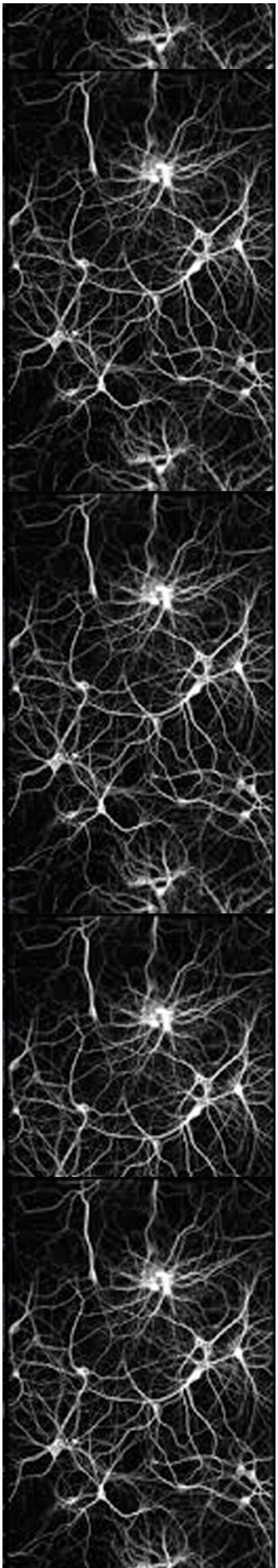

MAXIMAL STRENGTH TRAINING FATIGUE AND BALANCE IN MULTIPLE SCLEROSIS

Doctoral Thesis

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MAXIMAL STRENGTH TRAINING, FATIGUE AND BALANCE IN MULTIPLE SCLEROSIS

Doctoral Thesis

A dissertation presented by

Ramon Jesús Gómez i Illan

Graduate in Physical Activity and Sport Science

Elx, September 2017

El Dr. D. Juan Carlos Marzo Campos, Director del Departamento de Psicología de la Salud de la Universidad Miguel Hernández de Elche.

AUTORIZA:

Que el trabajo de investigación titulado: "MAXIMAL STRENGTH TRAINING, FATIGUE AND BALANCE IN MULTIPLE SCLEROSIS" realizado por D. Ramon Jesús Gómez i Illan bajo la dirección del Dr. D. Raúl Reina Vaíllo y el Dr. D. Francisco José Vera García sea depositado en el Departamento y posteriormente defendido como Tesis Doctoral en esta Universidad ante el tribunal correspondiente.

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Fdo.: Juan Carlos Marzo Campos

Director del Departamento de Psicología de la Salud
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Maximal strength training, fatigue and balance in Multiple Sclerosis

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Directors:

PhD. D. Raúl Reina Vaillo

PhD. D. Francisco José Vera García

Elx, September 2017

A mis padres, por ofrecerme su apoyo

incluso cuando no lo merecí.

A mi mujer, Cris,

por dejarme perseguir mis sueños

aún sabiendo que era a costa de los suyos.

Es en momentos como éste en el que uno se da cuenta de lo afortunado que ha sido en la vida, especialmente por las personas que el destino ha puesto caprichosamente en su camino.

Al no tener más credo que la ciencia, ni más Biblia que los libros que mi madre me animaba a leer, y que muchos profesores desde niño han sabido poner en mis manos, sé que el orden que nosotros creemos perfecto en realidad procede del caos y al mismo tiempo está abocado a él, como si de una hermosa locura se tratase. Somos fruto de la casualidad, e infinitas casualidades mueven nuestro mundo, pues de cada casualidad nace una nueva causalidad, con sus efectos.

La casualidad quiso que una tarde de verano un amigo me animara a estudiar aquello que siempre quise y que nunca tuve tiempo de hacer, mi anhelada licenciatura en Ciencias de la Actividad Física y el Deporte. La misma casualidad llevó a una paciente de esclerosis múltiple (EM) de mi mujer a querer hacer deporte: "Pregúntale a tu marido". Pero el marido sabía aquello que quizás es más difícil saber. Que no sabía nada. De aquí en adelante, relaciones causa-efecto:

Una búsqueda en Google. El anuncio de un Máster. Universidad Miguel Hernández de Elche. Un mail. Una respuesta del Dr. Manuel Moya. Una cita en un despacho: "Sr. Reina, quiero hacer un estudio con pacientes de esclerosis múltiple".

Nunca me he atrevido a preguntarle qué pensó de mi aquella tarde. Soy consciente de que no hay páginas en este libro para agradecer la confianza que depositó en mí desde el minuto número uno. Gracias de corazón Dr. Reina, aunque a mí solo me salga llamarte Raúl, y quizás ahí esté tu grandeza: ser un tío humilde, que tuvo la valentía de embarcarse en un viaje y querer aprender conmigo. Gracias por dar la

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Y como toda causa tiene su efecto, con David llegaron Carmen y Gregori. La primera para poner firmeza militar en las sesiones de entrenamiento que conjuga con un saber tratar a nuestros pacientes que la harán conseguir en el ámbito de la actividad física y la salud lo que se proponga. Y el segundo, Gregori, un luchador al que tengo la suerte de conocer desde hace muchos años, al que convencí para que se embarcará en este mundo, y del que todos destacamos su seriedad y su bondad. Gracias a ambos por vuestra dedicación y apoyo.

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Desde Kant, la causalidad es una categoría del entendimiento, y de la relación causa-efecto, del principio de causalidad, han bebido las ciencias empíricas como la física, la matemática y la estadística. Según Newton, la causa siempre precede al efecto.

Y si en efecto hoy puedo preparar la defensa de mi Tesis es por la causa de varias personas a las que he reservado el final de mis agradecimientos:

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Para tener buena salud lo haría todo menos tres cosas: hacer gimnasia, levantarme temprano y ser persona responsable.

Oscar Wilde

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Table 11. Correlations among the improvements (%) observed in strength, perceived fatigue and functional parameters displayed by the participants of the maximal strength training group.

