promise for future adoption in exercise training and other therapeutic interventions for fatigue management in PwMS, in particular, having the potential to shed more light on how underpinning neurophysiological changes impact perceptions of MS fatigue. In the present study,

MVC showed low measurement error for the knee-extensors compared to the wrist-flexors, which might suggest poorer reliability for larger muscle groups, or for muscle groups that are more severely affected by MS (see Tables 5.3 and 5.4). The findings of this chapter demonstrated moderate test re-test reliability for VA, SICI MEP amplitude, and with corticospinal excitability (MEP/Mmax) found to be moderate to good, consistent with previous research for PwMS more generally. Furthermore, the greater coefficient of variation for this latter measure in the present study (>10%), signifies a higher intra-subject variability. A possible reason for lower reproducibility was that the average responses to transcranial magnetic stimulation measurements were lower in PwMS due to the uncomfortable nature of the tests, which should be taken into account when taking multiple measures of MEP. Interestingly, day-to-day reliability demonstrated greater reliability in the lower-limb compared with the upper limb muscles in PwMS, also observed for VA. Another interesting observation was the low coefficient of variations and typical errors in the knee-extensors compared to the wrist flexors in MS-HF, which may suggest greater reliability for muscle groups requiring less fine motor control, perhaps having adverse implications for motor control in every-day upper-limb tasks, such as lifting and carrying shopping bags and hoovering.

A high level of test-retest reliability was shown for patient-reported outcomes, including fatigue, mood and sleep quality, in PwMS experiencing different levels of fatigue. The high test-retest reliability of fatigue scale scores over this 7-14-day period is particularly reassuring, as the occurrence of severe MS-fatigue can be sporadic, and scores may be influenced by recent symptoms. However, a limitation of this study was the low motivation to participate in the research due to multiple site visits amongst PwMS, which could have implications for the generalisability of the results to the broader MS population, particularly PwMS who are less willing volunteer for research studies. These patient-reported outcomes are potential confounders for the reliability of neurophysiological measures and may be sporadically present when such clinical measurements are taken in PwMS, especially relevant for MS-HF. However, in the studies presented in this thesis, participant welfare was checked in the lead-up to assessment visits and re-scheduled if participants were experiencing undue levels of MS-fatigue or other debilitating MS symptoms. This flexible approach might have influenced the higher reproducibility observed and should be considered for future experimental research. Based on the high reproducibility and tolerance to most of the

neurophysiological assessments undertaken, the results of Chapter 5 (Study 2) support their utility in future studies of MS-HF.

Thus, on basis of the promising findings reported in Chapter 5 (Study 2), Chapter 6 (Study 3) aimed to identify reliable neurophysiological correlates of severe MS-fatigue in homogenous groups of PwMS partitioned on the basis of fatigue status (MS-HF vs MS-LF). The primary findings at rest were impaired patterns of muscle strength (MVC), shorter time to task failure and voluntary activation (VA), with no perceptible impairment of intramuscular muscle contractile properties ($Q_{tw,pot}$) in MS-HF versus MS-LF. Therefore, the presence of a high level of perceived MS-fatigue seems to be associated with decrements in central nervous system function rather than skeletal muscle (peripheral) impairments in the resting, unfatigued state, as previously highlighted (Liepert et al. 2005; Morgante et al. 2011; Conte et al. 2016; Chalah et al. 2019). Of course, associated psychosocial issues, including depression and poor sleep quality may have been key factors causing a lack of motivation to perform an MVC or any voluntary movement. Performance fatigability was also compared between MS-HF and MS-LF in Chapter 6 (Study 3). There is only limited evidence of an association between performance fatigability and perceived MS fatigue (assessed using self-reported fatigue scales) in the literature (e.g., Sharma et al., 1995; Iriarte et al., 1998; Ng et al., 2004), suggesting that these two fatigue constructs may be unrelated independent. However, Chapter 6 (Study 3) suggests that performance fatigability and perceived MS fatigue are both related to central drive (VA) but not impaired skeletal muscle contractile function ($Q_{tw, pot}$; Steens et al., 2012).

Chapter 6 (Study 3) also showed reductions in post-fatigue task variables (MVC, VA and $Q_{tw,pot}$) in both muscle groups studied amongst MS-HF (Table 6.2 and 6.3) that were two-fold greater than the typical error values reported in the previous chapter, as well as impaired central drive and modulation of neural drive after a fatigue task (i.e. VA and SICI). Interestingly, longer SPs are indicative of increased intracortical inhibition, greater disability and poorer motor function in other clinical populations, such as Huntington's (Priori et al., 1994) and stroke (Classen et al., 1997, Gray et al., 2017). Therefore, future research into the SP and its relationship with SICI in MS-HF is warranted. Finally, the differences observed in the present Chapter concerning corticospinal excitability and inhibition for MS-HF (see Table 6.2 and 6.3) were greater

than the typical error presented in Chapter 5. Therefore, it can be concluded that these measures are sensitive to detecting differences between MS-HF and MS-LF induced by task-related fatigue. This suggests that PwMS suffering from high levels of fatigue, require a greater demand on central components and less peripheral disturbance. These key findings are consistent with simple tasks being perceived as more effortful in MS-HF, due to more impaired central nervous system function (or impairments within specific brain regions and networks) resulting in less ability to increase cortical drive to maintain force. The proposed decline in voluntary drive and force production at the level of skeletal muscle is substantiated by the post-fatigue task data and previous research (Andreasen et al., 2009; Skurvydas et al., 2011; Steens et al., 2012b; Steens et al., 2012c). It is also consistent with previous work showing force decrements could be attributable to deconditioning effects on skeletal muscle atrophy and central drive (Kent-Braun et al., 1994a, 1994b, 1997; Haan et al., 2000; Sharma et al., 2005; Skurvydas et al., 2011), as PwMS are generally less physically active than healthy populations (Molt et al., 2005).

Finally, Chapter 7 (Study 4) contributed new knowledge regarding the utility of PRE as a feasible therapeutic exercise option for MS-HF. The study presented in this chapter showed that PRE was feasible, with excellent retention (6 weeks, 94%; 12 weeks, 88%) and high adherence (>75% of all sessions) in MS-HF. Chapter 7 (Study 4) showed that there were no PRE-induced symptom exacerbations in a cohort of participants that were all experiencing high levels of MS fatigue, which could reflect the importance of proper instruction and tailoring of PRE to specific capabilities (i.e., standing or seated PRE alternatives and use of fans during sessions to prevent heat sensitivities). The excellent level of adherence to the programme translated into preliminary evidence of efficacy in respect of reductions in perceived fatigue (MFIS), mood, anxiety, pain and health-related quality of life following supervised PRE, which were maintained following home-based training. The lack of observed changes in FSS and CFS might have been due to the one-dimensional format of these self-report tools which could potentially be less amenable to change following short-term programmes of PRE. Thus, the results of the present study suggest that the MFIS could be a more sensitive measure for exercise studies in PwMS, and particularly those investigating the impact of PRE in those with high levels of perceived fatigue.

Chapter 7 (Study 5) also showed that 6-weeks of supervised PRE led to improved muscle strength and activation in the upper and lower extremities, and with an improvement in time to task failure also shown after additional 6 weeks of home-based PRE. The magnitude of muscle strength improvements reported was greater than the typical error reported in Chapter 5 (lower: 14.4, upper: 11.2), indicative of real clinically-important change, and supporting previous resistance training studies in PwMS not categorised by fatigue status (Swensson et al., 1994; Kasser and Cubbin, 1996; Harvey et al., 1999; DeBolt & McCubbin, 2004; Taylor et al., 2006; Aimet et al., 2006). The present study identified a greater improvement in upper-limb versus lower-limb strength, and this may have been due to more pronounced MS-related impairments in the lower extremities amongst our sample population of PwMS. Time to task failure also improved after supervised and home-based PRE, suggesting that along with an increase in strength, there was a tangible impact on the ability to sustain muscular work, and this could be important for day-to-day functioning. Interestingly, central adaptations were also evidenced by increased VA following 6-weeks of supervised PRE in the lower-limb, but with no further improvement after home-based PRE. This change was greater than the typical error (1.9%) showing a real change outside the variability of the measure in highly fatigued PwMS but curiously, translated into a lesspronounced improvement in lower-limb force production. To date, no studies have reported neural drive changes using VA in MS-HF after PRE, warranting further exploration of this. However, the promising preliminary data from this feasibility studyneeds to be heeded with caution, as a larger scale trial with longer-term follow-up needsto be conducted before definite conclusions can be drawn.

It is important to mention that while PRE has shown both neural and secondary adaptative benefits for highly fatigued individuals, this could also be applied to, and benefit, less-fatigued PWMS. As MS is a progressively condition, PRE might help slow fatigue development over time in less-fatigued PwMS by preventing worsening of neurological lesion/disturbance development. However, this needs to be confirmed in future robust randomised controlled trials. This thesis acknowledges that use of a dichotomous recruitment model (MS-HF versus MS-LF) has the potential limitation that MS fatigue may be sporadic in nature, where some PwMS experience high levels of fatigue on some days but not others. To further advance the design of optimal exercise interventions for people experiencing high levels of MS fatigue in the future,

measuring fatigue over a longer period of time would provide a greater degree of confidence in the dichotomous recruitment model.

In conclusion, the results presented in this thesis add to the current body of literature by: (i) consolidating the existing evidence base via a comprehensive systematic review and meta-analysis of cross-sectional studies that examined MS fatigue via a dichotomised model (MS-HF versus MS-LF); (ii) showing that neurophysiological measures linked to MS fatigue can be reliably measured in the upper- and lower-limbs of MS-HF; (iii) providing new insights into neurophysiological differences that exist between MS-HF and MS-LF; and (iv) showing that PRE is a feasible exercise modality in MS-HF that has potential to reduce the debilitating effects of fatigue and other commonly reported adverse health effects.

8.3 Directions for Future Research

A current gap in the literature is the impact of exercise therapy for ameliorating cognitive impairments (and cognitive fatigue) in people experiencing high levels of MS fatigue. Cognitive impairment reportedly affects around 65% of PwMS and can occur in the absence of physical disability (Hoffman et al., 2007). Dysfunctions in speed of information processing, attention, memory and executive functions are most typically observed in PwMS (Rogers and Panegrys, 2007). During Chapters 5 and 6 throughout the fatiguing exercise task, participants described their "mental struggle" to focus on performing the task while watching the visual cue displayed on the computer screen. This might be reflective of more compromised cognitive processing and greater susceptibility to cognitive fatigue in MS-HF. This could be further explored using electroencephalography, measuring activity-related evoked potentials during the visual and auditory aspects of the fatiguing exercise task used in this thesis, to identify impairments related to the speed of information processing. Further to this, Chapter 4 identified neuroimaging techniques to be the most useful for demonstrating neurostructural differences in PwMS partitioned by fatigue status, e.g., highlighting lesions within specific brain regions and areas with impaired connectivity as well as elevated demands on functioning neural circuits, which may influence the severity of MS fatigue symptoms. Functional magnetic resonance imagery perhaps has the most to offer in this respect, and its use in future studies of MS-HF at rest and during a fatiguing task is warranted. This approach would improve our understanding of how different

patterns of movement-associated cortical and subcortical activation might contribute to the severity of fatigue symptoms in PwMS, further extending the findings of work presented in this thesis and that of others (e.g., Filippi et al, 2002).

Based on the positive findings of Chapter 7 (Study 5), a fully powered randomised controlled trial of PRE in highly fatigued PwMS is also warranted. This trial should take into consideration how the intervention could be implemented within clinical practice, if PRE is shown to be clinically and cost-effective. This would mean ascertaining what would be required to run such a service within the national health service or via referral to a community-based exercise class with the remit of training PwMS correct PRE technique. Qualitative work embedded in the trial could involve focus groups with patient representatives, physiotherapists, health commissioners and community-based exercise professionals to understand the barriers and facilitators to implementation. The trial should also explore dose-response relationships between PRE and MS fatigue (as well as other important health outcomes) as a means of developing PRE recommendations, i.e., the frequency, intensity, duration and week volume of PRE required for PwMS to realise optimal health benefits.

High adherence was also reported for the supervised training group. This might reflect the benefits of this programme in relation to the flexible approach applied and the range of resistance exercises used, i.e., two 1hr sessions a week, broken down to 2 x 30 minutes of upper and lower body exercises, respectively, as well as regular breaks being encouraged. Adherence was also very good during the home-based exercise, perhaps due to first 6 weeks of supervised exercise being used to build confidence and learn proper and safe exercise technique, alongside regular contact with myself with the aim of maintaining rapport and self-confidence. Finally, during this unprecedented worldwide COVID-19 pandemic, where access to therapeutic exercise support has been limited or non-existent, this thesis provides encouraging evidence of an accessible exercise modality which can be supported remotely and adopted by many MS-HF in their home environment. The intervention comprised a mixture of face to face and home-based exercise, along with regular remote support and this thesis shows that such a flexible blend of exercise training can be beneficial and well adopted during a future, more socially distanced care setting (post COVID-19 pandemic). The extent to which this approach removes a common barrier to exercise participation in PwMS (i.e., travel

to an exercise facility), especially those experiencing the highest levels of MS fatigue and including those with more severe MS disability, is another important avenue for future research. The extent to which this approach removes common barriers to exercise participation in PwMS, especially those experiencing the highest levels of MS fatigue, and including those with more severe MS disability, is another important avenue for future research

8.4 Significance, Originality and Impact of this thesis

The originality of this work is the identification and recruitment of the PwMS by fatigue status (highly-fatigued and less-fatigued) and using a fatigue self-reported scale as the primary outcome not the secondary outcome, as used in previous work. Although the recruitment process for all studies was challenging, the main originality, significance and rigour of this work is that it identified those with high level of MS fatigue and distinguished important neurophysiological differences between people in the two fatigue states at baseline and after a performance task. The neurophysiological outcomes identified in this thesis can collectively, with other secondary outcomes assessed, be used to power future randomised controlled trials of resistance exercise, to further understand the impact of this intervention on perceived fatigue and fatigability in people with MS. Another novel aspect was the use of a metronome during progressive resistance exercise. External pacing may help to evoke neuroplastic adaptations which bypass the neurophysiological lesions and MS disturbances, and this should be further explored in future research. In summary, this thesis provides robust preliminary evidence suggesting that this type of exercise training could be beneficial for highly fatigued PwMS.

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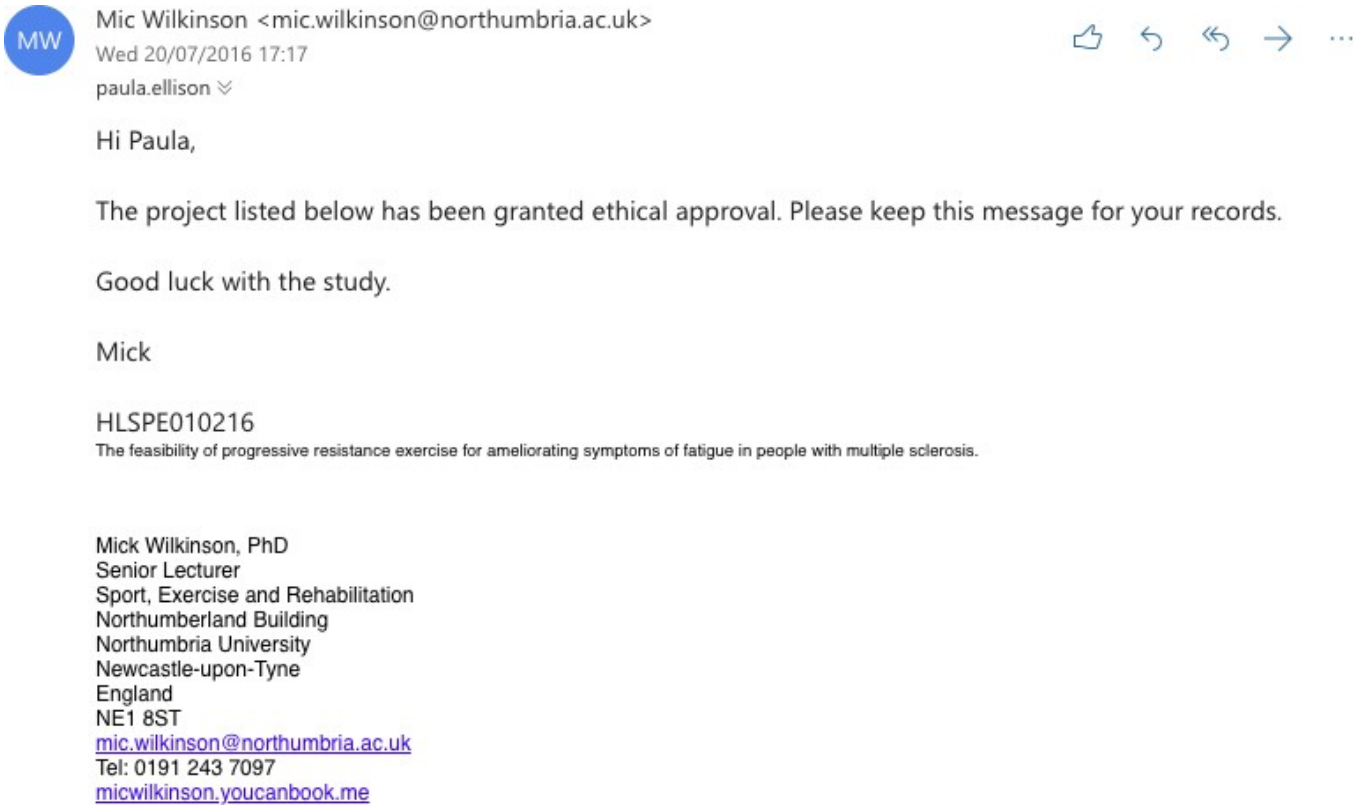
APPENDICE

Appendix 1 –Institutional Ethical Approval



MW

Mic Wilkinson <mic.wilkinson@northumbria.ac.uk>
Wed 20/07/2016 17:17
paula.ellison

Hi Paula,

The project listed below has been granted ethical approval. Please keep this message for your records.

Good luck with the study.

Mick

HLSPE010216
The feasibility of progressive resistance exercise for ameliorating symptoms of fatigue in people with multiple sclerosis.

Mick Wilkinson, PhD
Senior Lecturer
Sport, Exercise and Rehabilitation
Northumberland Building
Northumbria University
Newcastle-upon-Tyne
England
NE1 8ST
mic.wilkinson@northumbria.ac.uk
Tel: 0191 243 7097
micwilkinson.youcanbook.me

Appendix 2 –National Health Service Ethical Approval

R&D 7335

SM

Sneddon, Margaret <Margaret.Sneddon@nuth.nhs.uk>
Wed 08/04/2015 15:38
Duddy, Martin <Martin.Duddy@nuth.nhs.uk>; Wincup, Joanne <Joanne.Wincup@nuth.nhs.uk>; Crossman, John <John.Crossman@nuth.nhs.uk>; John Saxton; paula.ellison

7335 Duddy.pdf
125 KB

Dear Dr. Duddy

Study Title: Neurophysiology of fatigue in people with multiple sclerosis
R&D Ref: 7335

The above study has now been given full Newcastle upon Tyne Hospitals NHS Foundation Trust R&D approval. A letter to this effect has been signed by the Research Management & Governance (RM&G) Manager (see attached).

Please can you forward this email to all other relevant members of the team as appropriate?

You may now begin work on this study and a hard copy of this letter will follow in the post.

Kind regards
Margaret

Margaret Sneddon | Research & Development Assistant Administrator | Joint Research Office | The Newcastle upon Tyne Hospitals NHS Foundation Trust
Level 6, Leazes Wing
Royal Victoria Infirmary
Queen Victoria Road
Newcastle Upon Tyne
NE1 4LP

Telephone (direct line): 0191 282 **4926** | Reception: 0191 282 5959 | Fax: 0191 282 4524 | http://www.newcastlejro.org.uk/

Newcastle Joint Research Office

If your query relates to a Freedom of Information request please re-direct your query to patient.relations@nuth.northy.nhs.uk for Newcastle upon Tyne Hospitals NHS Foundation Trust, or to rec-man@ncl.ac.uk for Newcastle University

****
This message may contain confidential information. If you are not the intended recipient please inform the sender that you have received the message in error before deleting it.

Appendix 3 – Transcranial Magnetic Stimulation Screening Questionnaire

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NHS Foundation Trust

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Tel 0191 227 3571
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Participant Name: **Date:** **Version:**

Screening Questionnaire

Please answer the following questions by ticking the Yes or No boxes below. When you are finished the researcher will go over the answers with you.

Question	Yes	No
1. Do you have a heart pacemaker, artificial heart valves, pacing wires or defibrillator?		
2. Do you have any implanted devices (e.g. programmable hydrocephalus shut; nerve stimulator; cochlear implant; aneurysm clip; insulin, drug or infusion pump)?		
3. Have you had any surgery to your head (including ears/eyes/brain), neck or spine?		
4. Have you ever sustained any injuries involving metal to the eyes and/or any other part of the body?		
5. Have you ever had a fit or blackout, or do you have epilepsy?		
6. Have you ever had an magnetic resonance imagery?		

Thank you for taking the time to answer the questions.

Appendix 4– Oldfield Handed Inventory Questionnaire

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Participant Name: **Date:** **Version:**

Edinburgh Handedness Inventory Questionnaire

Please indicate your preferences in the use of hands in the following activities by *putting + in the appropriate column*. Where the preference is so strong that you would never try to use the other hand unless absolutely forces to, ***put ++*****.** If any case, you are really indifferent put + in both columotor nerve stimulation. Some of the activities require both hands. In these cases, the part of the task, or object, for which hand preference is wanted is indicated in brackets. **Please try to answer all the questions**, and only leave a blank if you have no experience at all of the object or task.

	Left	Right
1. Writing		
2. Drawing		
3. Throwing		
4. Scissors		
5. Toothbrush		
6. Knife (without fork)		
7. Spoon		
8. Broom (upper hand)		
9. Striking Match (match)		
10. Opening box (lid)		
11. Which foot do you prefer to kick with?		
12. Which eye do you use when using only one?		

Thank you for taking the time to answer the questions.

Appendix 5 – Participant Information Sheet

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

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Version:
Date completed:

Participant Information Sheet

Study Title: A Feasibility Study of Progressive Resistance Exercise in Fatigued People with Multiple Sclerosis.
Investigator: Paula Ellison

Introduction

You are being invited to take part in a research study. The research is being carried out by Paula Ellison and colleagues at Northumbria University with collaborators at University of East Anglia and Oxford Brookes University. We are working together with the Neurology Department at The Royal Victoria Infirmary Hospital, Newcastle to further understand the effects of exercise on key fatigue and health outcomes. This is so we may be able to further understand fatigue in people with multiple sclerosis and extend our knowledge on fatigue management strategies. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

What is the purpose of this study?

Over half of all people with multiple sclerosis experience fatigue as one of their most disabling symptoms, defined as *"a subjective lack of physical and/or mental energy that interferes with activities of daily life"*. The purpose of this study is to look at how

well people with multiple sclerosis who experience high levels of fatigue respond to exercise therapy recognised as progressive resistance exercise compared with no exercise. Resistance exercise may have more fatigue-reducing effects than aerobic exercise (running and cycling). Resistance exercise can be performed in fully supported (or seated) positions; body core temperature does not increase to the same extent as aerobic exercise and is easily transferrable to the home environment. We want to look at whether progressive exercise using resistance bands is a possible intervention for people with multiple sclerosis and understand the impact of the intervention on key health and fatigue outcomes.

Why have I been chosen?

We are looking for **relapsing-remitting multiple sclerosis (relapsing remitting MS)** who are experiencing **high levels of fatigue**. Your local consultant neurologist and/or MS nurse believes you may satisfy our criteria for participating and/or you have showed an interest to the advert for this study. We believe your participation can provide us with useful information about this problem in MS.

Do I have to take part?

No, it is up to you to decide whether or not to take part in this study. If you choose to take part, you will be given this information sheet to keep and will be asked to **sign a consent form**. If you decide to take part in this study, your general practitioner (GP) will be contacted. You are still free to withdraw at any time and without giving reason. If you start to take part in the study, but decide to withdrawal at a later date, we may use data collected unless requested otherwise at the point of withdrawal.

What will happen to me if I take part?

You will be asked to come in for a familiarisation session (~1 hr) to explain all the tests and then a baseline assessment (two x 1 ½ hr sessions separated by 2-7 days) will take place. Following baseline assessment of fatigue and health outcomes, you will be randomly assigned into one of two groups: (i) experimental group, or (ii) control group. There is an equal chance of being assigned to either group. The experimental group will attend two 1 hour supervised resistance exercise sessions per week (separated by at least 48 hours) for a total of 6-weeks. These sessions will take part on Monday and Friday and will be in a group setting of 4-6 people. At 6-weeks you will be reassessed (two x 1 ½ hr sessions separated by 2-7 days) and asked to complete the training

independently at home with regular contact with the researcher over the phone. At 12-weeks you will undergo your final assessment (two x 1 ½ hr sessions separated by 2-7 days). The control group will carry on standard care and attend assessments at familiarisation, baseline, and 6- and 12-weeks. Following 12-weeks of standard care, you will be provided with free resistance exercise bands along with a program and receive a one-on-one phone call to discuss your fitness objectives and goals concerning how resistance exercise may benefit you.

Neurophysiological assessment

During this assessment, you will perform simple motor tasks of the wrist and leg muscles. You will also be given a booklet, which will contain a number of fatigue and health related questionnaires. You will be able to sit with the researcher and go through the questionnaires individually and have the opportunity to raise any questions. Some of the questionnaires may be considered intrusive and you should not feel obliged to answer all the questions. This booklet will be completed at home.

What the visit will involve:

On arrival of the testing session:

- You and the researcher will go through the questionnaire booklet.
- You will then be briefly talked through the testing process and what is expected.
- You will then have time to ask any questions and discuss any queries.

During this visit you will complete a screening questionnaire to assess any potential reasons for you not to participate such as, metal implants and epilepsy. For your comfort you will be seated in an upright chair and the wrist or leg muscles will be stabilised in a specially designed rig. During the visits we will be measuring the activity of your wrist and leg muscles, which will require the application of small stick on electrodes to your leg and arm muscles. We will measure the pathways from the brain connecting to the muscles and the origin of fatigue.

Transcranial magnetic stimulation.

This involves using a device for producing pain-free stimulation to the brain that is involved in controlling movement. In response to this stimulus, muscles of the body

generate a natural brief contraction. This muscle activity can be recorded and provide information on how well signals sent from the brain connect to the muscles in the wrist and legs.

Electrical stimulation.

This involves a device for applying non-invasive stimulation of the targeted muscle at rest and during a simple motor task. This will allow further understanding into the origin of fatigue. In response to this stimulus, muscles of the body generate a natural brief contraction and will provide information on the strength of the muscle and the measure of muscle activity.

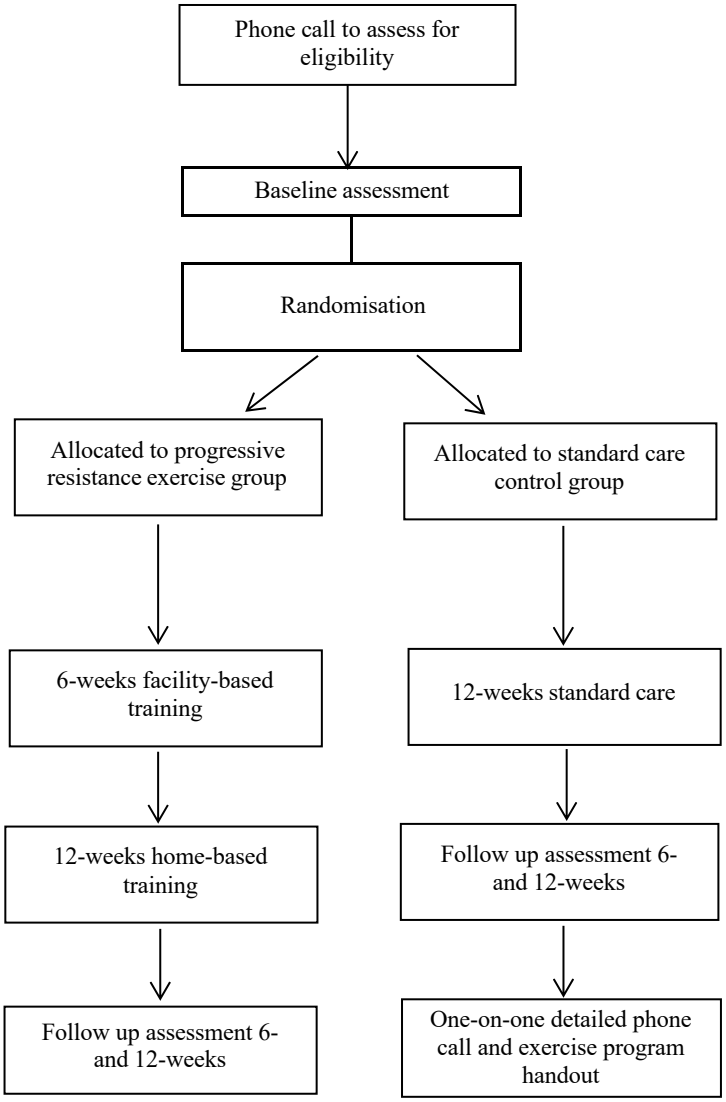
Progressive resistance exercise (PRE)

You will be prescribed an individualised resistance exercise programme and given an exercise log to record the content of each session. For 0-6 weeks you will attend the facility for supervised resistance exercise sessions. Progressive resistance exercise will be performed using resistance exercise bands, with the intensity of the exercise progressing according to your individual capabilities. This will be based on your rating of difficulty during the exercise. Each session will be supervised and monitored for progress and you will be provided with support and advice. If you feel you would need protective eyewear, this will be provided. During weeks 6-12, you will not attend the facility for resistance exercise but will complete two self-directed home-based exercise sessions per week. Home-based exercise sessions will mirror the facility-based sessions undertaken in weeks 0-6, in terms of the muscle groups being targeted, intensity and duration. Fortnightly telephone contacts from the researcher during this period will ensure that support is maintained, the exercise programme is properly progressed, and that you have the opportunity to discuss any issues arising.

Standard care control group

You will maintain your usual daily activity and standard medical care during weeks 0-12 weeks. Following 12-weeks of standard care, you will be provided with free resistance exercise bands and program and receive a one-on-one phone call to discuss your fitness objectives and goals and how resistance exercise may benefit you. You will be encouraged to start this training at home.

The *diagram* below gives a brief overview of what taking part in the study would involve:



What are the possible disadvantages and risks of taking part?

As you will be performing repetitive movement of your wrist and leg muscles, there is a **small risk** you may experience an increase in **tiredness or pain**. This is likely to be mild, but we will monitor this while you are in the study. If you experience increased tiredness or pain, which cannot be explained by anything other than taking part in the study, you may be withdrawn from that treatment and upon consensus to continue to provide outcome data. As this study requires an 'exercise' and 'control' group design, you may be chosen to take part as a 'control'. This will involve maintaining your normal

daily lifestyle throughout the study course and come in for your neurophysiological testing sessions only. You will, however, receive an exercise program, resistance bands and a one-on-one phone call with the researcher to discuss resistance exercise benefits for you and health goals of exercise at the end of the study duration.

Is there any discomfort involved?

There might be some brief, mild discomfort from the electrical stimulation. If you find the stimulations too uncomfortable, you will be invited to rest between tests, and you may rest at any time during the experiment.

What are the possible benefits of taking part?

All participants will benefit from a more comprehensive assessment of their wrist and leg function than is available to them in routine clinical practice. Participants allocated to the progressive resistance exercise group may find that a program of supported progressive resistance exercise is practical for them and proves successful in terms of indicative changes in key fatigue and health outcomes. There is no benefit for the participants allocated to the control group. The control group will however be given a one-on-one consultancy with the researcher and could benefit from learning about potential benefits associated with resistance exercise.

What will happen if I don't carry on with the study?

You can withdraw from the study at any time, but any information collected may be used unless you request otherwise at the point of withdrawal.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. In any documentation other than consent form you will be referred to as a participant number rather than name allowing you to remain

anonymous. Any information collected will be kept under protected password locked computer and key lock cabinet for safekeeping.

What will happen to the results of the research study?

The results of this study are likely to be published in scientific journals. No personally identifiable information will be published. You may request an individualised report ten weeks after study participation.

Who is organising and funding the research?

The University of Northumbria and Multiple Sclerosis Society.

Who has reviewed the study?

This study was given a favourable opinion by the NATIONAL HEALTH SERVICE Research Ethics Committee**.** In addition, the research and development department at the hospital trust has agreed for this research to be carried out.

For further information about the study, please contact the Researcher or Principle Investigator on:

Researcher:

Paula Ellison

University of Northumbria

Tel: 0191 243 7018

Email: paula.ellison@northumbria.ac.uk

Principle Investigator:

Dr Martin Duddy (Consultant Neurologist)

Royal Victoria Infirmary (RVI)

Tel: 0191 282 5995

Email: Martin.duddy@nuth.national health service.uk

If you want to speak to an independent adviser (someone outside this study), the contact details are provided below:

Dr Mark Baker (consultant Neurologist)

Royal Victoria Infirmary (RVI)

Tel: 0191 282 4578

Email: Mark.Baker@nuth.national health service.uk

If you feel you would need to make a compliant, the contact details are provided below:

Patient Advice and Liaison Service (PALS)
Freephone: 0800 0320202 (09.00-4.30 Monday to Friday)
Text: 01670 511098
Fax: 01670 511260
Email: northoftynepals@nhct.national health service.uk

If you have read this Participant Information Sheet and would be interested in taking part in this study, please contact the research nurses on the contact details provided below:

Lisa Robson and Joanna Forsyth (MS Research Nurses)
Royal Victoria Infirmary (RVI)
Tel: 0191 282 9303

Appendix 6 – Patient Recruitment Letter

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

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Queen Victoria Road
Newcastle upon Tyne
NE1 4LP

Tel: 0191 233 6161
Fax: 0191 201 0155

[*Insert first line address*]
[*Insert second line address*]
[*Insert Town*]
[*Insert County*]
[*Insert Postcode*]

northumbria UNIVERSITY NEWCASTLE
Faculty of Health and Life Sciences
Northumberland Building
Newcastle upon Tyne
NE1 8ST
Tel 0191 227 3571
Fax 0191 227 4515

[Insert Date]

Dear [*Insert Recipient Name*]

You are being invited to take part in a research study titled:

'The feasibility of progressive resistance exercise for ameliorating symptoms of fatigue in people with multiple sclerosis'.

The study is funded by The Multiple Sclerosis Society and has been given a favourable ethical opinion by the University of Northumbria and a Research Ethics Committee. I would like to offer you the opportunity to learn more about the purpose of the study and what your participation would involve. This information has been outlined in a Participant Information Sheet which will be emailed or posted to you upon your request. Please note that you are under no obligation to participate in this entirely voluntary study. You can request a Participant Information Sheet by contacting the researcher at the contact details stated below:

Paula Ellison
Researcher
University of Northumbria
Tel: 07989673237
Email: paula.ellison@northumbria.ac.uk

If you would like to discuss this study with the Primary Investigator of the research team, Dr Martin Duddy at the Royal Victoria Hospital, is happy to respond to queries. His contact details are stated below.

Dr Martin Duddy
Consultant Neurologist
The Royal Victoria Infirmary
Tel: 0191 282 5995
Email: martin.duddy@nuth.national health service.uk

Yours faithfully,
Paula Ellison
Researcher

Appendix 7 – Consent Form

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

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Version:
Date completed:

CONSENT FORM

Title of Study: A Feasibility Study of Progressive Resistance Exercise in Fatigued People with Multiple Sclerosis.

Please **initial** box

1. I have read the participant information sheet for the above study and have been given a copy to keep. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand the procedures involved in the study. ☐
3. I understand that my participation is entirely voluntary and that I am free to withdraw at any time without giving any reason. ☐
4. I understand that I will not benefit financially from this research. ☐
5. I know how to contact the research team if i have a queryor require any additional information. ☐
6. I understand that all forms and data collection sheets will be treated as confidential and will remain anonymous. ☐
7. I understand that data will be limited to use in this study. ☐
8. I agree to participate in this study. ☐

Name of Participant (NAME IN BLOCK LETTERS)	Signature	Date
Name of Person taking consent (NAME IN BLOCK LETTERS	Signature	Date

Appendix 8 - Fatigue Severity Scale

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

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Participant Name: **Date:** **Version:**

Fatigue Severity Scale (FSS)

Please circle a number to the right of each of the following nine statements to indicate how much you agree with the statement. "1" represents "*strongly disagree*", "4" represents "*neither disagree nor agree*", while "7" represents "*strongly agree*".

1. My motivation is lower when I am fatigued.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family and/or social life.	1	2	3	4	5	6	7

Thank you for taking the time to answer the questions.

Appendix 9 – The Hospital Anxiety and Depression Scale

The Newcastle upon Tyne Hospitals NHS
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Participant Name: **Date:** **Version:**

Hospital Anxiety and Depression Scale (HADS)

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings, he or she will be able to help you more. This questionnaire is designed to help the clinician to know how you feel. Read each item below and **underline** the reply which come closest to how you have been feeling in the past week. (Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long, thought-out response.)