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ABBREVIATIONS GLOSSARY

10MWT	Ten Meter Walking Test
2MWT	Two Minutes Walking Test
6MWT	Six Minutes Walking Test
CI	Confidence interval
CL	Confidence limits
CNS	Central nervous system
CoP	Center of pressure
d_g	Hedge's g index
EDSS	Expanded Disability Status Scale
ES	Effect size
FSS	Fatigue Severity Scale
ICC	Intraclass correlation coefficient
MFIS	Modified Fatigue Impact Scale
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MST	Maximal strength training
PPMS	Primary progressive multiple sclerosis
PT_{IK}	Isokinetic peak torque
PT_{IM}	Isometric peak torque
pwMS	Persons with multiple sclerosis
QoL	Quality of life
r	Pearson correlation coefficient
RCT	Randomized controlled trial
RM	Repetition maximum
RRMS	Relapsing-remitting multiple sclerosis

SD	Standard deviation
SMD	Standardised mean difference
SPMS	Secondary progressive multiple sclerosis
T25FW	Timed 25-foot Walk Test
TC_{MRE}	Trunk control in sitting posture
TE	Typical error
TS_{MRE}	Tandem with stronger leg backwards
TUG	Timed Up and Go Test
TW_{MRE}	Tandem with weaker leg backwards
VO_{2max}	Maximum rate of oxygen consumption

PREFACE

Multiple sclerosis (MS) is a chronic and progressive autoimmune disease, being the main cause of disability in young adults after traffic accidents. During the last years, the scientific literature has established that a better physical condition implies a better general state of the person who suffers MS, including a better cardiovascular health, reduced fatigue, improved balance and lower risk of falls, among others, leading to an improvement of the quality of life.

Several researches have attempted to improve some of the symptoms that this pathology entails through physical exercise. Although it has been found that a better fitness condition would imply a higher quality of life, there is interest in establishing what type of exercise could be the best to improve each symptom. The heterogeneity of people with MS who participate in studies of physical exercise and quality of life makes the research in this population a complex issue.

One of the symptoms that patients perceive as one of the most disabling is the loss of stability. It is common that people with MS, in the course of the disease, suffer problems with postural control, increasing the risk of falls that can lead to bone fractures and other clinical complications. Postural control is a complex action that depends on the contribution of the sensory system (i.e. visual, vestibular and somatosensory), the motor system (e.g. force production, especially in the trunk and the lower body, and bilateral asymmetries) and perceived fatigue. Improving postural control is one of the main objectives of rehabilitation programs for people with MS and, therefore, many studies have tried to establish which exercises would be most suitable for this purpose. Thus, one of the main objectives of Study 1 of this Doctoral Thesis was *to explore the main factors that influence the loss of stability in people with MS*.

Many of the tests that measure the degree of stability in people with MS come from the clinical scope, sometimes lacking an adequate analysis of their reliability. In this sense, another of the main objectives of Study 1 of this Doctoral Thesis was *to design a protocol that allows assessing the stability in a reliable and precise way*. In this study we have assessed the relative and absolute reliability of a stability test battery, both in the upright and the sitting position, by using a force platform and the analysis of the centre of pressure pathway. In addition, the results of the postural control tests applied in the laboratory were related to other clinical and field tests widely used to measure functional mobility and gait performance in this population (*Timed Up and Go Test* and *Timed 25-foot Walk Test*), to determine if a better postural control implies a better walking performance in people with MS. The results show that the proposed postural control tests, both in tandem and in sitting position, show relative reliability values between high and excellent, as well as good absolute reliability. These data indicate that these tests allow to discriminate the degree of stability in people with minimal symptoms, such as those with a moderate condition, and, moreover, to verify the effect of different interventions for the improvement of stability. The data of the correlations suggest that trunk stability can influence general stability and, therefore, become a variable to be trained to improve postural control, which has an influence on the quality of life of these individuals.

Study 2 of this Doctoral Thesis addressed two of the three factors that influence the lack of stability in persons with MS: muscle weakness (i.e. lack of force production) and perceived fatigue, being its main objective *to reduce perceived fatigue in people with MS through participation in a maximum strength training*.

Previous studies suggest that strength training at high intensities improves neural transmission and reduces the level of pro-inflammatory cytokines, thus contributing to a reduction in fatigue. In this study, a group of people with MS participated in a 12-week intervention program, consisting of a high-intensity strength training, reaching intensities considered as maximum strength (90% of 1 maximum repetition). The results show that perceived fatigue evaluated with the *Fatigue Severity Scale* and the *Modified Fatigue Impact Scale* reduced significantly after the training program. In addition, this program reduced the time taken to perform the *Timed Up and Go Test* significantly, one of the most commonly used functional tests used to verify functional mobility in people with MS. A correlation analysis also shows how a lower body strength increase was related to both a perceived fatigue decrease and a gait test performance improvement.

Findings of this Doctoral Thesis may help rehabilitation teams that work with people with MS to assess postural control in a reliable and precise way. In this sense, the stability test battery may help to categorize persons with MS according to performance in the proposed tests and, subsequently, to evaluate the results of possible interventions aimed to improve stability. On the other hand, the strength training program analysed in this study may be used as a basis for future research to design larger interventions to verify that maximum strength training can reduce perceived fatigue in people with MS.

Key words: balance, reliability, fatigue, maximal strength training, multiple sclerosis.

RESUMEN

La esclerosis múltiple (EM) es una enfermedad autoinmune y evolutiva, principal causa de discapacidad en adultos jóvenes detrás de los accidentes de tráfico, siendo considerada hasta el momento como una enfermedad crónica. Durante los últimos años, la literatura científica ha constatado que un mejor estado físico implica un mejor estado general de la persona con EM, incluyendo una mejor salud cardiovascular, disminución de la fatiga, mejora del equilibrio y prevención de caídas, entre otros, conllevando a una mejora global de la calidad de vida.

Han sido numerosas las investigaciones que, a través del ejercicio físico, han intentado la mejora de algunos síntomas que la patología acarrea. Si bien se ha constatado que a mejor estado de fitness habría una mayor calidad de vida, existe un interés por constatar qué tipo de ejercicio sería el mejor para mejorar cada síntoma. Sin embargo, la heterogeneidad presente entre las personas con EM que participan en estudios de ejercicio físico y calidad de vida hacen que la investigación sea compleja.

Uno de los síntomas que los pacientes perciben como más incapacitantes es la pérdida de estabilidad. Es frecuente que muchas personas con EM, con el transcurso de la enfermedad, tengan problemas con el control postural, implicando en muchos casos caídas que pueden provocar fracturas y otras complicaciones clínicas. El control postural es una tarea compleja que depende de la contribución del sistema sensorial (es decir, visual, vestibular y somato-sensorial), el sistema motor (por ejemplo: producción de fuerza, especialmente del tronco y del tren inferior, y asimetrías bilaterales) y la fatiga percibida. Mejorar el control postural es uno de los principales objetivos de los programas de rehabilitación de personas con EM y, por tanto, son muchas las investigaciones que han intentado encontrar qué

ejercicios serían los más idóneos para ello. Así, uno de los objetivos principales del Estudio 1 de esta Tesis Doctoral es *explorar los principales factores que inciden en la pérdida de estabilidad en personas con EM*.

Muchos de los test que miden la estabilidad en personas con EM provienen del ámbito clínico, careciendo además en ocasiones de un análisis adecuado de su fiabilidad. En este sentido, otro de los objetivos principales del Estudio 1 de esta Tesis Doctoral ha sido *diseñar un protocolo que permita evaluar la estabilidad de manera precisa y fiable*. Se han analizado la fiabilidad relativa y absoluta de una batería de test de estabilidad, tanto en posición erguida como sedente, mediante el uso de una plataforma de fuerzas y el análisis del desplazamiento del centro de presiones, por parte de un grupo de pacientes con EM. Los resultados de los test de control postural aplicados en laboratorio se han relacionado con otros test clínicos y de campo, tanto de movilidad funcional como de rendimiento de la marcha (*Timed Up and Go Test* y *Timed 25-foot Walk Test*), a fin de dilucidar si un mejor control postural implica una mejor calidad a la hora de andar en personas con EM. Los resultados mostraron como los test de control postural propuestos, tanto en posición tándem como en posición sedente, obtuvieron valores de fiabilidad relativa entre altos y excelentes, así como una buena fiabilidad absoluta. Estos datos indican que estos test permiten discriminar el grado de estabilidad en personas con sintomatología mínima, como por ejemplo aquellos con una afección moderada, así como comprobar el efecto de diferentes intervenciones para la mejora de la estabilidad. Los datos de las correlaciones realizadas sugieren que la estabilidad del tronco puede influir en la estabilidad general y, por tanto, convertirse en una variable a ser entrenada con el fin de mejorar el control postural, lo cual tiene un efecto en la calidad de vida de este colectivo.

El Estudio 2 aborda dos de los tres factores que inciden en la falta de estabilidad en personas con EM: la debilidad muscular (o falta de producción de fuerza) y la fatiga percibida, siendo el principal objetivo del Estudio 2 *reducir la fatiga percibida en personas con EM mediante la participación en un entrenamiento de fuerza máxima*.

Estudios previos apuntan a que los entrenamientos de fuerza a altas intensidades mejoran la transmisión neural y reducen el nivel de citoquinas pro-inflamatorias, pudiendo así contribuir a una reducción de la fatiga. En este estudio participó un grupo de personas con EM en una intervención de 12 semanas de duración, consistente en un entrenamiento de fuerza de alta intensidad, llegando a intensidades consideradas como de fuerza máxima (90% de una repetición máxima). Los resultados mostraron como la fatiga percibida evaluada con la *Fatigue Severity Scale* y el *Modified Fatigue Impact Scale* se redujo de manera significativa tras el programa de entrenamiento. Además, el entrenamiento programado redujo significativamente el tiempo empleado en realizar el *Timed Up and Go Test*, uno de los test funcionales más usados con el fin de comprobar la movilidad funcional en personas con EM. Asimismo, un análisis de correlación mostró como un aumento de la capacidad de producción de fuerza del tren inferior se relacionó significativamente con una disminución de la fatiga percibida y con la mejora del rendimiento en el test de marcha.

Los hallazgos de la presente Tesis Doctoral pueden ayudar a equipos rehabilitadores especializados en personas con EM a evaluar el control postural de manera fiable y precisa. En este sentido, la batería de test de estabilidad analizada en el estudio 1 podría ayudar a categorizar a personas con EM según el rendimiento en los test presentados, evaluando posteriormente el resultado de posibles intervenciones orientadas a la mejora de la estabilidad. Por su parte, el entrenamiento de fuerza realizado puede servir como base de futuras investigaciones para diseñar intervenciones con más participantes, a fin de constatar que un entrenamiento de fuerza máxima puede reducir la fatiga percibida en personas con EM.

Palabras clave: equilibrio, fiabilidad, fatiga, entrenamiento de fuerza máxima, esclerosis múltiple.

CHAPTER 1

Introduction

1. INTRODUCTION

1.1. Aetiology, Demographic Data and Types of Multiple Sclerosis

Multiple sclerosis (MS) is an immune-mediated and chronic inflammatory disease of the central nervous system (CNS) that occurs in genetically susceptible people.[1] MS is the most common neurological condition and it is the leading cause of disability affecting young adults in developed countries.[2]

The prevalence in Spain has been growing since the first studies were started, approximately 40 years ago, and we can highlight two different periods: in the first one, from 1968 to 1991 the prevalence was between 5 to 23 patients/100.000 people; in the second one, from 1994 to 1999 the prevalence increased to between 32 to 65 patients/100.000 people.[3] Studies published after the year 2000 reported between 70-80 patients/100.000 people (Figure 1).

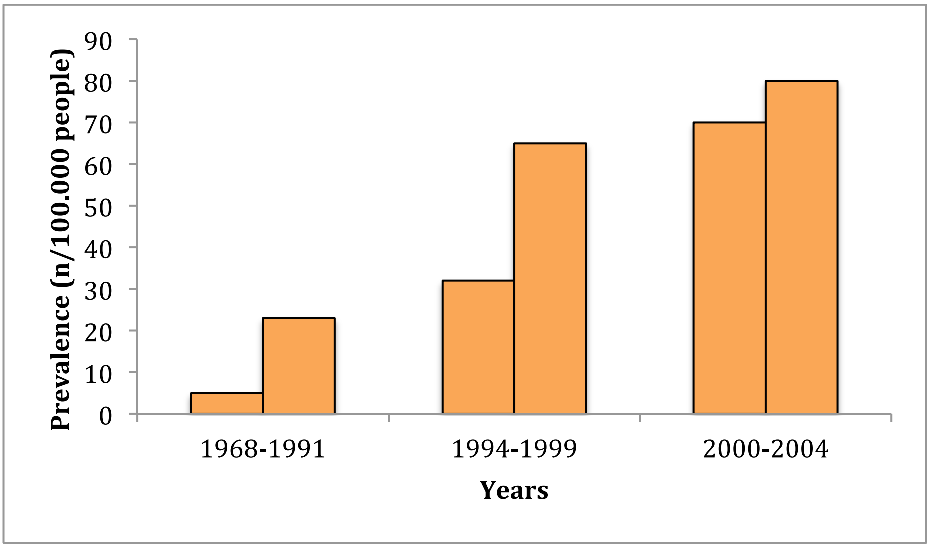


Figure 1. Multiple sclerosis prevalence in Spain.