I feel tense or 'wound up' Most of the time A lot of the time From time to time, occasionally Not at all	**I feel as if I am slowing down** Nearly all the time Very often Sometimes Not at all
I still enjoy the things I used to enjoy Definitely as much Not quite so much Only a little Hardly at all	**I get a sort of frightened feeling like 'butterflies' in my stomach** Not at all Occasionally Quite often Very often

I get a sort of frightened feeling as if something awful is about to happen Very definitely and quite badly Yes, but not too badly A little, but it doesn't worry me Not at all	**I have lost interest in my appearance** Definitely I don't take as much care as I should I may not take quite as much care I take just as much care as ever
I can laugh and see the funny side of things As much as I always could Not quite so much now Definitely not so much now Not at all	**I feel restless as if I have to be on the move** Very much indeed Quite a lot Not very much Not at all
Worrying thoughts go through my mind A great deal of the time A lot of the time Not too often Very little	**I look forward with enjoyment to things** As much as I ever did Rather less than I used to Definitely less than I used to Hardly at all
I feel cheerful Never Not often Sometimes Most of the time	**I get sudden feelings of panic** Very often indeed Quite often Not very often Not at all
I can sit at ease and feel relaxed Definitely Usually Not often Not at all	**I can enjoy a good book or radio or television programme** Often Sometimes Not often Very seldom

Thank you for taking the time to answer the questions.

Appendix 10 – Modified Fatigue Impact Scale

The Newcastle upon Tyne Hospitals NHS
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Participant Name: **Date:** **Version:**

Modified Fatigue Impact Scale (MFIS)

Following a list of statements that describe how fatigue may affect people. Fatigue is a feeling of physical tiredness and a lack of energy that many people experience from time to time. In medical conditions like MS, feelings of fatigue can occur more often and have a greater impact than usual. Please read each statement carefully, and then circle the number that best indicates how often fatigue has affected you in this way during the past 4 weeks. (If you need help marking your responses, tell the interviewer the number of the best response). Please answer every question. If you are not sure which answer to select, please choose the one answer that comes closest to describing you. The interviewer can explain any words or phrases that you do not understand.

Because of my fatigue during the **past 4 weeks**….

	Never	Rarely	Sometimes	Often	Almost always
1. I have been less alert.	0	1	2	3	4
2. I have had difficulty paying attention for long periods of time.	0	1	2	3	4

3. I have been unable to think clearly.	0	1	2	3	4
4. I have been clumsy and uncoordinated.	0	1	2	3	4
5. I have been forgetful.	0	1	2	3	4
6. I have had to pace myself in my physical activities.	0	1	2	3	4
7. I have been less motivated to do anything that requires physical effort.	0	1	2	3	4
Because of my fatigue during the past 4 weeks**….**					
	Never	**Rarely**	**Sometimes**	**Often**	**Almost always**
8. I have been less motivated to participate in social activities.	0	1	2	3	4
9. I have been limited in my ability to do things away from home.	0	1	2	3	4
10. I have trouble maintaining physical effort for long periods.	0	1	2	3	4
11. I have had difficulty making decisions.	0	1	2	3	4
12. I have been less motivated to do anything that requires thinking.	0	1	2	3	4
13. My muscles have felt weak.	0	1	2	3	4
14. I have been physically uncomfortable.	0	1	2	3	4

15. I have had trouble finishing tasks that require thinking.	0	1	2	3	4
16. I have had difficulty organising my thoughts when doing things at home or at work.	0	1	2	3	4
17. I have been less able to complete tasks that require physical effort.	0	1	2	3	4
18. My thinking has been slowed down.	0	1	2	3	4
19. I have had trouble concentrating.	0	1	2	3	4
20. I have limited my physical activities.	0	1	2	3	4
21. I have needed more rest more often for longer periods.	0	1	2	3	4

Thank you for taking the time to answer the questions.

Appendix 11 – Chalder Fatigue Scale

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Participant Name: **Date:** **Version:**

Chalder Fatigue Scale

We would like to know more about any problems you have had with feeling tired, weak or lacking in energy in the last month. Please answer **ALL** the questions by **ticking** the answer which applies to you most closely. If you have been feeling tired for a long while, then compare yourself to how you felt when you were last well. Please **tick only one box per line**.

	Less than usual	No more than usual	More than usual	Much more than usual
Do you have problems with tiredness?				
Do you need to rest more?				
Do you feel sleepy or drowsy?				
Do you have problems starting things?				
Do you lack energy?				

Do you have less strength in your muscles?				
Do you feel weak?				
Do you have difficulties concentrating?				
Do you make slips of the tongue when speaking?				
Do you find it more difficult to find the right word?				
	Better than usual	**No worse than usual**	**Worse than usual**	**Much worse than usual**
How is your memory?				

Thank you for taking the time to answer the questions.

Appendix 12 – Pittsburgh Sleep Quality Index

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

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Participant Name: **Date:** **Version:**

Pittsburgh Sleep Quality Index (PSQI)

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, when have you usual gone to bed at night?
   Usual bed time _____
2. During the past month, how long (in minutes) has it usually take you to fall asleep each night?
   Number of minutes _____
3. During the last month, when have you usually gotten up in the morning?
   Usual getting up time _____
4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed.)
   Hours of sleep per night _____

For each of the remaining questions, **tick** the best response. Please answer **ALL** questions.

5. During the past month how often have you had trouble sleeping because you….

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(a)…cannot get to sleep within 30 minutes				
(b)…wake up in the middle of the night or early morning				
(c)…have to get up to use the bathroom				
(d)…cannot breathe comfortably				
(e)…cough or snore loudly				
(f)…feel too cold				
(g)..feel too hot				
(h)…had bad dreams				
(i)…have pain				
(j) Other reason (s), please describe				
How often during the past month have you had trouble sleeping because of this?				

	Very Good	Fairly Good	Fairly Bad	Very Bad
6. During the past month, how would you rate your sleep quality overall?	☐	☐	☐	☐

	Not during past month	Less than once a week	Once or twice a week	Three or more times a week
7. During the past month, how often have you taken medicine (prescribed or 'over the counter') to help you sleep?	☐	☐	☐	☐
8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?	☐	☐	☐	☐

	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
9. During the past month, how much of a problem has it been for you to keep up enough enthusiam to get things done?	☐	☐	☐	☐

	No bed partner or roommate	Partner/ roommate in other room	Partner in same room, but not same bed	Partner in same bed
10. Do you have a bed partner or room mate?	☐	☐	☐	☐

If you have a roommate or bed partner, **ask him/her** how often in the past month you have had…

	Not during the past month	**Less than once a week**	**Once or twice a week**	**Three or more times a week**
(a)…loud snoring				
(b)…long pauses between breathes while asleep				
(c)…leg twitching and jerking while you sleep				
(d)…episodes of disorientation or confusion during sleep				
(e) Other restlessness while you sleep; please describe				

Thank you for your time.

Appendix 13 – NARCOMS Pain Scale

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NHS Foundation Trust

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Newcastle upon Tyne
NE1 4LP

Tel: 0191 233 6161
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northumbria UNIVERSITY NEWCASTLE
Faculty of Health and Life Sciences
Northumberland Building
Newcastle upon Tyne
NE1 8ST
Tel 0191 227 3571
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Participant Name: **Date:** **Version:**

NARCOMS Pain Questionnaire

Please read all the categories, and ***check the single category*** that most accurately describes your pain (regardless of cause) in the past month.
Compare your current condition to your experience before you developed MS.

☐ 0 **Normal**: No symptoms of pain.
I have not noticed any problems with pain.

☐ 1 **Minimal Pain**
I notice some problems with pain, but they do not interfere with my activities.

☐ 2 **Mild Pain**
Occasionally, pain forces me to change some of my activities (e.g. once a week or less).

☐ 3 **Moderate Pain**
Frequently, pain affects some of my activities (e.g. several times a week).

☐ 4 **Severe Pain**
Every day, pain problems force me to modify my daily activities.

☐ 5 **Total Disabling Pain**
Every day, pain problems *prevent* me from doing many of my daily activities,

Thank you for your time.

Appendix 14– Rating of Perceived Exertion Scale

RATING OF PERCEIVED EXERTION

6

7 Very, very light

8

9 Very light

10

11 Light

12

13 Somewhat hard

14

15 Hard

16

17 Very hard

18

19 Very, very hard

20

Appendix 15– Characteristics of neuroimaging studies included in this review (N=47).

Author	N (by disease type)	MS Subgroups	Age (y)	Male/ Female	EDSS Scores	Disease Duration (y)	Perceived Fatigue Measure	Technique	Outcomes	MS-HF	MS-LF	HC	Summary of findings
Andreason *et al*. (2010)**	34 RR 7 HC	17 MS-HF 17 MS-LF	MS-HF: 43 (27-53) MS-LF: 39 (23-53) HC: 39 (31-45)	MS-HF: 5/12 MS-LF: 9/8 HC: 1/6	MS-HF: 3 (1-3.5) MS-LF: 2 (1.5-3.5) HC: 0 (0-2)	MS-HF: 5 (1-14) MS-LF: 3 (0-9)	FSS [>5 (Mean)] MS-HF: 6.3 (5-7) MS-LF: 2.8 (1-4) HC: 2.7 (2-4)	magnetic resonance imagery (DTI), MRS 3.0 Tesla scanner (GE Signa HDx)	Brain parenchymal fraction (%) Lesion load (%) NAA/Cr	81.5 ± 5.7 0.53 ± 0.37 1.29 ± 0.2	82.4 ± 2.5 0.36 ± 0.28 1.32 ± 0.19	81.1 ± 2.5 1.38 ± 0.13	Brain parenchymal fraction, lesion volume and NAA/Cr and DTI/MT indices were similar for MS-HF and MS-LF. Greater regional atrophy of grey matter structures and nearby white matter in MS-HF vs HC, found in frontal/parietal and basal ganglia regions.
Bakshi *et al.* (1999)	66 MS	46 MS-HF 20 MS-LF	MS-HF: 41.0 ± 1.4 MS-LF: 43.0 ± 4.0	MS-HF: 14/32 MS-LF: 4/16		MS: 9.7 (0.5-43)	FSS [>5.0 (mean)] Means for the 2 groups not reported. MS-HF 5 MS-LF 4	magnetic resonance imagery 1.0- or 1.5-Tesla	Brain atrophy; T1-hypointense and T2-hyperintense lesions.	Data only reported as correlation coefficients.	Data only reported as correlation coefficients.		No significant differences were found in any magnetic resonance imagery measures between MS-HF and MS-LF groups. No significant correlation between fatigue and any of the regional or global magnetic resonance imagery measures.
Bernitsas *et al.* (2017)	29 RR	15 MS-HF 14 MS-LF	MS-HF: 43 ± 2.9 MS-LF: 39 ± 1.7		MS-HF: 2 (1-4) MS-LF: 1.5 (1-4)	MS-HF: 10 ± 1.7 MS-LF: 8.6 ± 1.9	FSS [>5 (Mean)] MS-HF: 6 ± 0.12 MS-LF: 1.89 ± 0.2	magnetic resonance imagery (DTI) 3.0 Tesla scanner (Siemens Verio)	T2 Lesion volume (ml) Thalamus volume (ml) Pallidus volume (ml) Superior cerebellar peduncle volume (ml) Fractional anisotropy (FA) Mean diffusivity ($\times 10^{-3}$ mm^2/s)	14.0 ± 9.7 11.5 ± 1.1 2.6 ± 0.27 207.3 ± 27.5 0.24 ± 0.02 0.88 ± 0.08	15.3 ± 22.1 14 ± 2.2 3.0 ± 0.49 246.1 ± 35.9 0.27 ± 0.03 0.82 ± 0.04		Significantly lower subcortical grey matter volumes (thalamus, pallidus, and superior cerebellar peduncle) found in basal ganglia regions. FSS scores inversely correlated with thalamus and pallidus volumes. Lower fractional anisotropy and greater mean diffusivity in MS-HF vs MS-LF, demonstrating neuronal disruption.
Bisecco *et al.* (2016)	60 RR 29 HC	30 MS-HF 30 MS-LF	MS-HF: 41.2 (21-62) MS-LF:	MS-HF: 10/20	MS-HF: 2.0	MS-HF:	FSS [>4 (Mean)] MS-HF:	magnetic resonance	Normalised brain volume (ml)	428 ± 97	1444 ± 89	1513 ± 71	Normalised brain volume, grey matter, white matter, T2 lesion volume were not significantly

			40.2 (23-54) HC: 40.7 (25-61)	MS-LF: 9/21 HC: 13/16	(1.0- 6.0) MS-LF: 1.5 (1- 6.0)	14.5 (1- 44) MS-LF: 11.5 (1- 27)	5.2 (4.2-6.8) MS-LF: 2 (1-3.6) HC: 2 (1-3.9)	imagery (DTI) 3.0 Tesla scanner (Medical System)	Grey matter volume (ml) White matter volume (ml) T2 Lesion volume (ml)	777 ± 63 650 ± 43 10.1 ± 13.8	793 ± 61 651 ± 35 11.2 ± 12.1	824 ± 52 688 ± 35	different between MS-HF vs MS-LF. MS-HF showed more extensive white matter damage than MS-LF for mean diffusivity and fractional anisotropy.
Bisecco *et al.* (2017)	59 RR 29 HC	28 MS-HF 31 MS-LF	MS: 40.1 ± 10.1 MS-HF: 40.5 (21-62) MS-LF: 39.6 (23-54) HC: 39.8 ± 10.6	MS: 21/38 MS- HF: 10/18 MS-LF: 11/20 HC: 13/16	MS: 2.0 (1.0- 6.0) MS- HF: 2.0 (1.0- 5.5) MS-LF: 1.5 (1- 6.0)	MS: 12.5 (1- 44) MS- HF: 13.8 (1- 44) MS-LF: 11.2 (1- 27)	FSS [>4 (Mean)] MS: 3.6 (1-6.4) MS-HF: 5.1(4.1-6.4) MS-LF: 2 (1-3.6) HC: 1.9 (1-3.9)	magnetic resonance imagery , fMRI 3.0 Tesla scanner (GE Medical)	T2 Lesion volume (ml) Normalised brain volume (ml) Grey matter volume (ml) White matter volume (ml)	8.3 ± 12.9 1439 ± 96 784 ± 64 654 ± 40	11.2 ± 11.8 1450 ± 89 794 ± 61 656 ± 37	1519 ± 80 830 ± 57 689 ± 37	Significantly increased functionality in posterior cingulate cortex but decreased in anterior cingulated cortex in MS-HF vs MS-LF and HC. Reorganisation found in both default mode network and sensorimotor network at rest. T2 lesion volume, normalised brain volume, grey matter and white matter volume were not significantly different between MS-HF vs MS-LF but were lower than HC.
Calabrese *et al.* (2010)	152 RR 42 HC	71 MS-HF 81 MS-LF	MS-HF: 33.3 ± 8.2 MS-LF: 34.4 ± 8.8 HC: 35.5 ± 10.2	MS- HF: 26/45 MS-LF: 29/52 HC: 16/26	MS- HF: 3.3 ± 1.8 MS-LF: 2.2 ± 1.5	MS- HF: 9.9 ± 7.1 MS-LF: 8.7 ± 1.5	FSS [4 (Mean)] MS-HF: 5.1 ± 0.75 MS-LF: 2.2 ± 1.0	magnetic resonance imagery 1.5 Tesla scanner (Achieva MR)	Global mean cortical thickness (mm) T2 lesion volume (ml) Putamen (ml) Caudate (ml) Thalamus (ml) Superior frontal gyrus cortical thickness (mm)	2.17 ± 0.25 9.2 ± 7.9 3.8 ± 1.3 4.1 ± 0.5 4.7 ± 0.9 2.30 ± 0.28	2.25 ± 0.21 8.8 ± 7.7 4.5 ± 0.8 5.1 ± 0.5 6.8 ± 0.8 2.57 ± 0.21	2.50 ± 0.11 5.1 ± 0.9 5.2 ± 0.8 6.1 ± 0.8	Significant reductions in putamen, caudate and thalamus volumes and cortical thickness of the superior frontal gyrus and inferior parietal gyrus in MS-HF vs MS-LF and MS vs HC. T2 lesion volume was not significantly different for MS-HF vs MS-LF.

									Inferior parietal gyrus cortical thickness (mm)	2.04 ± 0.28	2.52 ± 0.21		
Codella *et al.* (2002)	28 MS 30 HC	14 MS-HF 14 MS-LF	MS-HF: 39.1 ± 8.9 MS-LF: 37.6 ± 6.6 HC: 41.2 ± 7.1	MS-HF: 3/11 MS-LF: 6/8 HC:10/20	MS-HF: 1.0 (0.0-1.0) MS-LF: 1.0 (0.0-1.0)	MS-HF: 6.0 (1-40) MS-LF: 8.0 (3-22)	FSS [>25 (Total)] MS-HF: 38.9 (28-55) MS-LF: 19.7 (13-24)	magnetic resonance imagery (DTI, MTI) 1.5 Tesla scanner	T2 Lesion volume (ml)	8.9 ± 10.8	7.2 ± 4.7		T2 lesion volume and DTI indices were not significantly different for MS-HF vs MS-LF but the latter differed between MS and HC.
									Mean diffusivity ($\times 10^{-3}$ mm^2/s)	0.93 ± 0.06	0.96 ± 0.04	0.91 ± 0.05	
									Fractional anisotropy	0.20 ± 0.01	0.20 ± 0.01	0.23 ± 0.01	
									Magnetisation transfer ratio (%)	40.0 ± 0.6	40.4 ± 1.2	40.6 ± 1.0	
Cogliati Dezza *et al.* (2015)**	27 MS 8 HC	15 MS-HF 12 MS-LF	MS-HF: 37.3 ± 4 MS-LF: 36.9 ± 7.5 HC: 37 (25-48)	MS-HF: 4/11 MS-LF: 4/8 HC: 1/7	MS-HF: 1 (0-3) MS-LF: 1 (0-2)	MS-HF: 3.9 ± 4.1 MS-LF: 7.1 ± 3.9	MFIS [>36 (Total)] MS-HF: 42.1 ± 7.3 MS-LF: 19.9 ± 8.6	Magnetic resonance imagery 1.5 Tesla scanner (Achieva, Phillips)	Thalamus volume (ml)	14.1 ± 1.8	13.3 ± 1.5	14.7 ± 1.5	Thalamus volume and rolandic thickness/asymmetry were not significantly different for MS-HF vs MS-LF or HC.
									Intracranial volume (ml)	1440 ± 200	1490 ± 230	1500 ± 210	
									Central sulcus area (mm)				
									Left	1.72 ± 0.07	1.72 ± 0.18	1.78 ± 0.14	
									Right	1.71 ± 0.10	1.68 ± 0.18	1.72 ± 0.15	
Colombo *et al.* (2000)**	30 MS	15 MS-HF 15 MS-LF	MS-HF: 30.4 (18-49) MS-LF: 39 (18-49)	MS-HF: 3/12 MS-LF: 4/11	MS-HF: 1.5 (0-1.5) MS-LF: 1.5 (0-1.5)	MS-HF: 2.8 (1-7) MS-LF: 3.7 (1-9)	FSS [>25(Total)] MS-HF: 40 (25-60) MS-LF: 14 (10-21)	magnetic resonance imagery 1.5 Tesla scanner	Total lesion load-volume	32 (5-82)	22 (6-60)		Significantly higher volume of lesions for MS-HF vs MS-LF, found in the parietal lobe and white matter regions (internal capsule, periventricular areas).
Cruz Gomez *et al.* (2013)	60 RR 18 HC	32 MS-HF 28 MS-LF	MS-HF: 37.72 ± 5.9 MS-LF: 34.96 ± 5.87 HC: 31.06 ± 5.67	MS-HF: 11/21 MS-LF: 10/18 HC: 10/8	MS-HF: 3.2 ± 1.68 MS-LF: 2.2 ± 0.96		FSS [>4 (Mean)] MS-HF: 5.6 ± 0.85 MS-LF: 2.21 ± 0.96	fMRI 1.5 Tesla scanner (Siemens Avanto)	T1 lesion volume (ml)	6.03 ± 14.02	3.16 ± 3.97		Grey matter and white matter atrophy in MS-HF vs MS-LF, found in areas related to the sensorimotor networks. Decreased resting functionality between the supplementary motor area and associative somato-sensory cortex in MS-HF vs MS-LF and HC and correlations with FSS scores.
									Intracranial volume (ml)	1101.16 ± 144.74	1141.34 ± 121.98	1261.24 ± 102.63	

Damasceno *et al.* (2016)	49 RR 30 HC	22 MS-HF 27 MS-LF	MS-HF: 31.86 ± 6.84 MS-LF: 30.18 ± 6.96 HC: 29.52 ± 7.53	MS-HF: 3/19 MS-LF: 8/19 HC: 7/23	MS-HF: 2.75 (1.5-4) MS-LF: 1.5 (0-3.0)	MS-HF: 7.00 ± 4.82 MS-LF: 5.62 ± 4.79	FSS [>4 (Mean)] MS: 3.54 ± 1.65 MS-HF: 5.19 ± 0.68 MS-LF: 2.20 ± 0.73 HC: 2.65 ± 0.88	magnetic resonance imagery 3.0 Tesla scanner (Achieva, Phillips)	Brain cortical grey matter volume (ml) T1 lesion volume (ml) Brain cortical lesions (mm^3) Cerebellar cortical lesion volume (mm^3) Cerebellar grey matter volume (ml) Thalamus volume (ml) Putamen volume (ml) Caudate volume: (ml) Amygdala volume (ml) Accumbens volume (ml)	426.20 ± 35.22 7.7 ± 12.0 900.0 ± 973.6 91.56 ± 93.18 88.87 ± 8.42 12.65 ± 1.42 10.22 ± 2.10 6.47 ± 0.99 3.50 ± 0.61 1.28 ± 0.27	425.58 ± 51.88 4.7 ± 4.0 874.20 ± 870.0 27.40 ± 56.29 92.53 ± 16.96 12.06 ± 1.97 10.82 ± 1.73 6.70 ± 1.05 3.66 ± 0.50 1.33 ± 0.26	440.82 ± 35.13 94.36 ± 11.43 94.36 ± 11.43 13.75 ± 1.18 12.29 ± 1.40 7.56 ± 0.75 3.86 ± 0.55 1.55 ± 0.26	Significantly greater cerebellar cortical lesion volume, brain cortical volume and most subcortical grey matter structures (thalamus, caudate, putamen, amygdala, accumbens) in MS-HF vs MS-LF and MS vs HC. Supports the theory of cortico-striatal network impairment in MS fatigue.
Derache *et al.* (2013)	17 RR	11 MS-HF 6 MS-LF	MS-HF: 38 (20-49) MS-LF: 26.5 (20-47)	MS-HF: 1/10 MS-LF: 0/6	MS-HF: 2 (0-3) MS-LF: 1.5 (1-2)	MS-HF: 3.9 (0.3-15.4) MS-LF: 3.1 (0.6-4.1)	EMIF-SEP [45 (scaled)] MS-HF: 56.9 (46.3-81.3) MS-LF: 37.8 (12.2-43.1)	Positron emission tomography (Seimens ECAT Exact HR+ scanner) magnetic resonance imagery 1.5 Tesla scanner (GE Inc. SIGNA	Regional grey matter density. Regional and global deep white matter lesion volume, regional and global juxtacortical and/or overlapping lesion volume.	Only difference scores between the groups and correlations reported.	Only difference scores between the groups and correlations reported.		Significant lower grey matter density in MS-HF versus MS-LF for the bilateral middle, superior and inferior frontal, left temporal and parietal cortex. Total fatigue score was negatively correlated with grey matter density in these same regions.

								Echo speed 8.3)					
Dobryakova *et al.* (2018)^	17 RR 1 SP 1 PP 14 HC	13 MS-HF 6 MS-LF	MS: 44.16 ± 7.46 HC: 37.29 ± 12.29				FSS [>36 (Total)] MS-HF: 60 ± 3 MS-LF: 28 ± 8	magnetic resonance imagery , fMRI (+task) 3.0 Tesla	Grey matter volume (ml) White matter volume (ml)	756 ± 25 692 ± 48	776 ± 54 703 ± 58	810 ± 40 739 ± 28	Lower grey matter volume and white matter volume in MS-HF vs MS-LF and HC.
Filippi *et al.* (2002)	29 RR 15 HC	15 MS-HF 14 MS-LF 15 HC	MS-HF: 39.3 ± 8.2 MS-LF: 37.6 ± 6.6		MS-HF: 1 (0-1) MS-LF: 1 (0-1)	MS-HF: 7 (1-40) MS-LF: 6.5 (2-10)	FSS [25 (total)] MS-HF: 39.5 ± 7.1 MS-LF: 19.3 ± 5.2	magnetic resonance imagery /fMRI 1.5 Tesla (Vision, Siemens)	Pattern of brain activation during a simple motor task (maximum finger-tapping frequency and the nine-hole peg test).	Data reported as brain scans and brain activation sites as Talairach coordinates.	Data reported as brain scans and brain activation sites as Talairach coordinates.	Data reported as brain scans and brain activation sites as Talairach coordinates.	Compared to MS-HF, MS-LF showed more significant activations of the ipsilateral cerebellar hemisphere, ipsilateral rolandic operculum, ipsilateral precuneus, contralateral thalamus and contralateral middle frontal gyrus during a simple motor task. In contrast, MS-HF had more significant activation of the contralateral cingulate motor area. Significant inverse correlations were found between FSS scores and relative activation of the contralateral intraparietal sulcus, ipsilateral rolandic operculum and thalamus.
Gobbi *et al.* (2014a)	91 RR 22 SP 10 PP 90 HC	81 MS-HF 66 MS-LF	MS-HF: 42.8 ± 11 MS-LF: 40.5 ± 10.5 HC: 41.9 ± 12.3	MS-HF: 32/49 MS-LF: 28/38 HC: 33/57	MS-HF: 3.5 (1.0-7.0) MS-LF: 2.5 (0.0-7.0)	MS-HF: 13.3 ± 9.1 MS-LF: 12.1 ± 6.7	FSS [>4 (Mean)] MS-HF: 5.2 (4-6.8) MS-LF: 2.4 (1-3.9)	magnetic resonance imagery (DTI) 3.0 Tesla scanner (Intera, Philips Medical Systems)	Normalised brain volume (ml) Grey matter volume (ml) White matter volume (ml) T1 lesion volume (ml) T2 lesion volume (ml)	1487 ± 106 670 ± 76 817 ± 50 6.4 ± 7.6 8.9 ± 10.0	1509 ± 107 685 ± 70 825 ± 61 5.8 ± 5.9 8.4 ± 8.0	1577 ± 85 735 ± 50 841 ± 48	T1 and T2 lesion volume, normalised brain volume, grey matter and white matter volume did not significantly differ between MS-HF vs MS-LF but MS was lower vs HC. Reduced fractional anisotropy of the right anterior thalamic radiation and right uncinate fasciculus in MS-HF versus MS-LF.

Gobbi *et al.* (2014b)	81 RR 18 BN 17 SP 8 PP 90 HC	64 MS-HF 59 MS-LF	MS-HF: 42.3 ± 10.3 MS-LF: 41.0 ± 10.5 HC: 39.7 ± 13.7	MS-HF: 26/38 MS-LF: 26/33 HC: 39/51	MS-HF: 2.5 (1-7.0) MS-LF: 1.5 (0.-7.0)	MS-HF: 13.1 (1-44) MS-LF: 11.9 (1-32)	FSS [>4 (Mean)] MS-HF: 5.1 (3.0-6.6) MS-LF: 2.3 (1.0-3.9)	magnetic resonance imagery 3.0 Tesla scanner (Intera, Philips Medical Systems)	Normalised brain volume (ml) T1 lesion volume (ml) T2 lesion volume (ml)	1488 ± 107 6.8 ± 7.9 9.7 ± 10.7	1501 ± 112 6.1 ± 6.1 8.8 ± 8.3	1609 ± 86	Normalised brain volume, T1 and T2 lesion volumes were not significantly different for MS-HF vs MS-LF.
Gonzalez Campo *et al.* (2019)	27 RR 28 HC	14 MS-HF 13 MS-LF	MS-HF: 42.2 ± 11 MS-LF: 36.3 ± 9.4 HC: 35.8 ± 11.0	MS-HF: 5/14 MS-LF: 4/9 HC: 5/23	MS-HF: 1.4 ±1.9 MS-LF: 1.0 ± 1.4	MS-HF: 11.3 ±9.3 MS-LF: 7.9 ± 4.9	MFIS [37 (Total)] MS-HF: 53.2 (37-76) MS-LF: 19.9 (4-32)	magnetic resonance imagery 1.5 T Phillips Intera scanner with a standard head coil	Introception condition accuracy score	–0.49 ± 0.83	0.64 ± 0.99	0.55 ± 0.87	Decreased introception condition accuracy score and reduced grey matter voume in introceptive areas (bilateral insula, right anterior cingulate cortex) in MS-HF versus HC. Increased connectivity between the right anterior cingulate cortex and left insula in MS-HF versus HC.
Hanken *et al*. (2015)	49 RR 17 HC	28 MS-HF 25 MS-LF	MS-HF: 41.9 ± 6.8 MS-LF: 44.5 ± 11.2 HC: 37.4 ± 9.9	MS-HF: 4/24 MS-LF: 6/19 HC: 6/11	MS-HF: 2.9 ± 2.0 MS-LF: 2.8 ± 1.7	MS-HF: 7.8 ± 8.3 MS-LF: 7.8 ± 6.1	FSS [>36 (Total)] MS-HF: 54.6 ± 5.1 MS-LF: 29.8 ± 9.3 HC: 24.3 ± 7.8	magnetic resonance imagery (DTI) 3.0 Tesla scanner (Siemens Verio)	Brain parenchymal fraction (%) Lateral ventricles (ml) Third ventricle (ml) Fourth ventricle (ml)	79.3 ± 3.6 26.6 ± 15.5 2.6 ± 1.7 2.1 ± 0.9	78.7 ± 3.2 28.2 ± 16.0 2.6 ± 1.1 2.0 ± 0.8	81.4 ± 3.0 17.3 ± 6.9 2.0 ± 1.0 1.9 ± 0.8	Brain parenchymal fraction, lateral, third and fourth ventricle volumes were not significantly different for MS-HF vs MS-LF or HC.
Hanken *et al.* (2016)	69 RR 17 SP 9 PP 15 HC	18 MS-HF 42 MS-LF	MS-HF: 43.1 ± 6.3 MS-LF: 42.9 ± 11.7 HC: 37.0 ± 10.5	MS-HF: 4/14 MS-LF: 18/24 HC: 6/9	MS-HF: 3.4 ± 2.2 MS-LF: 3.1 ± 1.8	MS-HF: 6.8 ± 6.0 MS-LF: 7.8 ± 8.6	FSS [>5 (Mean)] MS-HF: 56 ± 3 MS-LF: 30 ± 12	magnetic resonance imagery 1.5 Tesla scanner (Phillips)	Brain parenchymal fraction (%) Cortical thickness by region (mm): Gyrus rectus Left Olfactory cortex left Inferior parietal right Precuneus right	80.8 ± 4.8 3.0 ± 0.4 2.9 ± 0.3 3.0 ± 0.4 3.0 ± 0.3	81.0 ± 4.3 3.2 ± 0.3 2.9 ± 0.3 3.2 ± 0.2 3.1 ± 0.2	81.8 ± 2.6 3.3 ± 0.2 3.1 ± 0.1 3.1 ± 0.1 3.2 ± 0.1	Significantly decreased cortical thickness in right inferior parietal lobe, right cingulate cortex and the right precuneus for MS-HF vs MS-LF and HC.

									Superior temporal pole right	3.5 ± 0.4	3.6 ± 0.3	3.8 ± 0.2	
									Medial temporal pole right	3.4 ± 0.4	3.6 ± 0.4	3.8 ± 0.3	
									Anterior cingulate right	2.9 ± 0.4	3.0 ± 0.2	3.0 ± 0.2	
									Middle cingulate left	2.9 ± 0.4	2.9 ± 0.3	3.1 ± 0.2	
									Middle cingulate right	2.9 ± 0.4	3.0 ± 0.2	3.1 ± 0.2	
									Insula left	2.7 ± 0.3	2.7 ± 0.3	2.9 ± 0.1	
									Insula right	2.7 ± 0.3	2.7 ± 0.2	2.9 ± 0.2	
									Parahippocampus right	2.9 ± 0.3	2.9 ± 0.4	3.0 ± 0.2	
Hidalgo de la Cruz *et al.* (2017)	122 MS 94 HC	36 MS-HF 86 MS-LF	MS-HF: 44.3 ± 12.4 MS-LF: 35.0 ± 11.8 HC: 41.5 ± 14.6	MS-HF: 13/23 MS-LF: 37/49 HC: 46/48	MS-HF: 4.0 (0.0-6.5) MS-LF: 1.5 (0.0-8.0)	MS-HF: 13.4 ± 9.8 MS-LF: 10.8 ± 6.2	MFIS [>38 (Total)] MS-HF: 48.0 (38.0-70.0) MS-LF: 20.0 (0.0-37.0)	magnetic resonance imagery (DTI), fMRI 3.0 Tesla scanner	Normalised brain volume (ml)	1502 ± 102	1545 ± 86	1577 ± 84	Significantly higher T1 and T2 lesion volumes and lower normalised brain volume and grey matter volume in MS-HF vs MS-LF. Resting state functional connectivity was not significantly different for MS-HF vs MS-LF or HC.
									Grey matter volume (ml)	682 ± 74	720 ± 58	736 ± 57	
									White matter volume (ml)	819 ± 42	826 ± 46	841 ± 43	
									T1 lesion volume (ml)	6.0 ± 6.5	3.5 ± 3.5		
									T2 lesion volume (ml)	9.0 ± 8.3	5.7 ± 5.3		
									nRThal volume (ml)	9.6 ± 1.2	9.8 ± 0.9	10.3 ± 0.8	
									nLThal volume (ml)	9.8 ± 1.0	10.1 ± 0.9	10.7 ± 0.8	
Jaeger *et al.* (2018)	77 RR 41 HC	39 MS-HF 38 MS-LF	MS-HF: 40 (18) MS-LF: 34.5 (18) HC: 36 (21)	MS-HF: 7/32 MS-LF: 14/24 HC: 15/26	MS-HF: 2.5 (1) MS-LF: 2 (1.5)	MS-HF: 6.8 (10.3) MS-LF: 5.1 (9.1)	FSS [>4 (Mean)] MS-HF: 5.2 (1.3) MS-LF: 2.6 (1.9) HC: 1.9 (1.3)	magnetic resonance imagery , fMRI, 3.0 Tesla (Siemens Tim Trio scanner)	Total T1 white matter lesion volume (ml)	3.7 (2.9)	3.6 (4.2)		Significantly reduced functional connectivity of the whole caudate nucleus with sensorimotor and frontal, parietal, and temporal cortex regions in MS-HF vs MS-LF and HC. T1 lesion volume, normal brain volume, grey matter volume and white matter volume was not significantly different for
									Normalised brain volume (ml)	1522.4 ± 65.5	1548 ± 88.4	1565.5 ± 82.3	
									Grey matter volume (ml)	804.2 ± 57.2	824.2 ± 63.8	829 ± 63.6	
									White matter volume (ml)	718.2 ± 41.2	723.8 ± 38.1	736.5 ± 40.6	

									Caudate volume (ml) Putamen volume (ml)	9.3 ± 1.0 12.5 ± 0.9	9.5 ± 0.78 12.7 ± 0.9	9.7 ± 1.08 13.3 ± 0.9	MS-HF vs MS-LF but was lower for MS-HF than HC.
Lin *et al.* (2019)^	34 RR 14 SP 4 PP 6 RSP 26 HC	33 MS-HF 25 MS-LF	MS-HF: 53 ± 9.4 MS-LF: 53.6 ± 11.1 HC: 49.85± 14.4	MS-HF: 8/25 MS-LF: 14/11 HC: 8/18	MS-HF: 4.0 (2.5-6.5) MS-LF: 2.5 (1.5-3.5)	MS-HF: 24 ± 11.3 MS-LF: 18.8 ± 8.8	FSS [>5 (Mean)] MS-HF: 5.7 ± 0.9 MS-LF: 2.6 ± 0.9 HC: 2.59 ± 1.26	magnetic resonance imagery, fMRI, 3.0 Tesla (GE Signa Excite HD 12.0 8-channel scanner)	T2 lesion volume (ml) Intracranial volume (ml) Thalamus volume (ml)	18.8 ± 22.0 1439.8 ± 81.1 13.2 ± 1.2	12.0 ± 14.5 1419.4 ± 66.5 13.4 ± 1.5	0.48 ± 1.23 1457.8 ± 143.5 15.1 ± 1.3	Decreased functional connectivity for MS vs HC between the left medial thalamic nuclei and left angular gyrus and reduced functional connectivity between the left posterior thalamic nuclei and left supramarginal gyrus, as well as decreased right medial thalamic nuclei connectivity with bilateral caudate/thalamus and left cerebellar areas. MS also had increased FC between the left anterior thalamic nuclei and anterior cingulate cortex bilaterally. Data for MS-HF and MS-LF obtained by communication with the author.
Morgante *et al.* (2011)**	33 RR 12 HC	16 MS-HF 17 MS-LF	MS-HF: 41.1 ± 10.9 MS-LF: 38 ± 9.4	MS-HF: 7/9 MS-LF: 4/13	MS-HF: 1.8 ± 0.6 MS-LF: 1.6 ± 0.6	MS-HF: 8.4 ± 3.4 MS-LF: 7.9 ± 3.8	FSS [>4 (Mean)] MS-HF: 4.9 ± 0.8 MS-LF: 2.2 ± 0.9	magnetic resonance imagery 1.5 Tesla scanner (Magnetom Impact)	Total brain volume (ml) Grey matter volume (ml) White matter volume (ml) T1 lesion volume (ml) T2 lesion volume (ml)	983.8 ± 102.8 425.6 ± 64.4 558.2 ± 84.4 1.3 ± 1.6 4.3 ± 5.0	995.7 ± 72.6 447.1 ± 50.7 548.6 ± 58.5 0.8 ± 1.0 3.2 ± 3.4		Significantly higher T1 lesion volume in MS-HF vs MS-LF. Total brain volume, grey matter volume, white matter volume and T1 and T2 lesion volumes were not significantly different for MS-HF vs MS-LF.
Niepel *et al.* (2006)	34 RR 19 HC	20 MS-HF 11 MS-LF	MS: 38 (32-42)	MS: 7/27	MS: 2.5 (2-3)	MS: 9 (3-13)	FSS [≥5 (Mean)] MS-HF≥5 MS-LF≤4 Means for the 2 MS groups not reported.	magnetic resonance imagery, 1.5 Tesla scanner (Vision MT)	T2 lesion volume (ml)	5.9 (2.9-12.7)	4.2 (2.0-7.4)		Median T2 lesion volume was not significantly different for MS-HF vs MS-LF.