The exact aetiology of MS is unclear, but an interaction between environmental and genetic factors is a plausible cause.[2] The result is an inflammation of the nerve fibers that causes a destruction of myelin, oligodendrocytes and axons. This demyelination compromises nerve fiber function by slowing axonal conduction velocity leading to all type of impairments. Injuries have a predilection for the optic nerves, periventricular white matter, brain stem, cerebellum and spinal cord white matter.[4]

Given the considerable clinical, genetic and pathological heterogeneity of MS, perhaps more than one pathogenetic mechanism contributes to tissue injury. This possibility has therapeutic implications, because more than one approach to treatment may be required to treat these diseases effectively.[4]

1.1.1. Types of Multiple Sclerosis

In 1996, the United States National Multiple Sclerosis Society Advisory Committee on Clinical Trials in Multiple Sclerosis defined the MS clinical subtypes in *Relapsing-Remitting MS (RRMS), Secondary-Progressive MS (SPMS), Primary-Progressive MS (PPMS),* and *Progressive Relapsing MS* (PRMS)[5] (Figure 2).

Relapsing-Remiting	With full recovery from relapses
	With sequelae/residual deficit after an incomplete recovery
Progressive	**PP**: Progressive accumulation of disability from onset with or without temporary plateus, minor remissions and improvements.
	SP: Progressive accumulation of disability after inital relapsing course, with or without occasional relapses and minor remissions.
	PR: Progressive accumulation of disability from onset but clear acute clinical attacks with or without full recovery.

Figure 2. 1996 clinical subtypes of multiple sclerosis (adapted from Lublin and colleagues[5]). Abbreviations: PP, primary-progressive; SP, secondary-progressive; PR, progressive relapsing.

In 2014, Lublin and collegues[6], after new findings in clinical trials, i.e., the advances in magnetic resonance imaging (MRI) and biological markers, published a review of 1996 Lublin and collegues[5] MS clinical subtypes, defining the following MS phenotypes (Figure 3):

- *Clinically Isolated Syndrome (CIS)*: first clinical appearance of the disease that shows characteristics of inflammatory demyelination that could be MS, but has yet to fulfil criteria of dissemination in time.[7]
- *Relapsing-Remitting Multiple Sclerosis (RRMS)*: disease progression with clearly defined relapses with either full recovery or leaving some residual neurological deficit.[5]
- *Secondary-Progressive Multiple Sclerosis (SPMS)*: History of gradual worsening after an initial relapsing disease course, with or without acute exacerbations

during the progressive course.[6] The transition from RRMS to SPMS is usually gradual.

- *Primary-Progressive Multiple Sclerosis* (PPMS): similar progression than SPMS but with absence of exacerbations prior to clinical progression.[6]

Lublin's group[6] also defined the *Radiologically Isolated Syndrome* (RIS), in which incidental imaging findings suggest an inflammatory demyelination in the absence of clinical signs or symptoms, but is not considered an MS subtype. RIS may raise the suspicion of MS depending on the morphology and location of MRI lesions.[6]

Lublin and collegues[6] also include new modifiers of basic MS phenotypes: disease *activity* (clinical relapses or MRI lesions) and the disease *progression* (clinical evidence in *progressive MS subtypes with or without relapses)*, thus providing temporal information about the disease process. They also recommended at least an annual assessment of activity limitation.[6]

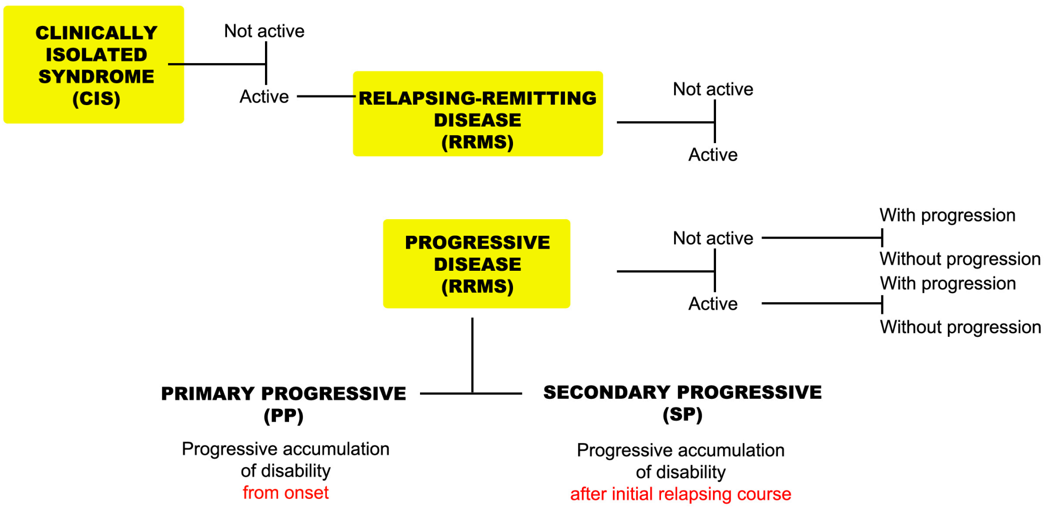


Figure 3. 2014 clinical subtypes of multiple sclerosis (adapted from Lublin and collegues[6]).

1.2. Symptoms, Causes and Consequences

MS presents a great variety of symptoms that worsen quality of life (QoL) in persons with MS (pwMS). According to Noseworthy and colleagues,[4] RRMS usually starts with sensory disturbances, unilateral optic neuritis, diplopia, trunk and limb paraesthesia evoked by neck flexion, limb weakness, clumsiness, gait ataxia, neurogenic bladder and bowel symptoms, and fatigue. These symptoms can be exacerbated when the body temperature increases (Uhthoff's symptom). Furthermore, patients can suffer prominent cortical signs (aphasia, apraxia, visual-field loss and early dementia), cognitive impairment, depression, emotional lability, dysarthria, dysphagia, vertigo, progressive quadriparesis and sensory loss, ataxic tremors, pain, sexual dysfunction or spasticity.[4]

Symptoms can cause disability to patients over time, measured with the Expanded Disability Status Scale[8] (EDSS). This scale ranges from 0 to 10 with 0.5-unit increments representing a higher level of disability. Usually, steps 1.0 to 4.5 refer to pwMS who are able to walk without aids (Figure 4).

Figure 4. The Expanded Disability Status Scale (EDSS).

Among the symptoms that MS causes, balance impairment and fatigue are probably the most disabling ones.[4] Fatigue affects how pwMS deal with daily activities of daily living, worsening their QoL.[9] Fatigue also increases balance impairment in pwMS[10] which is one of the main causes of frequent falls.[11] Thus, decreasing perceived fatigue and improving balance confidence are two of the main topics in MS rehabilitation programs.

1.2.1. Balance Impairment

One of the symptoms which most negatively affects QoL in pwMS is balance impairment because of the fall risk and its consequences, often associated with morbidity, trauma, immobilization and bone fractures.[12] Postural control impairments reduce walking ability, dynamic stability and the ability to perform physical tasks of daily living.[13, 14] Therefore, the reduction of the aforementioned capacities may increase the probability of falls in this population.[15, 16] This is relevant because about 90% of pwMS report impaired balance and mobility, and 50% of them have a fall at least once per year.[11, 17] Approximately 75% of the pwMS report balance impairments, having a moderate-to-severe impact on their daily life functions.[18] It is believed that balance impairment can be felt by patients before the clinical symptoms appear,[19] thus balance deficit in trunk sway observed in MS patients during stance and gait tasks are highly correlated with their EDSS.[20]

Balance impairment is the result of the interaction of some factors (Figure 5): i) sensory (visual,[21, 22] vestibular[23] and somatonsery[24]) contributions; ii) reduced strength production, probably due to a reduced central activation and/or increased strength asymmetry; and iii) increase of the symptomatic perceived fatigue, explaining the poor performance and confidence in balance in pwMS.[25]

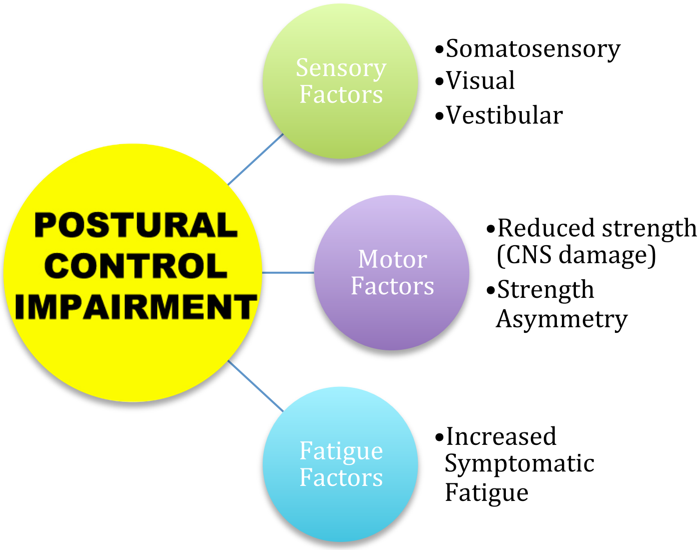


Figure 5. Balance impairment factors in persons with multiple sclerosis (adapted from Van Emmerik and colleagues[25])

Improving balance and reducing falls in pwMS is one of the researchers' main aims to increase QoL in pwMS.

1.2.2. Perceived Fatigue

Fatigue is one of the most important and frequent factors which affects QoL in pwMS. Two-thirds of the MS patients have rated fatigue as one of the worst symptoms of their disease.[26] At least 3 in every 4 patients indicate experiencing symptoms of fatigue at least once per week,[27] which has been identified as one of the main causes of unemployment within this population.[28] Furthermore, increase in fatigue is usually accompanied by other symptoms such as depression, pain, anxiety or cognitive dysfunction.[27]

The Multiple Sclerosis Council for Clinical Practice Guidelines defines fatigue as "a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities";[29] so fatigue is a subjective symptom that can have a physical origin but also a mental one. Perceived fatigue is usually measured using self-reported questionnaires because of the absence of any biomarkers indicating the presence of the symptom. Despite this, efforts to identify objective measures of fatigue have led to a variety of performance-based approaches.[30] During sustained contractions, Schwid and collegues[31] found that motor fatigue (different than from perceived fatigue) was greater in MS patients than in healthy people, but the authors did not find associations between motor fatigue and pwMS weakness. Motta and collegues[32] found strong correlations between the performance in an inertial sensor-based gait analysis and fatigue, in which the fatigued patients showed the worst results.

Although the exact causes of fatigue in MS have not been clearly determined, there is some link with the neurodegeneration process of the pathology (central fatigue) and physical inactivity.[9] Currently, the treatment of fatigue is complex,[33] combining pharmacological intervention with psycho-physiological techniques, such as "energy conservation"[34] or electromagnetic therapy.[35] Furthermore, whilst medicines do not appear to be free from side effects, psychic-physiological interventions do not appear to be able to eliminate fatigue significantly.

As described above, fatigue could also be an essential component of balance impairment in pwMS. MS fatigue has been correlated with perceived walking impairment and balance confidence,[36] reporting poor performance in speed walking tests[37] and negative correlations with performance in standing balance tests.[38] Chung and colleagues[38] found that higher perceived fatigue, assessed with the *Fatigue Severity Scale* (FSS), correlated with postural sway during quiet standing tasks in pwMS. Herbert and Corboy[10] found that the *Modified Fatigue Impact Scale* (MFIS) correlated negatively (physical and cognitive subscales) with balance during a task in which somatosensory feedback was nullified and vision was manipulated.[10] Thus, symptomatic fatigue is related to balance, predicting balance as a function of central sensory integration in pwMS.

The high prevalence of this symptomatology, or the limited effectiveness of some treatments, make essential the investigation of other interventions that can, if not eliminate, reduce fatigue as much as possible in pwMS. In this way, reducing fatigue in this population could improve their balance performance and confidence. Some authors[9, 39] suggest physical exercise as an effective tool to make it possible. In this way, we propose an exercise training protocol in the Study 2 of this Doctoral Thesis.