Pardini *et al.* (2010)	40 RR	15 MS-HF 25 MS-LF	MS-HF: 41.3 ± 4.4 MS-LF: 36.0 ± 9.0	MS:12/28	MS-HF: 1.6 ± 1.2 MS-LF: 1.5 ± 0.7	MS-HF: 5.9 ± 7.3 MS-LF: 5.8 ± 3.9	MFIS [>38 (Total)] MS: 31.1 ± 18.0 MS-HF: 20.2 ± 10.0 MS-LF: 51.4 ± 9.9	magnetic resonance imagery (DTI) 1.5 Tesla scanner (MR system)	T2 Lesion load-volume (ml) Normalised Brain Volume (ml)	8.6 ± 16.8 1600 ± 900	7.4 ± 9.5 1500 ± 200		Significant involvement of different frontal (fronto-frontal, fronto-straital, fronto-occipital and fronto-limbic) networks in the pathophysiology of MS fatigue. Significant correlation between MFIS and white matter regions, within fronto-striatal networks.
Pellicano *et al.* (2010)^	20 RR 4 SP 24 HC	8 MS-HF 16 MS-LF	MS: 45.4 ± 9.7 HC: 45.1 ± 11.1	MS: 7/17 HC: 7/17	MS: 1.5 (0.0-6.5)	MS: 12.6 ± 8.4	MFIS [>38 (Total)] MS: 30.3 ± 16.1 HC: 13.4 ± 12.1	magnetic resonance imagery, 3.0 Tesla scanner (Sigma MI)	T2 Lesion volume (ml)	10.33 ± 9.8	8.60 ± 6.3		T2 lesion volume was significantly higher and thickness of the posterior and inferior parietal cortex, supramarginal gyrus and thalamus volume lower for MS-HF vs MS-LF.
Pravata *et al.* (2016)	22 RR 12 HC	11 MS-HF 11 MS-LF 12 HC	MS-HF: 46.6 ± 9.3 MS-LF: 40.0 ± 5.8 HC: 41.4 ± 8.0	MS-HF: 7/4 MS-LF:7/4 HC: 6/6	MS-HF: 2.5 (0-3.5) MS-LF: 1.5 (0-3.0)	MS-HF: 9.5 ± 3.8 MS-LF: 6.0 ± 4.4	FSMC [≥22 (Cognitive Scale)] MS-HF: 33.6 ± 4.8 MS-LF: 14.3 ± 3.8 HC: 14.4 ± 4.1	magnetic resonance imagery, fMRI, (3.0 Tesla Siemens "Skyra" scanner)	Brain resting-state functional connectivity (RS-FC) scans before, immediately after and 30 min after execution of the paced auditory serial addition test (PASAT).	Data reported as graphs and correlation coefficients.	Data reported as graphs and correlation coefficients.	Data reported as graphs and correlation coefficients.	MS-HF experienced stronger RS-FC 30 min post-PASAT between the left superior frontal gyrus and occipital, frontal and temporal areas. Also, in MS-HF, the left superior frontal gyrus was hyperconnected with the left caudate nucleus immediately post task and hypoconnected at 30 min post with the left anterior thalamus.
Riccitelli *et al.* (2011)	24 RR 14 HC	10 MS-HF 14 MS-LF	MS-HF: 38.0 ± 7.7 MS-LF: 38.6 ± 8.5 HC: 38.7 ± 8.4	MS-HF: 6/4 MS-LF: 6/8 HC: 6/8	MS-HF: 1.5 (1.5-2.0) MS-LF: 1.5 (0-1.5)	MS-HF: 8.2 ± 6.2 MS-LF: 10.6 ± 6.6	FSS [>4 (Mean)] MS-HF: 4.4 (4-6.1) MS-LF: 2.1 (1.4-3.3)	magnetic resonance imagery 1.5 Tesla scanner (Vision)	Total brain volume (ml) Grey matter volume (ml) White matter volume (ml) T2 Lesion load-volume (ml)	1596 ± 79 795 ± 66 801 ± 55 7.7 ± 5.0	1560 ± 51 770 ± 45 790 ± 60 8.9 ± 10.7	1649 ± 48 826 ± 58 822 ± 42	Significantly greater atrophy of left central sulcus, precentral gyrus and primary motor cortex region in MS-HF vs MS-LF and HC. T2 lesion volume, total brain volume, white matter volume, grey matter volume and intracranial volume were not significantly different for MS-HF vs MS-LF but were lower compared to HC.
Rocca *et al.* (2009)	24 RR 14 HC	11 MS-HF 13 MS-LF	MS-HF: 33.8 ± 6.2 MS-LF: 31.2 ± 4.3	MS-HF: 1/10	MS-HF: 1.0 (0.0-1.5)	MS-HF: 6 (2-12) MS-LF:	FSS [25 (Total)] MS-HF:	magnetic resonance imagery, fMRI	Normalised brain volume (ml)	1493 ± 131	1540 ± 100	1519 ± 115	T2 lesion volume and normalised brain volume were similar for MS-HF and MS-LF and for MS vs HC. fMRI disruption in

			HC: 32.2 ± 5.5	MS-LF: 1/12 HC: 2/12	MS-LF: 1.0 (0.0-1.5)	6 (2-10)	37.7 ± 7.7 MS-LF: 15.6 ± 4.8	1.5 Tesla scanner (Vision Siemens)	T2 lesion volume (ml)	8.1 ± 8.5	8.8 ± 6.0		frontal-parietal lobes and basal ganglia regions in MS-HF vs MS-LF.
Rocca *et al.* (2012)	35 RR 20 HC	20 MS-HF 15 MS-LF	MS-HF: 38.8 (29-65) MS-LF: 38.8 (29-60) HC: 37.3 (24-53)	MS-HF: 6/14 MS-LF: 8/7 HC: 7/13	MS-HF: 3.5 (1.5-5.5) MS-LF: 3.0 (0-5.0)	MS-HF: 10.5 (2-23) MS-LF: 11.2 (0.5-27)	FSS [>4 (Mean)] MS-HF: 4.7 (4-6) MS-LF: 2.2 (1-3.9)	magnetic resonance imagery, fMRI 1.5 Tesla scanner (Siemens Magnetom)	T2 lesion volume (ml)	6.6 ± 6.1	22.1 ± 16.5		Significantly greater brain white matter fractional anisotropy and reduced fMRI activation in the left anterior and posterior cervical cord quadrants in MS-HF vs MS-LF and HC.
									Mean diffusivity ($\times 10^{-3}$ mm^2/s)				
									Grey matter average	0.94 ± 0.06	0.97 ± 0.07	0.89 ± 0.03	
									White matter average	0.79 ± 0.02	0.82 ± 0.06	0.77 ± 0.02	
									Cervical cord average	0.94 ± 0.09	0.96 ± 0.04	0.85 ± 0.09	
									Fractional anisotropy (FA)				
									White matter average	0.39 ± 0.02	0.36 ± 0.03	0.41 ± 0.02	
									Cervical cord average	0.47 ± 0.04	0.49 ± 0.04	0.59 ± 0.06	
Rocca *et al.* (2014)	63 RR 35 HC	31 MS-HF 32 MS-LF	MS-HF: 41 (23-63) MS-LF: 39.5 (27-58) HC: 40.7 (23-63)	MS-HF: 14/17 MS-LF: 15/17 HC: 16/19	MS-HF: 2.5 (1.0-5.5) MS-LF: 2.0 (1.0-6.5)	MS-HF: 13.0 (0.6-32) MS-LF: 11.65 (0.8-25.5)	FSS [>4 (Mean)] MS-HF: 5.0 (4-6.4) MS-LF: 2.1 (1.2-3.8)	magnetic resonance imagery (DTI) 3.0 Tesla scanner (Intera; Philips Medical Systems)	Normalised brain Volume (ml)	1477 ± 109	1525 ± 90	1572 ± 93	Significantly greater T2 lesion volume and atrophy of the right accumbens, right inferior temporal gyrus, left superior frontal gyrus, and forceps major in MS-HF vs MS-LF and HC. Lower fractional anisotropy (forceps major, left inferior fronto occipital fasciculus and right anterior thalamic radiation) in MS-HF vs MS-LF and HC. T1 lesion volume, normal brain volume, grey matter volume and white matter volume were not significantly different for MS-HF vs MS-LF but were lower compared to HC.
									Grey matter Volume (ml)	665 ± 85	691 ± 60	726 ± 58	
									White matter Volume (ml)	811 ± 46	835 ± 61	846 ± 52	
									T1 lesion volume (ml)	6.0 ± 6.1	5.7 ± 5.6	0.02 ± 0.04	
									T2 lesion volume (ml)	8.7 ± 9.7	8.5 ± 8.1	0.03 ± 0.09	
									Mean cortical lesions (ml)	2 (0-6)	1 (0-8)		
									Thalamus volume (ml)	14.03 ± 1.13	14.27 ± 1.27	15.90 ± 1.13	

									Caudate volume (ml)	6.12 ± 0.64	6.43 ± 0.71	6.77 ± 0.57	
									Putamen volume (ml)	8.48 ± 0.71	8.69 ± 0.92	9.18 ± 0.71	
									Accumbens volume (ml)	0.75 ± 0.13	0.85 ± 0.14	0.85 ± 0.13	
									Amygdala volume (ml)	2.70 ± 0.22	2.67 ± 0.22	2.59 ± 0.22	
									Hippocampus volumen (ml)	6.87 ± 0.57	7.05 ± 0.64	7.30 ± 0.50	
									Pallidus volumen (ml)	3.16 ± 0.28	3.28 ± 0.28	3.26 ± 0.28	
									Mean diffusivity ($\times 10^{-3}$ mm^2/s):				
									Grey matter	0.92 ± 0.05	0.92 ± 0.05	0.90 ± 0.04	
									White matter	0.78 ± 0.03	0.78 ± 0.03	0.76 ± 0.02	
									Fractional anisotropy:				
									Grey matter	0.16 ± 0.01	0.16 ± 0.01	0.15 ± 0.01	
									White matter	0.38 ± 0.02	0.38 ± 0.02	0.39 ± 0.02	
Rocca *et al.* (2016)	79 RR 26 HC	50 MS-HF 29 MS-LF	MS-HF: 42.6 ± 11.2 MS-LF: 40.0 ± 9.1 HC: 39.2 ± 13.4	MS-HF: 17/33 MS-LF: 10/19 HC: 9/17	MS-HF: 2.0 (1.0-4.0) MS-LF: 1.5 (0.0-4.0)	MS-HF: 12.9 ± 8.2 MS-LF: 10.6 ± 7.6	MFIS [>38 (Total)] MS-HF: 50.4 (38-71) MS-LF: 22.5 (4-35)	magnetic resonance imagery /fMRI 3.0 Tesla (Intera; Philips Medical Systems)	Normalised brain volume (ml)	1434 ± 117	1448 ± 118	1566 ± 296	Abnormal recruitment of sensorimotor networks in fronto-parietal–temporal lobes and basal ganglia. Normalised brain volume, grey matter volume, white matter volume, T1 and T2 lesion volumes were not significantly different for MS-HF vs MS-LF or HC.
									Grey matter volume (ml)	637 ± 80	648 ± 80	766 ± 58	
									White matter volume (ml)	795 ± 43	800 ± 43	858 ± 41	
									T1 Lesion volume (ml)	4.4 ± 5.6	4.1 ± 4.5		
									T2 Lesion volume (ml)	6.2 ± 7.5	5.7 ± 6.0		

Roelcke *et al.* (1997)	37 MS 16 HC	19 MS-HF 16 MS-LF 16 HC	MS-HF: 43 ± 8 MS-LF: 42 ± 10 HC: 40 ± 15	MS-HF: 8/11 MS-LF: 7/9 HC: 7/9	MS-HF: 3.6 ± 1.3 MS-LF: 3.9 ± 1.7	MS-HF: 10 ± 8 MS-LF: 14 ± 8	FSS [>5 (Mean)] MS-HF: 6.0 ± 0.6 MS-LF: 2.7 ± 0.8	FDG-positron emission tomography scans 933/04-16 tomograph (CTI, Knoxville, 4 rings, 7 planes, 8 mm FWHM)	Regional and global cerebral glucose metabolism using positron emission tomography and 18F-fluorode-oxyglucose. Global metabolic rate of glucose (μmol/100 mL/min)	 34.7 ± 4.4	 35.4 ± 4.5	 43.3 ± 6.9	Reduced cerebral glucose metabolism bilaterally for MS-HF versus MS-LF in the prefrontal area involving the lateral and medial prefrontal cortex and adjacent white matter, in the premotor cortex, putamen, and the right supplementary motor area. Reductions also observed in the white matter extending from the rostral putamen toward the lateral head of the caudate nucleus. Suggests MS fatigue is associated with frontal cortex and basal ganglia dysfunction.
Sander *et al.* (2016)	30 RR 12 SP 13 HC	17 MS-HF 25 MS-LF	MS-HF: 42.8 ± 12.8 MS-LF: 50.5 ± 8.8 HC: 48.6 ± 5	MS-HF: 10/18, MS-LF: 5/9 HC: 4/9	MS-HF: 4.6 ± 1.3 MS-LF: 3.0 ± 2.0		FSMC [28 (Cognitive fatigue scale)] FSMC (Cog): MS-HF: 36.5 (21) MS-LF: 21.0 (14) FSS: MS-HF: 46 (10.6) MS-LF: 29 (10.3)	magnetic resonance imagery (DTI) 3.0 Tesla scanner (Siemens Skyra)	Brain parenchymal fraction (%) T1 lesion volume (ml) Total brain volume (ml) Lateral ventricles Third and fourth ventricle volume Corpus callosum index Axial and radial diffusivity of the corpus callosum	81 ± 4 3.71 ± 2.57 1201 ± 109 40.92 ± 24.68 4.22 ± 1.47 0.326 ± 0.067 0.0013 ± 0.0001	81 ± 4 7.07 ± 15.77 1219 ± 131 36.00 ± 30.87 3.43 ± 4.46 0.329 ± 0.068 0.0013 ± 0.0001	85 ± 15 0.03 ± 0.08 1281 ± 73 16.78 ± 6.43 2.72 ± 1.27 0.43 ± 0.05 0.0012 ± 0.0000	Brain parenchymal fraction, total brain volume, lateral ventricle volume, third and fourth ventricle volume, T1 lesion volume, axial and radial diffusivity were not significantly different for MS-HF vs MS-LF but differed from HC.
Sepulcre *et al.* (2009)^	28 RR 5 PP 5 SP 22 CIS 20 HC	43 MS-HF 17 MS-LF	MS: 36.4 ± 9 HC: 37.4 ± 8.7	MS: 22/38 HC: 8/12	MS: 2.0 (0.0-7.0)	MS: 2.7 (1-36)	MFIS-5 (score range = 0-20) [<5 used to define absence of fatigue] Means for the 2 MS groups not reported.	magnetic resonance imagery, 1.5 Tesla scanner (Siemens Symphony)	T1 Lesion volume (ml) T2 Lesion volume (ml)	18.4 ± 6.5 56.6 ± 16.8	6.5 ± 3.2 19.1 ± 8.3		Greater grey matter atrophy (left superior frontal gyrus, bilateral middle frontal gyrus) in MS-HF vs MS-LF. Higher T1 and T2 lesion volumes for MS-HF vs MS-LF (left frontal and right parieto-temporal white matter regions mainly affected). Reported T1 and T2 gadolinium enhancing lesion volumes, so data were excluded from the meta-analysis.

Specogna *et al.* (2012)	24 RR 15 HC	12 MS-HF 12 MS-NF 15 HC	MS-HF: 40.9 ± 8.9 MS-LF: 38.7 ± 8.1	MS: 4/20	MS-HF: Mean= 1.5 MS-LF: Mean= 1.5	MS: Mean= 7	FSS [>5] Means for the 2 MS groups not reported.	magnetic resonance imagery 1.5 Tesla scanner (Philips Achieva)	Cortical activation during execution of a motor task (sequential finger tapping).	Data presented as brain scans and activation coordinates.	Data presented as brain scans and activation coordinates.	Data presented as brain scans and activation coordinates.	MS-HF demonstrated greater activation of the right premotor area, putamen and dorsolateral prefrontal cortex (i.e. motor attentional network) in comparison with MS-LF.
Stefancin *et al.* (2019)	22 RR	10 MS-HF 12 MS-LF	MS-HF: 27.0 ± 5.5 MS-LF: 25.8 ± 5.4	MS-HF: 3/7 MS-LF: 6/4	MS-HF: 2.3 (0-6) MS-LF: 1.2 (0-4)	MS-HF: 5.5 ± 3.8 MS-LF: 5.8 ± 3.8	FSS [>4 (mean)] MS-HF: 5.5 ± 0.9 MS-LF: 2.0 ± 0.8	magnetic resonance imagery 3T Siemens Biograph mMR	T2 Lesion volume (ml)	4.7 ± 2.8	12.4 ± 19.6		No significant difference in T2 lesion volume between MS-HF and MS-LF.
Tartaglia *et al.* (2004)	60 MS	34 MS-HF 26 MS-LF	MS-HF: 42.1 ± 6.9 MS-LF: 38.1 ± 10.2		MS-HF: 3.8 ± 2.2 MS-LF: 2.7 ± 2.2	MS-HF: 10.59 ± 7.3 MS-LF: 10.35 ± 9.5	FSS [>5 (Mean)] RELAPSING REMITTING MS : 4.66 ± 1.5 SECONDARY PROGRESSIVE MS : 4.67 ± 1.8	MRS 1.5 Tesla scanner (Phillips Medical)	T2 Lesion volume (ml) NAA/Cr CHO/Cr	13.44 ± 13.4 2.69 ± 0.29 1.44 ± 0.15	11.24 ± 13.2 2.99 ± 0.33 1.48 ± 0.18		Significantly lower NAA/Cr in MS-HF vs MS-LF, suggesting diffuse periventricular axonal injury is associated with MS fatigue.
Tedeschi *et al.* (2007)	222 RR	197 MS-HF 25 MS-LF	MS-HF: 39.0 ± 9.2 MS-LF: 34.0 ± 9.1		EDSS <2	MS-HF: 10 ± 6.6 MS-LF: 6 ± 5.7	FSS [5 (Mean)] Means for the 2 groups not reported.	magnetic resonance imagery 1.0 Tesla scanner (Genesys Sigma)	Abnormal white matter fraction White matter fraction Grey matter fraction T1 lesion volume (ml) T2 lesion volume (ml)	0.02 ± 0.01 0.34 ± 0.03 0.49 ± 0.04 2.6 ± 3.8 17.5 ± 16.7	0.01 ± 0.01 0.35 ± 0.03 0.52 ± 0.03 0.9 ± 1.7 7.1 ± 6.6		Significantly higher lesion volume, white matter and grey matter atrophy in MS-HF vs MS-LF.
Tellez *et al.* (2008)	40 RR 21 HC	17 MS-HF 13 MS-LF	MS-HF: 38.5 ± 7.6 MS-LF:	MS-HF: 4/13	MS-HF: 2.5	MS-HF: 9.3 ± 7.3	FSS [5 (Mean)] MS: 4.8 ± 1.5	MRS 1.5 Tesla scanner	Frontal white matter lesion volume (%)	0.12 ± 0.18	0.09 ± 0.02		Significantly lower NAA/Cr in the lentiform nucleus region in

			37.8 ± 9.8	MS-LF: 3/10	(1.0-3.0) MS-LF: 1.5 (0.3.0)	MS-LF: 7.0 ± 6.2	MS-HF: 5.9 ± 0.7 MS-LF: 3.6 ± 1.15 HC: 3.2 ± 1.2	(Magnetom Vision)	Lentiform nucleus lesion volume (%) NAA/Cr Frontal white matter Lentiform nucleus NAA/Cho Frontal white matter Lentiform nucleus Cho/Cr Frontal white matter Lentiform nucleus	0.03 ± 0.05 1.67 ± 0.17 1.36 ± 0.09 1.48 ± 0.24 1.86 ± 0.30 1.14 ± 0.17 0.81 ± 0.13	0.01 ± 0.04 1.73 ± 0.12 1.48 ± 0.10 1.53 ± 0.17 1.92 ± 0.50 1.14 ± 0.12 0.76 ± 0.14	 1.77 ± 0.19 1.47 ± 0.13 1.45 ± 0.24 1.88 ± 0.40 1.15 ± 0.33 0.81 ± 0.20	MS-HF vs MS-LF and HC, indicative of axonal dysfunction.
Tomasevic *et al.* (2013)**	20 RR	11 MS-HF 9 MS-LF	MS-HF: 38.5 ± 3.2 MS-LF: 35.9 ± 7.8	MS-HF: 3/8 MS-LF: 3/6	MS-HF: 0.4 ± 0.5 MS-LF: 0.3 ± 0.5	MS: 4.7 ± 3.8	MFIS-physical scale [16 (Mean)] MS-HF: 36.6 ± 10.2 MS-LF: 16.6 ± 8.6	magnetic resonance imagery 1.5 Tesla scanner (Achieva, Phillips)	Brain parenchymal fraction (%) T2 lesion volume (ml) Lesion relative fraction (%) Thalamus volume (ml): Central sulcus cortical thickness (mm): Left Right	82 ± 1 11.0 ± 8.3 0.02 ± 0.01 14.6 ± 1.8 1.71 ± 0.07 1.70 ± 0.09	81 ± 2 17.2 ± 8.1 0.03 ± 0.03 13.4 ± 1.6 1.73 ± 0.18 1.67 ± 0.18		T2 lesion volume, thalamus volume and brain parenchymal fraction were not significantly different for MS-HF vs MS-LF.
van der Werf *et al.* (1998)	26 RR 19 SP	32 MS-HF 13 MS-LF	MS: 37.6 ± 8.4	RR: 8/18 SP: 9/10	MS: Mean= 3.5		Feeling tired several times a week; Daily fatigue score (range: 0-16)	magnetic resonance imagery 1.0 Tesla proton density & T2-weighted spin echo	Conventional T1- and T2-weighted magnetic resonance imagery provided several measures for cerebral abnormalities.	Data reported as graphs and correlation coefficients.	Data reported as graphs and correlation coefficients.		Regional lesion load was not significantly different for MS-HF vs MS-LF. Fatigue severity was not related to the total extent of cerebral abnormalities, or to magnetic resonance imagery - based atrophy measures.

							Means for the 2 MS groups not reported.						Suggests factors other than focal lesions or cerebral atrophy mediate levels of perceived MS fatigue.
Wilting *et al.* (2016)	79 MS 40 HC	38 MS-HF 41 MS-LF 40 HC	MS-HF: 34.5 (20-58) MS-LF: 30 (17-54)	MS-HF: 8/30 MS-LF: 15/26 HC: 22/18	MS-HF: 1.5 (0-5.5) MS-LF: 0.5 (0-3.5)	MS-HF: 2 (0-10) MS-LF: 2 (0-10)	FSMC [>27 (Cognitive Scale)] Means for the 2 MS groups not reported.	magnetic resonance imagery (DTI) 3 Tesla scanner (Magnetom Tim Trio, Siemens)	Lesion volume (ml) Mean grey matter fraction (%) Mean white matter fraction (%) Mean cerebrospinal fluid fraction (%) Brain parenchymal fraction (%) Thalamus fractional anisotropy Thalamus mean diffusivity ($\times 10^{-3}$ mm^2/s) Basal ganglia fractional anisotropy Basal ganglia mean diffusivity ($\times 10^{-3}$ mm^2/s) Frontal cortex fractional anisotropy Thalamus mean diffusivity ($\times 10^{-3}$ mm^2/s)	3.5 (0.4-41.2) 0.440 ± 0.036 0.395 ± 0.025 0.165 ± 0.028 0.835 ± 0.028 0.275 ± 0.027 1.426 ± 0.334 0.252 ± 0.014 0.980 ± 0.146 0.110 ± 0.005 0.527 ± 0.047	1.9 (0.1-30.6) 0.443 ± 0.027 0.392 ± 0.026 0.164 ± 0.024 0.836 ± 0.024 0.289 ± 0.021 1.266 ± 0.221 0.255 ± 0.015 0.912 ± 0.116 0.111 ± 0.006 0.509 ± 0.039	 0.456 ± 0.025 0.394 ± 0.023 0.150 ± 0.024 0.850 ± 0.024 0.300 ± 0.015 1.139± 0.115 0.262 ± 0.012 0.870 ± 0.077 0.115 ± 0.004 0.490 ± 0.029	Significant reduction in global grey matter fraction was found for MS-HF versus HC but not MS-LF. Reduced fractional anisotropy and increased mean diffusivity values were found in MS-HF versus MS-LF for the thalamus and basal ganglia, including the caudate nucleus, globus pallidus and putamen. Suggests morphologic and microstructural alterations in thalamic regions are related to cognitive fatigue in early MS. Fractional anisotropy and mean diffusivity values in the thalamus were significantly correlated with information processing speed, cognitive flexibility and overall cognitive impairment.
Yaldizli *et al.* (2011)	70 RR	28 MS-HF 42 MS-LF	MS-HF: 43.7 ± 11.4 MS-LF: 40.4 ± 10.5	MS-HF: 4/24 MS-LF: 5/37	MS-HF: 3.3 ± 1.2 MS-LF: 2.4 ± 1.7	MS-HF: 10.7 ± 8.6 MS-LF: 9 ± 6.8	FSS [4 (Mean)] MS-HF: 5.27 ± 1.09 MS-LF: 2.1 ± 1.04	magnetic resonance imagery 1.5 Tesla scanner (Sigma Magnetom)	T2 Lesion load (ml) Black holes on T1weighted magnetic resonance imagery: Yes No	14.0 ± 54.4 8 ± 28.6 20 ± 71.4	21.0 ± 55.4 32 ± 76.2 10 ± 23.8		Significantly greater atrophy of corpus callosum in MS-HF vs MS-LF.

									Contrast enhancing lesions on T1weighted magnetic resonance imagery Yes No	 1 ± 3.6 27 ± 96.4	 5 ± 11.9 37 ± 88.1		
Yarraguntla *et al.* (2019)	30 RR	16 MS-HF 14 MS-LF	MS-HF: 43 ± 2.9 MS-LF: 39 ± 1.7 HC:	MS-HF: 4/12 MS-LF: 7/7	MS-HF: 3 ± 0.4 MS-LF: 2.4 ± 0.6	MS-HF: 10 ± 1.7 MS-LF: 8.6 ± 1.9	FSS [≥ 5.1 (mean)] MS-HF: 6 ± 0.12 MS-LF: 1.89 ± 0.2	magnetic resonance imagery Siemens 3T Verio MR scanner	T2 lesion volume (ml)	14 ± 2.5	15.3 ± 5.9		No significant difference in T2 lesion volume between MS-HF and MS-LF.
Zaini *et al.* (2016) ^	19 RR 18 HC	10 MS-HF 9 MS-LF	MS-HF: 42 ± 8 MS-LF: 38 ± 5 HC: 38 ± 7	MS-HF: 10/0 MS-LF: 9/0 HC: 18/0	MS-HF: 1.8 (1.0-2.5) MS-LF: 1.5 (1.0-1.5)		FSS [>36 (Total)] MS-HF: 52 ± 6 MS-LF: 22 ± 10 HC: 18 ± 4	magnetic resonance imagery MRS 1.5 Tesla SCANNER (Siemens Sonata)	T2 lesion volume (ml)	11.6 ± 14.6	5.5 ± 6.4		Lower NAA/Cr concentration in the tegmentum of pons driven by higher Cr concentration in MS-HF vs HC (found in white matter regions). T2 lesion volume data obtained for MS-HF and MS-LF by communication with the lead author.
Zellini *et al.* (2009)	32 RR 13 HC	23 MS-HF 9 MS-LF	MS-HF: 40 (32-42.5) MS-LF: 36 (32-39) HC: 37 (30-43)	MS-HF: 4/19 MS-LF: 1/8 HC: 4/9	MS-HF: 3 (2.5-4) MS-LF: 2 (2-2.5)	MS-HF: 10 (3.5-12.5) MS-LF: 6 (2-12)	FSS [5 (Mean)] MS-HF: 5.8 (5.25-6.25) MS-LF: 3.4 (3.22-3.6)	magnetic resonance imagery 1.5 Tesla scanner (Vision MR)	T2 lesion volume (ml)	3.53 (1.66-11.72)	3.94 (1.98-4.83)		T1 and T2 lesion volume was not significantly different for MS-HF vs MS-LF.

Data are presented as mean ± SD or median with intracortical range or total range in parentheses; ^ Original data received from the lead author; ** article has both structural and function neurophysiological measurements; RR, relapsing-remitting multiple sclerosis; SP, secondary progressive multiple sclerosis; PP, primary progressive multiple sclerosis; RSP, relapsing secondary progressive multiple sclerosis; EDSS, Extended Disability Status Scale; MS, Multiple Sclerosis; MS-HF, multiple sclerosis-highly fatigued; MS-LF, multiple sclerosis-less fatigued; HC, healthy controls; FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; MRI; Magnetic Resonance Imagery, fMRI; Functional Magnetic Resonance Image

Appendix 16 - Characteristics of neurophysiological studies included in this review (N=24)

Author	N (by disease type)	MS Subgroups	Age (y)	Male/ Female	EDSS Scores	Disease Duration (y)	Perceived Fatigue Measure	Technique	Outcomes	MS-HF	MS-LF	HC	Summary of findings
Andreasen *et al.* (2009)	40 RR	19 MS-HF 21 MS-LF	MS-HF: 43 (27-53) MS-LF: 39 (23-53)		MS-HF: 3.0 (1.0-3.5) MS-LF: 2.0 (1.5-3.5)	MS-HF: 5.0 (1-14) MS-LF: 3.0 (0-9)	FSS [>5 (Mean)] MS-HF: 6.3 (5.0-7.0) MS-LF: 3.1 (1.0-4.0)	Biodex System 3 PRO (Biodex Medical Systems); Stimulator Digitimer model DS7 (Digitimer Ldt)	Maximum voluntary contraction force (N) Voluntary activation (%) Peripheral activation (%)	148 ± 32 95.9 ± 5.1 1.02 ± 0.08	173 ± 49 99.2 ± 0.99 1.05 ± 0.14		Significantly lower voluntary activation in MS-HF vs MS-LF. Maximum voluntary contraction force was not significantly different for MS-HF vs MS-LF.
Andreasen *et al.* (2010)**	34 RR 7 HC	17 MS-HF 17 MS-LF	MS-HF: 43 (27-53) MS-LF: 39 (23-53) HC: 39 (31-45)	MS-HF: 5/12 MS-LF: 9/8 HC: 1/6	MS-HF: 3 (1-3.5) MS-LF: 2 (1.5-3.5) HC: 0 (0-2)	MS-HF: 5 (1-14) MS-LF: 3 (0-9)	FSS [>5 (Mean)] MS-HF: 6.3 (5-7) MS-LF: 2.8 (1-4) HC: 2.7 (2-4)	Isometric dynam-ometer	Voluntary activation (%)	98.1 (85.1-100)	99.8 (96.9-100)		Significantly lower voluntary activation in MS-HF vs MS-LF.
Chalah *et al.* (2019)^	6RR 16PP 16SP	21 MS-HF 17 MS-LF	MS-HF: 51 (44-67) MS-LF: 53 (34-62)	MS-HF: 9/8 MS-LF: 11/10	MS-HF: 6.5 (5.5-6.5) MS-LF: 6.0 (3.0-6.5)	MS-HF: 11.9 ± 6.6 MS-LF: 11.5 ± 5.3	MFIS [45 (Total)] MS-HF: 58.67 ± 8.85 MS-LF: 32.82 ± 6.61	TRANSCRANIAL MAGNETIC STIMULATION (MC125, Mag Venture)	MEP threshold (%) SICI 2 ms (%) SICI 4 ms (%) ICF 12 ms (%)	54.7 ± 13.3 63.9 ± 20.9 44.3 ± 37.5 160.8 ± 68.9	61.6 ± 18.3 35.0 ± 40.8 9.5 ± 73.3 159.9 ± 78.2		SICI 2 ms (%) was significantly higher in MS-HF versus MS-LF. No difference between MS-HF and MS-LF for SICI 4 ms (%) or ICF 12 ms (%).
Cogliati Dezza *et al.* (2015)**	27 MS 8 HC	15 MS-HF 12 MS-LF	MS-HF: 37.3 ± 4 MS-LF: 36.9 ± 7.5 HC: 37 (25-48)	MS-HF: 4/11 MS-LF: 4/8 HC: 1/7	MS-HF: 1 (0-3) MS-LF: 1 (0-2)	MS-HF: 3.9 ± 4.1 MS-LF: 7.1 ± 3.9	MFIS [>36 (Total)] MS-HF: 42.1 ± 7.3 MS-LF: 19.9 ± 8.6	EEG (Micromed S.p.A., Mo-gliano Veneto)	Inter-hemispheric symmetry index at rest: Left Right Inter-hemispheric symmetry index - movement:	1.08 ± 0.08 2.94 ± 0.70 2.53 ± 0.55 1.06 ± 0.34	0.99 ± 0.10 3.28 ± 1.00 3.27 ± 0.76 0.99 ± 0.35	0.98 ± 0.08 3.43 ± 1.02 3.51 ± 0.86 0.99 ± 0.10	Significantly higher resting left hemispheric primary sensorimotor activity power and higher inter-hemispheric coherence during movement in MS-HF vs MS-LF and HC.