1.3. Physical Activity, Exercise Training and Multiple Sclerosis

Although it is common to use the expressions *physical activity* and *exercise* as synonyms, it is important to distinguish between the two terms. *Physical activity* is defined as any bodily movement produced by skeletal muscles resulting in energy expenditure;[40] while *exercise* is a planned, structured and repetitive physical activity undertaken over a prolonged period to maintain or to improve physical fitness and functional capacity.[40]

A few years ago, pwMS were advised not to engage in a strenuous physical activity because of the concerns that it might worsen their neurological status. This statement was based on the fact that some pwMS may have exacerbations when they come overheated.[41] This belief usually makes pwMS be normally less active than healthy people or people with other chronic diseases,[42, 43] promoting deconditioning and contributing to comorbidities such as obesity, metabolic syndrome or osteoporosis.[41]

A systematic review[44] involving 1295 participants studied the rate of relapse and adverse events of patients involved in exercise training protocols and healthy people as controls, determining that the rate of relapse was 6.3% for pwMS and 4.6% for controls; and the rate of adverse events was 1.2% for controls and 2.0% for MS patients. Thus, Pilutti and colleagues[44] supported that exercise training is generally safe in pwMS, encouraging them to experience the many benefits of exercise training documented in the literature. Evidence regarding positive effects of exercise training in MS patients is present in the literature since few years ago.[45-48] Common types of training in literature for pwMS are shown in Table 1.

Table 1. Usual types of training in literature in persons with Multiple Sclerosis.

Aerobic training	Exercise that depends primarily on the aerobic energy-generating process.
Endurance training	Exercise performed maintaining the optimum intensity of a prescribed load during an established relatively long duration.
Resistance training	Exercise performed to overcome internal or external resistance through a muscular effort.
Maximal strength training	Resistance training performed with high loads (i.e. >70% of one repetition maximum)
Bodyweight strength training	Resistance training developed with the subject´s own body weight.
Power training	Exercise training developed to enhance power muscle production.
Combined training	An intervention that combines two or more types of training (i.e. resistance and endurance training) in the same training session or in different sessions of

	the training program.
Functional training	Locomotor training intervention aimed at improving activities of daily living.
Balance training	The task-oriented intervention aimed at improving balance ability.
Gait training	The task-oriented intervention aimed at improving walking ability.
Video-based-console training	Home-based training performed under the instructions of a video-console game.
Functional electric stimulation	A technique that uses low energy electrical pulses to cause muscle contractions.

1.3.1. Exercise and Aerobic Performance

It has been reported that pwMS have lower levels of cardiorespiratory fitness compared to healthy, age-matched controls.[49, 50] There is consistent evidence supporting the effectiveness of aerobic training to improve aerobic capacity.[45, 51, 52] There is also evidence that cardiorespiratory fitness is associated with disability status,[53, 54] cortical plasticity,[55] grey and white matter integrity,[56] walking performance,[49] cognition[57] and fatigue.[58] Furthermore, cardiorespiratory fitness may reduce the risk of cardiovascular comorbidities.[51]

A meta-analysis by Platta and colleagues[51] presents an overall weighted mean effect size [ES = 0.47, stardand error (SE)= 0.09, 95% confidence interval (CI) = 0.30-0.65, $p < 0.01$], reflecting statistically significant and moderate effect in favor of the use of exercise training to improve cardiorespiratory fitness. In the same way, a meta-analysis by Langeskov-Christensen and colleagues[52] showed that aerobic training in pwMS may improve their VO_{2max}.

A review by Latimer-Cheung and colleagues[45] shows data from four[59-62] randomized controlled trials (RCT) with PEDro score >6 (i.e. high level of evidence), reporting that aerobic exercise training programs, with a frequency of 2 to 3 times per week for 30 to 60 min at moderate intensities (60-80% maximum heart rate), were enough to improve aerobic capacity. However, the effectiveness of programs combining aerobic and resistance training for improving aerobic capacity is not clear at all.[45]

1.3.2. Exercise and Muscular Strength

Literature supports that pwMS show muscle weakness compared with healthy people.[45, 51] Muscular strength improvements are important for mobility, balance, fatigue and activities of daily living,[48, 51] affecting bone health and metabolism if they are associated with a gain in lean mass.[45, 63] Muscular strength has also been associated with walking speed and endurance, gait outcomes and cognitive processing speed.[57]

The review by Latimer-Cheung and colleagues includes data of four[64-67] RCT (PEDro score >6), showing strong evidence that 2 to 3 sessions per week, during 8 to 20 weeks of supervised resistance training with an intensity of 70 to 80% of one repetition maximum (RM), are effective to increase muscle strength. Resistance training has been carried out in a traditional form (i.e. dumbbells, resistance machines, etc.), but also using elastic resistance bands,[68] leg/arm cycling machines,[59] robotic-assisted treadmill training[69] or water resistance exercises in a swimming-pool.[70, 71]

1.3.3. Exercise and Mobility: Walking Speed, Walking Endurance and Agility

Walking impairment is one of the most disabling symptoms in pwMS. Studies using exercise training to improve this outcome have evaluated walking speed, walking endurance and the agility/dynamic balance in pwMS. Some relevant findings are described below:

- *Walking Speed*

  Walking speed has been assessed using different clinical tools as the *10 Meter Walking Test* (10MWT) or the *Timed 25-foot Walk Test* (T25FW). Lattimer and colleagues´ review[45] shows that there are conflicting results from the 2 RCTs[72, 73] (PEDro score >6) regarding the effect of aerobic exercise on walking speed. However, other RCT[65] (PEDro score >6) reported a significant improvement in walking speed after 12 weeks of progressive resistance training 2 times/week. The same review[45] shows improvements in walking speed after 8 weeks of training combining cycling, balance, and plyometric exercises,[74] or 26 weeks combining home-based aerobic and resistance training 2 times per week.[68]

  Likewise, a recent meta-analysis[75] evidenced that exercise improves walking speed in pwMS. This study comprises 655 patients of different RCTs, including six interventions[65, 72, 74, 76-78] using 10MWT that significantly improved performance after training, in which the programs combining resistance and aerobic training obtained the best data.[77, 78] Pearson and collegues[75] also analysed the effect of exercise modality on walking speed, and found the strongest effect for combined training.

- *Walking Endurance*

Walking endurance has usually been tested using the *2 Minutes Walking Test* (2MWT) and the *6 Minutes Walking Test* (6MWT), both considered as clinical tools.

Lattimer and colleagues[45] found supportive, but not consistent, evidence that aerobic training could improve walking endurance in pwMS. Regarding resistance training, a randomized controlled trial (RCT) by Dalgas and colleagues[65] (PEDro score >6) evidenced a significant improvement in walking endurance after 12 weeks of progressive resistance training twice a week. Interventions combining exercise modalities also show significant results, as Rombert and colleagues[68] RCT (PEDro score >6), who obtained walking endurance improvements after 26 weeks of combined home-based exercise and resistance training twice a week.