									Left Right	0.27 ± 0.15 0.25 ± 0.16	0.27 ± 0.14 0.27 ± 0.11	0.15 ± 0.08 0.16 ± 0.08	
Colombo *et al.* (2000)**	30 MS	15 MS-HF 15 MS-LF	MS-HF: 30.4 (18-49) MS-LF: 39 (18-49)	MS-HF: 3/12 MS-LF: 4/11	MS-HF: 1.5 (0-1.5) MS-LF: 1.5 (0-1.5)	MS-HF: 2.8 (1-7) MS-LF: 3.7 (1-9)	FSS [>25 (Total)] MS-HF: 40 (25-60) MS-LF: 14 (10-21)	Magstim Stimulator (Cadwell MS10)	Central motor conduction time (ms): Right arm Left arm Right leg Left leg	 6.4 (5.3-19.4) 6.7 (5.3-12.3) 16.0 (12.1-31.7) 16.6 (11.1-26.0)	 6.6 (5.5-7.9) 6.8 (5.5-7.7) 15.0 (11.2-16.3) 14.8 (13.0-21.4)		Central motor conduction time was not significantly different for MS-HF vs MS-LF.
Conte *et al.* (2016)	25 RR 18 HC	12 MS-HF 13 MS-LF 18 HC	MS-HF: 41.3 ± 7.7 MS-LF: 38.3 ± 8.4 HC: 37.0 ± 8.0	MS-HF: 6/6 MS-LF: 6/7 HC: 9/9	MS-HF: 1.0 (0-3.5) MS-LF: 1.1 (0-3.5)	MS-HF: 5.2 ± 4.3 MS-LF: 6.3 ± 7.1	Presence or not of subjective fatigue. MFIS: MS-HF: 35.1 ± 10.1 MS-LF: 13.9 ± 8.8	5-Hz rTRANSCRANIAL MAGNETIC STIMULATION Super Rapid Magstim stimulator (Magstim Co. UK)	5 Hz rTRANSCRANIAL MAGNETIC STIMULATION (reflecting short-term plasticity) and paired associative stimulation (reflecting long-term plasticity) during 2 different attention-demanding conditions.	Data reported as graphs.	Data reported as graphs.	Data reported as graphs.	Effects of attention on cortical plasticity differ in MS-HF versus MS-LF. In MS-LF attention improves the MEP size increase whereas in patients with fatigue, attention leaves responses unchanged. Suggests MS fatigue reflects disrupted cortical attentional networks related to movement control.
Greim *et al.* (2007)	76 RR 51 HC	46 MS-HF 30 MS-LF	MS: 36.7 ± 8.6 HC: 35.2 ± 12.6	MS: 14/65 HC: 15/35	MS: 2.51 ± 1.89	MS: 6.9 ± 4.3	MS-HF: Mostly or daily tired MS-LF: Rarely or occasion-ally tired	Hand-dynam-ometer	Post fatigue task force (% baseline force)	87.5 ± 11.6	95.6 ± 12.9	96.8 ± 8.4	Greater fatigability in MS-HF vs MS-LF and HC.
Leocani *et al.* (2001)	33 RR 14 HC	15 MS-HF 18 MS-LF 14 HC	MS-HF: 33 ± 8 MS-LF: 32 ± 6	MS-HF: 3/12 MS-LF: 5/13	1.5		FSS [≥33 (Total)] Means for the 2 MS groups	29 channel EEG	Event-related desynch-ronisation (ERD)/event-related synch-ronisation (ERS) of the 10 and 18-22 Hz bands (cortical circuits involved in	Data reported as average topographic maps and regression lines.	Data reported as average topographic maps and regression lines.	Data reported as average topographic maps and regression lines.	Reduced post-movement 18 – 22 Hz ERS in MS-HF versus MS-LF and inverse correlation between the amount of ERS and the fatigue score. Suggests

							not reported.		control of voluntary movement).				inhibitory circuits acting on the motor cortex after movement termination may be involved in the patho-physiological mechanism of MS fatigue.
Liepert *et al.* (2005)	16 RR 6 HC	8 MS-HF 8 MS-LF	MS-HF: 42.5 ± 5 MS-LF: 40.3 ± 4.5 HC: 32.8 ± 10.3	MS-HF: 1/7 MS-LF: 2/6 HC: 6/0	MS-HF: 3.1 ± 0.93 MS-LF: 2.9 ± 0.9		FSS [4 (Mean)] MS-HF: 5.3 ± 0.4 MS-LF: 1.1 ± 0.2	Bistim device (Magstim Comp)	Resting motor threshold (%) Motor evoked potential amplitude (mV) Motor evoked potential latency (ms) SICI 2-3 ms (%) ICF 11-13 ms (%) Motor response (mV) Grip strength (Nm)	46.0 ± 7 0.54 ± 0.26 15.7 ± 1.23 54.6 ± 27.3 168 ± 37 18.6 ± 3.8 87 ± 20.2	46.2 ± 3.6 0.57 ± 0.19 15.7 ± 1.56 35.9 ± 10.2 179 ± 39 14.4 ± 6.5 102.5 ± 21.1	40.9 ± 6.1 0.65 ± 0.27 15.3 ± 1.24 31.2 ± 14 150 ± 35 19.5 ± 4.8 120 ± 14.4	Significant reductions in SICI 2-3 ms (%) at rest in MS-HF vs MS-LF and HC. Significantly lower grip strength in MS-HF vs HC. Motor response, resting motor threshold, motor evoked potential amplitude and latency was not different for MS-HF vs MS-LF or HC.
Morgante *et al.* (2011)**	33 RR 12 HC	16 MS-HF 17 MS-LF	MS-HF: 41.1 ± 10.9 MS-LF: 38 ± 9.4	MS-HF: 7/9 MS-LF: 4/13	MS-HF: 1.8 ± 0.6 MS-LF: 1.6 ± 0.6	MS-HF: 8.4 ± 3.4 MS-LF: 7.9 ± 3.8	FSS [>4 (Mean)] MS-HF: 4.9 ± 0.8 MS-LF: 2.2 ± 0.9	Magstim 200 Stimulator and Bistem module (Magstim Company Ltd) Neurolog system (Digitimer Ldt)	Central motor conduction time (ms) SICI 2 ms (%) ICF 10 ms (%)	7.3 ± 4.0 54 ± 40 132 ± 40	7.7 ± 6.2 47 ± 29 123 ± 41	5.6 ± 3.42 54 ± 21 140 ± 35	Significantly reduced pre-movement facilitation in MS-HF vs MS-LF and HC. Central motor conduction time was prolonged in both MS groups vs HC. SICI 2 ms (%) and ICF 10 ms (%) was not significantly different for MS-HF vs MS-LF or HC.
Ng *et al.* (2000)^	9 MS 11 HC	6 MS-HF 3 MS-LF	MS: 46 ± 1 HC: 43 ± 2	MS: 4/5 HC: 6/5	MS: 2 (1.5-4.5)		FSS [4 (Mean)] MS-HF: 5.6 ± 1.5 MS-LF:	Tailor-made force trans-ducer	Maximum voluntary contraction (N) Voluntary activation (%)	182.8 ± 60.7 97.2 ± 4.9	166.9 ± 7.9 98.7 ± 2.3	292 ± 123 100 (96-100)	Small group of PwMS and MS-LF (N=3), not justifying statistical comparisons. Data were acquired from the senior author.

							3.0 ± 0.6 HC: 3.0 ± 0.4		Post fatigue task force (% baseline force)	83.0 ± 25.3	49.8 ± 12.3	56 ± 20	
Ng *et al*. (2004)^	16 MS 18 HC	11 MS-HF 5 MS-LF	MS: 44 ± 2 HC: 47 ± 1	MS: 5/11 HC: 6/12	MS-HF: 3.4 ± 1.7 MS-LF: 2.7 ± 1.6		FSS [>4 (Mean)] MS-HF: 5.8 ± 0.8 MS-LF: 3.1 ± 0.8 HC 2.9 ± 0.2	Tailor-made force trans-ducer NS6 stimulator (Teca)	Maximum voluntary contraction force (N) Muscle activation (%)	116.8 ± 62.9 85.1 ± 23.8	126.3 ± 53.6 89.2 ± 22.5	157 ± 51 96.0 ± 13.0	Lower maximum voluntary contraction force and muscle activation in MS-HF vs MS-LF and HC.
Perretti *et al.* (2004)	41 RR 13 HC	32 MS-HF 9 MS-LF	MS-HF: 37.7 ± 10 MS-LF: 28.7 ± 7.1 HC: 30.7 ± 8.8	MS-HF: 18/14 MS-LF: 2/7 HC: 5/8	MS-HF: 3.4 ± 1.0 MS-LF: 2.3 ± 0.5		FSS [>37 (Total)] MS-HF: 51.6 ± 8.5 MS-LF: 25.1 ± 11.8 HC: 24.9 ± 6.4	Dynam-ometer (Pinch Gauge, B and L Engin-eering) MagPro Dantec Stimulator	Maximum voluntary contraction force (N) Motor evoked potential threshold (%) Motor evoked potential amplitude (mV) Motor evoked potential latency (ms) Motor evoked potential duration (ms)	85.3 ± 14.7 72.5 ± 9.1 0.79 ± 0.89 28.9 ± 5.6 21.4 ± 6.8	93.2 ± 25.5 67.8 ± 10.9 1.32 ± 1.25 25.0 ± 3.6 16.9 ± 4.3	90.2 ± 20.6 61.5 ± 8.0 2.33 ± 1.75 23.5 ± 2.1 15.9 ± 3.9	Maximum voluntary contraction force, motor evoked potential amplitude, threshold, latency, duration, and post-exercise MEP facilitation were not significantly different between MS-HF and MS-LF.
Romani *et al.* (2004)	60 MS	40 MS-HF 20 MS-LF	MS: 38.3 ± 8.1	MS-HF: 18/22 MS-LF: 9/11	MS-HF: 2.6 ± 1.4 MS-LF: 2.7 ± 1.7	MS-HF: 4.5 ± 2.4 MS-LF: 4.7 ± 2.3	FSS MS-HF>5.6 MS-LF<2.4	Force transducer, which measured thumb isometric adduction force.	Fatigability expressed as decline in force and voluntary activation after 45 s sustained MVC.	Data presented as scatterplots and correlation coefficients.	Data presented as scatterplots and correlation coefficients.		FSS fatigue scores did not correlate with fatigability. Suggests perceived MS fatigue is independent of fatigability.
Russo *et al.* (2015)	24 RR 10 HC	12 MS-HF 12 MS-LF 10 HC	MS-HF: 41 ± 7 MS-LF: 39 ± 9	MS-HF: 5/7 MS-LF: 7/5	MS-HF: 2.0 ± 1.0 MS-LF: 2.0 ± 1.0		FSS [≥36 (Total)] MS-HF: 50 ± 7 MS-LF: 20 ± 11	TRANSCR ANIAL MAGNETI C STIMULAT ION	Motor cortex excitability and the pre-movement facilitation (PMF) through TRANSCRANIAL MAGNETIC	Data presented as graphs.	Data presented as graphs.	Data presented as graphs.	Post-task PMF was significantly decreased in MS-HF versus MS-LF and abnormalities were correlated with the performance decay. Suggests possible link

								(Magstim 200 Co)	STIMULATION before and after 5 min of sequenced finger-tapping movements at a fixed frequency of 2 Hz.				between MS fatigue and functional impairment within circuits engaged in movement preparation, upstream the corticospinal tract.
Scheidegger *et al.* (2012)^	23 MS 13 HC	10 MS-HF 13 MS-LF	MS: 39.7 ± 11.4 HC: 28 (23-54)	MS: 19/4 HC: 10/3	MS: 3.15 ± 1.56		FSS [>36 (Total)] MS: 37.2 ± 14.6	Force transducer (Sensotec Inc)	Post fatigue task force (% baseline force)	35.2 ± 18.6	36.6 ± 15.0	44 ± 9	Fatigability was not significantly different between MS-HF vs MS-LF.
Sebastiao *et al.* (2017)	62 RR	36 MS-HF 26 MS-LF	MS-HF: 52.7 ± 6.9 MS-LF: 51.3 ± 8.8	MS-HF: 9/27 MS-LF: 8/18	MS-HF: 4.5 (2.0) MS-LF: 3.5 (3.5)	MS-HF: 13.9 ± 9.1 MS-LF: 12.2 ± 8.3	MFIS [>38 (Total)] MS: 4.5 (2.5) MS-HF: 3.5 (3.5) MS-LF: 4.5 (2.0)	Isometric Dynam-ometer (Biodex System 3)	Bilateral isometric peak torque (Nm) Knee flexor Knee extensor	 51.5 ± 19.9 139.8 ± 47.3	 66.9 ± 28.6 165.1 ± 58.3		Significantly lower knee flexor peak torque and cardiorespiratory capacity in MS-HF vs MS-LF.
Severijns *et al.* (2019) ^	13 RR 5 SP 1 PP	13 MS-HF 6 MS-LF	MS: 52 ± 9.3 HC: 52 ± 9.2	MS: 7/12 HC: 7/12	MS: 3.0 (1.5-6.5)	MS: 15.6 ± 9.2	FSS [>4 (Mean)] MS: 4.55 ± 1.60 HC: 2.29 ± 0.80	Tailor-made force sensor attached to bar	Voluntary activation (%)	92.7 ± 6.7	97.2 ± 1.7		Lower voluntary activation in MS-HF vs MS-LF.
Steens *et al.* (2012)^	20 MS 20 HC	18 MS-HF 2 MS-LF	MS: 20-58 HC: 21-57	MS: 7/13 HC: 6/14	MS-HF: 2.8 (0-5.0) MS-LF: 1.0 (0-2.0)	MS: 4 (1-23)	FSS [>4 (Mean)] MS-HF: 5.5 ± 0.8 MS-LF: 3.7 ± 0.2 HC: 2.9 ± 0.6	Force transducer Stimulator Digitimer model DS7 (Digitimer Ltd); Magstim 200 Stimulator	Maximum voluntary contraction force (N) Post fatigue task force (% baseline force) Voluntary activation (%)	30.7 ± 9.9 36.3 ± 13.1 92.1 ± 7.9	30.5 ± 6.4 33.8 ± 5.0 99.0 ± 1.5	34.8 ± 9.3 36.6 ± 11.9 96.7 (81.9-99.1)	Lower voluntary activation in MS-HF vs MS-LF and HC. Maximum voluntary contraction force and fatigability was not significantly different between MS-HF vs MS-LF and HC.

									Central motor conduction time (ms)	9.8 ± 2.6	10.7 ± 1.5	8.2 (6.2-9.8)	
Tomasevic *et al.* (2013)**	20 RR	11 MS-HF 9 MS-LF	MS-HF: 38.5 ± 3.2 MS-LF: 35.9 ± 7.8	MS-HF: 3/8 MS-LF: 3/6	MS-HF: 0.4 ± 0.5 MS-LF: 0.3 ± 0.5	MS: 4.7 ± 3.8	MFIS-physical scale [16 (Mean)] MS-HF: 36.6 ± 10.2 MS-LF: 16.6 ± 8.6	EEG (Micromed System Plus SAM32 (Micromed)	Cortico-muscular coherence (CMC) Frequency Amplitude Task performance correction rate	27.5 ± 4.8 0.07 ± 0.02 0.03 ± 0.02 1.40 ± 0.38	16.7 ± 3.6 0.06 ± 0.05 0.05 ± 0.04 2.20 ± 0.55		Significantly faster frequencies of cortico-muscular coherence and increase correction rate during handgrip in MS-HF vs MS-LF.
Vecchio *et al.* (2017)	27 RR 11 HC	16 MS-HF 11 MS-LF	MS-HF: 37.3 ± 4.0 MS-LF: 36.9 ± 7.5 HC: 36 (28-49)	MS-HF: 3/13 MS-LF: 4/7 HC: 2/9	MS-HF: 0.5 (0-2) MS-LF: 1 (0-2)	MS-HF: 4.9 ± 4.1 MS-LF: 5.7± 3.9	MFIS [>35 (Total)] MS-HF: 40.8 ± 13.0 MS-LF: 23.4 ± 6.2	EEG Model CUEE60M, Sei EMG srl Cittadella Italy	Alpha 2 band (10.5-13 Hz) Beta 1 band (13-20 Hz)	1.014 ± 0.00 1.007 ± 0.004	0.995 ± 0.011 0.989 ± 0.009	0.989 ± 0.005 0.985 ± 0.005	Functional connectivity changes of the left sensory cortical network at rest, mediated by beta band oscillatory activity in MS-HF vs MS-LF.
Wolkorte *et al.* (2015a)^	82 RR	61 MS-HF 21 MS-LF	MS-HF: 41 (21-65) MS-LF: 42 (25-64)	MS: 32/51		MS: 9.3 (0-34)	FSS [>4 (Mean)] MS-HF: 5.3 ± 0.6 MS-LF: 2.6 ± 0.8	Tailor-made force trans-ducer	Maximum voluntary contraction force (N) Post fatigue task force (% baseline force)	26.33 ± 9.17 27.47 ± 8.52	30.78 ± 9.57 36.03 ± 12.40		Lower maximum voluntary contraction force and greater fatigability in MS-HF vs MS-LF.
Wolkorte *et al.* (2015b)^	16 RR 18 HC	8 MS-HF 8 MS-LF	MS: 39 (21-57) HC: 38 (21-54)	MS: 11/7 HC: 11/7	MS: 1.2 (0-3.0) MS-HF: 1.4 ± 1.0 MS-LF: 0.7 ± 0.9	MS: 5.5 (1-16)	FSS [>4 (Mean)] MS: 3.9 (1.6-6.2) HC: 2.4 (1.3-4.6)	Tailor-made force trans-ducer	Maximum voluntary contraction force (N)	41.62 ± 24.62	37.87 ± 8.16	45 ± 11	Maximum voluntary contraction force was not significantly different between MS-HF vs MS-LF or HC.

Wolkorte *et al.* (2016)^	25 SP 25 HC	21 MS-HF 4 MS-LF	SECONDARY PROGRESSIVE MS : 53 (41-65) HC: 53 (40-63)	SECONDARY PROGRESSIVE MS : 8/17 HC: 8/17	MS-HF: 4.9 ± 1.4 MS-LF: 5.6 ± 1.8	SECONDARY PROGRESSIVE MS : 15 (4-37)	FSS [>4 (Mean)] MS-HF: 5.6 ± 0.7 MS-LF: 2.6 ± 0.6 HC: 2.5 (1.3-4.3)	Tailor-made force trans-ducer Digitimer model DS7 (Digitimer Ltd)	Maximum voluntary contraction (N) Voluntary activation (%) Post fatigue task force (% baseline force)	24.3 ± 10.3 83.7 ± 12.3 26.5 ± 8.5	27.4 ± 7.0 89.3 ± 9.7 30.9 ± 13.9	32.1 ± 9.6 93.9 ± 5.8 37.2 ± 12.3	Maximum voluntary contraction force was similar between MS-HF and MS-LF. Greater fatigability in MS-HF vs MS-LF.

Data are presented as mean ± SD or median with intracortical range or total range in parentheses; ^ Original data received from the lead author; ** article has both structural and function neurophysiological measurements; RR, relapsing-remitting multiple sclerosis; SP, secondary progressive multiple sclerosis; PP, primary progressive multiple sclerosis; RSP, relapsing secondary progressive multiple sclerosis; EDSS, Extended Disability Status Scale; MS, Multiple Sclerosis; MS-HF, multiple sclerosis-highly fatigued; MS-LF, multiple sclerosis-less fatigued; HC, healthy controls; FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; MRI, Magnetic Resonance Imagery, fMRI; Functional Magnetic Resonance Imagery; SICI, short-interval intracortical inhibition; ICF, intracortical facilitation; MEP, motor-evoked potential

Appendix 17 -. Methodological quality of the included studies evaluated using the Cross-Sectional/Prevalence Study Quality Scale, recommended by the Agency for Healthcare Research and Quality (AHRQ): EB reported; ─ not reported; U unclear; NA not applicable. Scores of 0-3 indicate “low quality”, 4–7 “moderate quality” and 8–11 “high quality”. <λ original data acquired from senior author of the publication; λI′ Studies not used for meta-analysis; Θ studies providing neuroimaging and neurofunctional data.