The meta-analysis by Pearson and colleagues[75] includes four interventions[65, 79-81] that improved 6MWT results, being strength training the intervention that obtained the best results;[65] and four studies[72, 76, 77, 82] with five intervention groups using the 2MWT showed a significant improvement in walking, in which an intervention that combines strength and endurance[77] obtained the best improvements. Pearson and colleagues[75] also analysed the effect of exercise modality on walking endurance, and they found that resistance training obtained the highest improvement in the 6MWT. However, combined training showed the best improvement in the 2MWT.

- *Agility, Dynamic Gait and Balance*

Walking endurance, dynamic gait and balance have usually been assessed using clinical tools as the *Timed Up and Go Test* (TUG). The review by Lattimer and colleagues[45] found that there were no studies with high-quality level of evidence (PEDro score >6),[45] reporting improvements in TUG. Regarding resistance training, Debolt and colleagues[64] (PEDro score >6) have not found significant improvements in TUG performance with 8 weeks of home-based resistance training. However, Cakt and colleagues[74] obtained significant improvements in TUG with a combined exercise training (leg cycling/balance/plyometric) for 8 weeks, twice a week. In addition, the meta-analysis by Pearson and collegues[75] have not found significant improvements in the TUG either, although the data suggest a tendency towards improvement.

1.3.4. Exercise and Balance

As already mentioned before, balance impairment is one of the most disabling symptoms in pwMS. Since a few years ago, several authors have attempted to improve the balance of pwMS using different exercise interventions as general exercise, resistance, endurance, and motor sensory training, but also using gait, balance and functional training, and even using video-game-based interventions.

In 2015, a review by Gunn and colleagues[19] suggested that balance might improve through exercise interventions. This review includes 16 RCTs, with two studies using strength training, one using endurance training, seven using general exercises (yoga, home-based exercises and physiotherapy), five using gait, balance and functional training, and three using video-console games. Their results show that *gait, balance and functional training* sub-group interventions yielded the greatest pooled effect size [standardised mean difference (SMD) = 0.82 (0.55 to 1.09)]. The *general exercise* programs suggested a moderate overall effect in balance performance. Furthermore, the *active video-console games* subgroup suggested a small positive effect in balance.

Of the reviewed studies, only two[64, 67] used resistance training, focusing on lower limbs and core stability. In addition, Broekmnans and colleagues[67] also have a group that included strength training complemented with functional electric stimulation, obtaining the best improvements in resistance training in those reviewed by Gunn and colleagues[19] (ES = 1.58, $p < 0.05$). The authors pointed out that the other group of Broekmans and colleagues[67] intervention only used seated resistance machines, so this training doesn't challenge participant's balance. Nevertheless, De Bolt and colleagues[64] used bodyweight strength training and this kind of training may have challenged balance in standing.

Only one endurance training following a cycling progressive resistance training[74] was reviewed by Gunn and colleagues,[19] obtaining significant improvements in balance (ES = 1.16, $p < 0.01$). Nevertheless, only one of the reviewed studies[64] by Gunn and colleagues[19] used a laboratory device to assess balance improvements, while the other 15 used a clinical test such as the *Functional Reach* or the *Berg Balance Scale*.

One of the main problems to quantify the improvements of exercise interventions on balance is that many of the clinical tests used to assess balance and mobility in pwMS may not be sensitive enough. Laboratory-based balance measurements are required to objectively assess the effectiveness of different interventions.

Posturography has been commonly applied in pwMS to quantify postural control performance, [20, 83-86] since it allows to obtain accurate data about stability and balance. However, its application shows some potential limitations, because the influence of postural control in functional mobility and walking ability may be biased. On one hand, the ability of posturography to classify minimally impaired MS individuals (i.e. EDSS ≤ 2) according to their balance performance is unclear, especially in early stages of the disease. In fact, little is known about the reliability of posturographic methodologies in pwMS. To the authors´ best knowledge, only three studies have analysed the reliability of posturographic tests to assess postural control in pwMS.[87-89] Overall, a fair-to-excellent relative reliability, assessed through the intra-class correlation coefficient index (ICC), has been reported.[87-89] Thus, posturography is a reliable tool to rank MS individuals according to their balance performance level in comparison to other individuals also affected by MS.[90] However, individuals from those studies are characterized by a heterogeneous MS profile, showing a broad range of EDSS scores, leading to an increase of ICC scores because of high trial-to-trial variability. Nonetheless, absolute reliability (i.e. trial-to-trial variation) was not analysed in those studies. Therefore, the absolute and relative reliability of posturographic protocols should be evaluated attending to the MS progression, as a previous stage to analyse the influence of postural control in functional mobility and walking capability in pwMS.

On the other hand, studies in other populations demonstrated that trunk control is an important factor for both performing daily living tasks while sitting[91, 92] and body balance,[93-95] but its role in pwMS has been scarcely studied. An experimental study with single cases[96] highlighted the potential benefits of core stability programs on walking in pwMS, needing more studies to confirm these findings. One of the possible reasons that can explain the lack of knowledge about the role of trunk control in pwMS could be related to the fact that no reliable protocols to assess trunk control have been implemented in this population. Postural control in pwMS has been commonly evaluated in upright stance,[86] where the influence of trunk control impairments may be diminished by the lower extremities involvement.

Overall, seated tests using force platforms have proven to be a reliable method to assess trunk control in different populations.[97-101] However, to the best of the author's knowledge, only one study has applied posturographic techniques in seated conditions,[102] finding a reduced trunk control in pwMS performing arm movements while sitting in comparison to healthy participants. No information about the reliability of these measures was provided, being one of the aims of this Doctoral Thesis.

Because quantifiable methods to assess postural control in standing and sitting positions in pwMS are required to test the effectiveness of interventions for improving balance in pwMS, we propose a laboratory protocol to assess postural control in pwMS in the Study 1 of this Doctoral Thesis.