Study	Define source of information (survey, record review)	List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications	Indicate time period used for identifying patients	Indicate whether or not subjects were consecutive if not population-based	Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants	Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)	Explain any patient exclusions from analysis	Describe how confounding was assessed and/or controlled	If applicable, explain how missing data were handled in the analysis	Summarize patient response rates and completeness of data collection	Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained	Total items positively reported	**Study quality rating**
Andreasen *et al*. (2009)					—	—					NA	8	**High**
Andreasen *et al*. (2010) 0				—	—	—			—		NA	6	**Mod**
Bakshi *et al.* (1999)						—		—	—		NA	7	**Mod**
Bernitsas *et al*. (2017)			—	—	—	—	—		—		NA	4	**Mod**
Bisecco *et al*. (2016)			—			—	—		—		NA	6	**Mod**
Bisecco *et al*. (2017)			—	—		—	—		—	—	NA	4	**Mod**
Calabrese *et al*. (2010)					—	—	—	—	—	—		5	**Mod**
Chalah *et al.* (2019) χ Δ			—	—	—	—		—	—		NA	4	**Mod**

Codella *et al*. (2002)			—	—	—	—	—		—	—	NA	3	**Low**
Cogliati Dezza *et al*. (2015) 0			—	—	—	—	—		—	—	NA	3	**Low**
Colombo *et al*. (2000) 0			—		—	—	—	—	—	—	NA	3	**Low**
Conte *et al.* (2016)				—		—		—			NA	7	**Mod**
Cruz Gomez *et al*. (2013)			—	—	—	—	—		—	—	NA	3	**Low**
Damasceno *et al*. (2016)			—	—		—	—		—		NA	5	**Mod**
Derache *et al.* (2013)				—	—	—	—		—		NA	5	**Mod**
Dobryakova *et al*. (2018) Δ			—	—	—	—				—	NA	5	**Mod**
Filippi *et al.* (2002)			—	—							NA	8	**High**
Gobbi *et al*. (2014a)			—		—	—	—		—		NA	5	**Mod**
Gobbi *et al*. (2014b)			—			—	—		—		NA	6	**Mod**
Gonzalez Campo *et al*. (2019)			—	—	—	—		—	—		NA	4	**Mod**
Greim *et al.* (2007)			—	—	—	—	—		—	—	NA	3	**Low**
Hanken *et al*. (2015)			—	—	—		—		—	—	NA	4	**Mod**
Hanken *et al.* (2016)			—	—	—	—	—		—		NA	4	**Mod**
Hidalgo de la Cruz *et al*. (2017)			—	—	—	—					NA	6	**Mod**
Jaeger *et al*. (2018)			—	—	—	—	—		—	—	NA	3	**Low**
Leocani *et al*. (2001)			—	—	—	—		—			NA	5	**Mod**

Liepert *et al*. (2005)			—	—	—	—	—	—	—	—	NA	2	**Low**
Lin *et al*. (2019) Δ			—	—	—	—				—	NA	5	**Mod**
Morgante *et al*. (2011) 0				—	—	—					NA	7	**Mod**
Ng *et al*. (2000) Δ			—	—	—	—	—	—	—	—	NA	2	**Low**
Ng *et al*. (2004) Δ			—	—	—	—		—			NA	5	**Mod**
Niepel *et al*. (2006)				—					—	—	NA	7	**Mod**
Pardini *et al.* (2010)			—		—	—	—	—	—	—	NA	3	**Low**
Pellicano *et al*. (2010) Δ			—	—	—	—	—	—	—	—	NA	2	**Low**
Perretti *et al.* (2004)			—		—	—	—		—	—	NA	4	**Mod**
Pravata *et al*. (2016)			—	—	—	—					NA	6	**Mod**
Riccitelli *et al*. (2011)			—		—	—	—		—	—	NA	4	**Mod**
Rocca *et al*. (2009)			—		—	—	—		—	—	NA	4	**Mod**
Rocca *et al*. (2012)			—			—			—		NA	7	**Mod**
Rocca *et al*. (2014)			—		—	—	—		—	U	NA	4	**Mod**
Rocca *et al*. (2016)			—			—	—		—		NA	6	**Mod**
Roelcke *et al*. (1997)		—	—	—	—			—			NA	5	**Mod**
Romani *et al.* (2004)			—	—	—	—			—			6	**Mod**
Russo *et al*. (2015)			—	—		—		—			NA	6	**Mod**

Sander *et al*. (2016)				—	—						NA	8	**High**
Scheidegger *et al*. (2012) Δ			—	—	—	—	—	U	—	—	NA	2	**Low**
Sebastiao *et al*. (2017)			—	—	—	—	—		—		NA	4	**Mod**
Severijns *et al*. (2019) Δ			—	—	—	—	—		—	—	NA	3	**Low**
Specogna *et al*. (2012)			—	—		—		—	—		NA	5	**Low**
Steens *et al*. (2012) Δ			—	—	—	—	—	—	—	—	NA	2	**Low**
Stefancin *et al*. (2019)			—	—	—	—		—	—		NA	4	**Mod**
Sepulcre *et al*. (2009) Δ				—					—	—	NA	7	**Mod**
Tartaglia *et al*. (2004)				—	—	—				—	NA	6	**Mod**
Tedeschi *et al*. (2007)			—	—	—	—	—		—	—	NA	3	**Low**
Tellez *et al*. (2008)			—	—	—	—					NA	6	**Mod**
Tomasevic *et al*. (2013) 0			—	—	—	—	—		—	U	NA	3	**Low**
van der Werf *et al*. (1998)			—	—		—		—	—		NA	5	**Mod**
Vecchio *et al*. (2017)			—	—	—	—	—		—	—	NA	3	**Low**
Wilting *et al*. (2016)		—	—	—	—	—		—			NA	4	**Mod**
Wolkorte *et al*. (2015a) Δ			—	—	—	—					NA	6	**Mod**
Wolkorte *et al*. (2015b) Δ				—	—	—					NA	7	**Mod**
Wolkorte *et al*. (2016) Δ			—	—	—	—					NA	6	**Mod**

Yaldizli *et al*. (2011)									—	—	NA	8	**High**
Yarraguntla *et al*. (2019)			—	—	—	—			—	—		5	**Mod**
Zaini *et al*. (2016) <I			—	—	—	—		U		U	NA	4	**Mod**
Zellini *et al*. (2009)			—	—		—			—	—	NA	5	**Mod**
Items reported (%)	100	100	20	23	24	11	52	68	30	52	5		

Appendix 18- Summary of the results of meta-analyses for neuroimaging studies (MS-HF versus MS-LF). Data are presented as absolute mean differences with 95% confidence intervals. MVC, maximum voluntary contraction force.

Appendix 19- Summary of the results of meta-analyses for neurophysiology studies (MS-HF versus MS-LF). Data are presented as absolute mean differences with 95% confidence intervals. MVC, maximum voluntary contraction force.

Variable	Number of studies	Number of Participants		Mean difference (95% CI)	*P*	Heterogeneity
		MS-HF	MS-LF			
Neuroimaging variables						
Mean normalised brain volume (ml)	**11**	**336**	**375**	**-22.74 (-37.72, -7.76)**	**0.003**	**^{2}=7.24; p=0.70; I^2=0%**
Brain parenchymal fraction (%)	6	129	159	0.17 (-0.54, 0.88)	0.64	^{2}=3.03; p=0.70; I^2=0%
Grey matter volume (ml)	**9**	**306**	**318**	**-18.81 (-29.60, -8.03)**	**0.0006**	**^{2}=5.71; p=0.68; I^2=0%**
White matter volume (ml)	9	306	318	-6.41 (-13.98, 1.15)	0.10	^{2}=2.94; p=0.94; I^2=0%
Thalamus volume (ml)	8	234	286	-0.56 (-1.44, 0.31)	0.21	^{2}=88.55; p<0.00001; I^2=92%
Putamen volume (ml)	**4**	**163**	**178**	**-0.40 (-0.69, -0.10)**	**0.008**	**^{2}=4.89; p=0.18; I^2=39%**
Caudate volume (ml)	4	163	178	-0.45 (-0.95, 0.04)	0.07	^{2}=27.43; p<0.00001; I^2=89%
Accumbens volume (ml)	**2**	**53**	**59**	**-0.09 (-0.15, -0.03)**	**0.003**	**^{2}=0.36; p=0.55; I^2=0%**
Amygdala volume (ml)	2	53	59	-0.00 (-0.15, 0.14)	0.95	^{2}=1.27; p=0.27; I^2=19%
Pallidus volume (ml)	2	46	46	-0.23 (-0.50, 0.04)	0.09	^{2}=2.90; p=0.09; I^2=66%
T1-weighted Lesion volume (ml)	**9**	**483**	**334**	**1.10 (0.47, 1.73)**	**0.0007**	**^{2}=8.90; p<0.35; I^2=10%**
T2-weighted lesion volume (ml)	21	730	596	1.19 (-0.43, 2.80)	0.15	^{2}=42.25; p<0.003; I^2=53%
Fractional anisotrophy	3	60	60	-0.01 (-0.02, 0.01)	0.29	^{2}=8.99; p=0.01; I^2=78%
Mean diffusivity ($\times 10^{-3}$ mm^2/s)	3	60	60	0.01 (-0.03, 0.05)	0.72	^{2}=9.04; p=0.01; I^2=78%
NAA/Cr ratio	3	67	56	-0.12 (-0.27, 0.03)	0.11	^{2}=7.63; p=0.02; I^2=74%
Cho/Cr ratio	2	51	39	-0.02 (-0.09, 0.04)	0.48	^{2}=0.34; p=0.56; I^2=0%

Variable	Number of studies	Number of Participants		Mean difference (95% CI)	*P*	Heterogeneity
		MS-HF	MS-LF			
Neurophysiological variables						
Upper-limb MVC (N)	**6**	**130**	**69**	**-3.55 (-7.11, 0.01)**	**0.05**	**^{2}=3.23; p=0.66; I^2=0%**
Lower-limb MVC (N)	**4**	**72**	**55**	**-19.23 (-35.93, -2.53)**	**0.02**	**^{2}=2.43; p=0.49; I^2=0%**
Upper-Limb voluntary activation (%)	**3**	**33**	**29**	**-5.77 (-8.61, -2.93)**	**< 0.0001**	**^{2}=0.45, p=0.80; I^2=0%**
Lower-limb voluntary activation (%)	**3**	**36**	**29**	**-2.16 (-4.24, -0.07)**	**0.04**	**^{2}=0.11; p=0.94; I^2=0%**
Motor evoked potential threshold (%)	3	61	34	-0.05 (-5.46, 5.36)	0.99	^{2}=3.09; p=0.21; I^2=35%
Motor evoked potential amplitude (mV)	2	40	17	-0.09 (-0.42, 0.23)	0.57	^{2}=1.18; p=0.28; I^2=15%
Motor evoked potential latency (ms)	2	40	17	1.70 (-2.09, 5.50)	0.38	^{2}=5.21; p=0.02; I^2=81%
Central motor conduction time (ms)	2	32	19	-0.74 (-2.75, 1.27)	0.47	^{2}=0.05; p=0.82; I^2=0%
Short interval intracortical inhibition (%)	3	45	42	-1.06 (-30.08, 27.96)	0.94	^{2}=10.64; p=0.005; I^2=81%
Intracortical facilitation (%)	3	45	42	1.74 (-18.36, 21.84)	0.87	^{2}=0.72; p=0.70; I^2=0%
Upper-limb post-fatigue task MVC (%)	**5**	**139**	**87**	**-5.61 (-9.57, -1.65)**	**0.006**	**^{2}=5.04; p=0.28; I^2=21%**

Appendix 20 - Summary of the results of meta-analyses for neuroimaging studies (MS-HF versus HC). Data are presented as absolute mean differences with 95% confidence intervals. MVC, maximum voluntary contraction force.

Variable	Number of studies	Number of Participants		Mean difference (95% CI)	*P*	Heterogeneity
		MS-HF	HC			
Neuroimaging variables						
Mean normalised brain volume (ml)	**9**	305	356	**-74.01 (-88.86, -59.16)**	**<0.00001**	**^{2}=7.80; p=0.45; I²=0%**
Brain parenchymal fraction (%)	**5**	**118**	**90**	**-2.06 (-3.12, -0.99)**	**0.0002**	**^{2}=5.65; p=0.23; I²=29%**
Grey matter volume (ml)	**8**	290	343	**-58.96 (-79.21, -38.72)**	**<0.00001**	**^{2}=27.73; p=0.0002; I²=75%**
White matter volume (ml)	**8**	290	343	**-33.22 (-44.28, -22.15)**	**<0.00001**	**^{2}=15.68; p=0.03; I²=55%**
Thalamus volume (ml)	**6**	208	235	**-1.67 (-2.25, -1.09)**	**<0.00001**	**^{2}=28.00; p<0.0001; I²=82%**
Putamen volume (ml)	**4**	163	148	**-1.07 (-1.50, -0.63)**	**<0.00001**	**^{2}=10.82; p=0.01; I²=72%**
Caudate volume (ml)	**4**	163	145	**-0.84 (-1.15, -0.53)**	**<0.00001**	**^{2}=8.95; p=0.03; I²=66%**
Accumbens volume (ml)	**2**	**53**	**59**	**-0.17 (-0.34, -0.01)**	**0.04**	**^{2}=4.19; p<0.04; I²=76%**
Amygdala volume (ml)	2	53	59	-0.10 (-0.56, 0.36)	0.67	^{2}=7.08; p<0.008; I²=86%
T1-weighted lesion volume (ml)	**2**	49	48	**4.66 (2.42, 6.90)**	**<0.0001**	**^{2}=3.42; p=0.06; I²=71%**
Fractional anisotrophy	2	45	65	-0.02 (-0.04, 0.01)	0.31	^{2}=25.86; p<0.00001; I²=96%
Mean diffusivity ($\times 10^{-3}$ mm²/s)	**2**	**45**	**65**	**0.02 (0.01, 0.03)**	**0.0009**	**^{2}=0.00; p=1.00; I²=0%**
NAA/Cr ratio	**2**	33	27	**-0.10 (-0.18, -0.01)**	**0.03**	**^{2}=0.01; p=0.91; I²=0%**

Appendix 21 - Summary of the results of meta-analyses for neurophysiological studies (MS-HF versus HC). Data are presented as absolute mean differences with 95% confidence intervals. MVC, maximum voluntary contraction force.

Variable	Number of studies	Number of Participants		Mean difference (95% CI)	*P*	Heterogeneity
		MS-HF	**HC**			
Neurophysiological variables						
Upper-limb MVC (N)	**5**	69	82	**-8.73 (-16.71, -0.75)**	**0.03**	**^{2}=9.01; p=0.06; I^2=56%**
Lower-limb MVC (N)	**2**	17	29	**-63.94 (-128.18, 0.31)**	**0.05**	**^{2}=1.91; p=0.17; I^2=48%**
Motor evoked potential threshold (%)	**2**	40	19	**8.46 (2.73, 14.18)**	**0.004**	**^{2}=1.75; p=0.19; I^2=43%**
Motor evoked potential amplitude (mV)	2	40	19	-0.74 (-2.13, 0.65)	0.30	^{2}=7.28; p=0.007; I^2=86%
Motor evoked potential latency (ms)	2	40	19	2.81 (-2.09, 7.71)	0.26	^{2}=14.24; p=0.0002; I^2=93%
Short interval intracortical inhibition (%)	2	24	18	11.93 (-10.99, 34.86)	0.31	^{2}=2.09; p=0.15; I^2=52%
Intracortical facilitation (%)	2	24	18	1.67 (-22.96, 26.30)	0.89	^{2}=1.17; p=0.28; I^2=15%
Upper-limb post-fatigue task MVC (%)	**4**	78	109	**-7.43 (-11.95, -2.90)**	**0.001**	**^{2}=4.28; p=0.23; I^2=30%**

Appendix 22 - Summary of the results of meta-analyses for neuroimaging studies (MS-LF versus HC). Data are presented as absolute mean differences with 95% confidence intervals. MVC, maximum voluntary contraction force.

Variable	Number of studies	Number of Participants		Mean difference (95% CI)	*P*	Heterogeneity
		MS-LF	HC			
Neuroimaging variables						
Mean normalised brain volume (ml)	**9**	333	356	**-51.59 (-71.80, -31.38)**	**<0.00001**	**^{2}=15.57; p=0.05; I²=49%**
Brain parenchymal fraction (%)	**5**	150	90	**-1.95 (-3.46, -0.44)**	**0.01**	**^{2}=15.27; p=0.004; I²=74%**
Grey matter volume (ml)	**8**	301	343	**-41.39 (-62.63, -20.16)**	**0.0001**	**^{2}=32.39; p<0.0001; I²=78%**
White matter volume (ml)	**8**	301	343	**-25.51 (-37.27, -13.76)**	**0.0001**	**^{2}=16.43; p=0.02; I²=57%**
Thalamus volume (ml)	**6**	263	235	**-1.10 (-2.13, -0.07)**	**0.04**	**^{2}=103.20; p<0.00001; I²=95%**
Putamen volume (ml)	**4**	178	148	**-0.65 (-0.93, -0.38)**	**<0.00001**	**^{2}=5.01; p=0.17; I²=40%**
Caudate volume (ml)	**4**	178	148	**-0.36 (-0.66, -0.06)**	**0.02**	**^{2}=8.48; p=0.04; I²=65%**
Accumbens volume (ml)	2	53	59	-0.10 (-0.31, 0.11)	0.36	^{2}=7.18; p=0.007; I²=86%
Amygdala volume (ml)	2	53	59	-0.03 (-0.29, 0.24)	0.85	^{2}=3.06; p=0.08; I²=67%
T1-weighted lesion volume (ml)	**2**	56	48	**5.81 (3.93, 7.69)**	**<0.00001**	**^{2}=0.18; p=0.68; I²=0%**
Fractional anisotrophy	**2**	46	65	**-0.02 (-0.04, -0.00)**	**0.04**	**^{2}=11.63; p=0.0007; I²=91%**
Mean diffusivity ($\times 10^{-3}$ mm^2/s)	**2**	**46**	**65**	**0.03 (0.00, 0.06)**	**0.03**	**^{2}=3.79; p=0.05; I²=74%**
NAA/Cr ratio	2	30	27	-0.05 (-0.12, 0.02)	0.19	^{2}=0.07; p=0.79; I²=0%

Appendix 23 - Summary of the results of meta-analyses for neurophysiological studies (MS-LF versus HC). Data are presented as absolute mean differences with 95% confidence intervals. MVC, maximum voluntary contraction force.

Variable	Number of studies	Number of Participants		Mean difference (95% CI)	*P*	Heterogeneity
		MS-LF	HC			
Neurophysiological variables						
Upper-limb MVC (N)	**5**	48	82	**-5.33 (-8.79, -1.86)**	**0.003**	**^{2}=2.65; p=0.62; I^2=0%**
Lower-limb MVC (N)	2	8	29	-74.31 (-166.56, 17.93)	0.11	^{2}=4.21; p=0.04; I^2=76%
Motor evoked potential threshold (%)	**2**	17	19	**5.60 (1.02, 10.18)**	**0.02**	**^{2}=0.04; p=0.84; I^2=0%**
Motor evoked potential amplitude (mV)	2	17	19	-0.33 (-1.15, 0.48)	0.42	^{2}=2.03; p=0.15; I^2=51%
Motor evoked potential latency (ms)	2	17	19	0.67 (-0.62, 1.96)	0.31	^{2}=0.51; p=0.47; I^2=0%
Short interval intracortical inhibition (%)	2	25	18	0.58 (-10.37, 11.53)	0.92	^{2}=1.04; p=0.31; I^2=4%
Intracortical facilitation (%)	2	25	18	3.90 (-40.99, 48.79)	0.86	^{2}=3.55; p=0.06; I^2 =72%
Upper-limb post-fatigue task MVC (%)	4	49	109	-2.91 (-6.78, 0.96)	0.14	^{2}=1.49; p=0.68; I^2=0%

Appendix 24 -Participant's movement through the trial CONSORT flow chart