1.3.5. Exercise and Fatigue

Despite the fact that historically pwMS were encouraged to avoid exercise or physical activity because most of them experienced both perceived fatigue and exacerbations due to Uhthoff's symptom, there is enough evidence to establish that well-prescribed exercise neither increases perceived fatigue[39, 45, 103-105] nor increases the risk of relapses in pwMS.[44, 104]

Recent reviews and meta-analysis analysing the influence of exercise on perceived fatigue agreed on the benefits of exercise to reduce this disabling symptom. Asano and Finlayson[105] evaluated the effectiveness of fatigue management interventions (exercise, education, medication), including 18 rehabilitation trials and 895 participants with MS. The revised rehabilitation interventions included exercise interventions (aerobic, aquatic, inspiratory muscle exercise, vestibular, progressive resistance training, yoga), educational intervention (group fatigue/energy management programs), and psychotherapies (cognitive behaviour therapy, mindfulness). The authors reported “strong evidence” for exercise-based interventions (ES = 0.57; CI = 0.10 to 1.04; p<0.02) to reduce patient-reported fatigue. Hence, despite this evidence, the literature has shown controversial results about the efficacy of exercises on fatigue.[39, 45, 103, 104] Some of the reason which may explain these results are that most of the studies: i) do not include participants' fatigue as inclusion criteria; ii) do not identify fatigue as a primary outcome; and iii) present a large heterogeneity of exercises therapies.[104] Based on the last limitation, as of today, there is no evidence of which type of training (i.e. aerobic, resistance, combined or others) is the best to improve fatigue perception.

The review by Latimer and colleagues[45] concludes that evidence regarding exercise training on symptomatic fatigue was inconsistent, although some types of exercise training are promising yet insufficient to determine an optimal dose.[45] The same authors reported that interventions including a resistance-training component might be most effective for fatigue reduction.[45] From this review, only three[60, 61, 106] of nine RCTs with the higher level of evidence (PEDro score >6) report significant improvements in symptomatic fatigue-related outcomes after moderate-intensity aerobic exercise, 2 to 3 times per week for at least 40 min per session. The protocols of the other 6 RCTs reviewed neither worsened nor improved fatigue symptoms. The same review[45] examined the effects of resistance training on symptomatic fatigue. Despite the fact that there are fewer studies examining the benefits of resistance training to reduce fatigue, the evidence is more favourable for this type of exercise than aerobic training alone.

In the same line, a meta-analysis by Pilutti and colleagues[39] comprises effect size (ES) from 17 RCTs and 568 pwMS, concluding that exercise training is associated with a significant small reduction of fatigue (ES = 0.45; standard deviation - SD - =

0.12, CI = 0.22 to 0.68, p < 0.01). These authors also marked that, in general, studies involving resistance training (alone or combined with other types) cause larger overall effect sizes, in accordance with Andreasen and colleagues,[103] who found that resistance training was consistently associated with a reduction in symptomatic fatigue.

Among the resistance training regimes, a study in which a maximal strength training program was applied to the lower body confirmed improvements in efferent neural transition in pwMS,[107] reducing perceived fatigue. This type of resistance training has shown to be a useful tool to reduce peripheral pro-inflammatory cytokine levels,[108] which has been related to fatigue symptoms during the disease.[109]

Asano and Finlayson[105] evaluated the effectiveness of fatigue management interventions (exercise, education, medication), including 18 rehabilitation trials and 895 participants with MS. The rehabilitation interventions evaluated included exercise interventions (aerobic, aquatic, inspiratory muscle exercise, vestibular, progressive resistance training, yoga), educational intervention (group fatigue/energy management programs), and psychotherapies (cognitive behaviour therapy, mindfulness). The authors reported “strong evidence” for exercise-based interventions (ES = 0.57; CI = 0.10 to 1.04; p < 0.02) for reducing patient-reported fatigue.

Publications such as those by Heine and colleagues[104] support the idea that further research is necessary to directly establish the mode of exercise training that is most effective for reducing fatigue in pwMS. This review[104] found a significant effect on fatigue in favour of exercise therapy (SMD = -0.53, CI = -0.73 to -0.33, p < 0.01) in coincidence with Latimer-Cheung[45], Pilutti[39] and Andreasen.[103] However, the results examining the different types of exercise intervention only found a significant effect for endurance training, mixed training and "other" training, but not for resistance (muscle power) training.

Evidence of resistance training effects upon fatigue is not clear. One reason for these findings may be related to the fact that most of the studies applied progressive programs up to sub-maximum loads (<80% of 1RM).[48] It is known that resistance training using high loads (80-100% of 1RM) enhances muscle fiber recruitment and neural drive to a higher extent than other resistance trainings.[110] In this way, high loads could be the best option[107] to confront with the decreased central neural drive associated with MS and to reduce the disease symptoms. In addition, as it has been stated before, this type of resistance training seems a useful methodology to reduce peripheral pro-inflammatory cytokine levels,[108] which had been related to fatigue symptoms during MS.[109] Despite these promising evidence, a recent pilot study applying high loads (85–95% of 1RM) did not find a significant reduction of perceived fatigue after the intervention, questioning the efficacy of high-intensity resistance training to reduce this symptom.[108, 111]

Based on the high prevalence of perceived fatigue and the scarce effectiveness of some treatments, the assessment of which interventions may reduce, if not eliminate, fatigue as much as possible in pwMS is essential. Hence, in the Study 2 of this Doctoral Thesis, we aimed to analyse if a resistance training using high loads may be a useful tool to improve fatigue symptoms in pwMS.

CHAPTER 2

Research Aims and Hypotheses

2. RESEARCH AIMS AND HYPOTHESES

Attending to the prevalence of balance and perceived fatigue impairments in pwMS, and how these symptoms are related and affect their QoL, our first objective was to improve balance performance in pwMS.

To assess improvements in balance, first, there is a need to develop quantifiable methods to assess postural control in standing and sitting positions in pwMS. This is the main purpose of Study 1 of this Doctoral Thesis.

On the other hand, one of the most disabling symptoms, which directly affect balance performance, is perceived fatigue. So, the principal purpose of the Study 2 of this Doctoral Thesis is to assess if a maximal strength training (MST) program could reduce perceived fatigue in pwMS.

2.1. Research Aims

2.1.1. Study 1

Principal Aims

2.1.1.1. To assess the relative and absolute reliability of two posturographic protocols in minimally (EDSS ≤ 2) and moderately impaired (2.5 ≤ EDSS ≤ 4) individuals with MS: tandem stance balance test and a sitting balance test on an unstable seat.

2.1.1.2. To analyse the potential influence of postural control parameters on functional mobility and walking performance, assessed by two of the most common clinical tests used in this population: *Timed Up and Go Test* and the *Timed 25-foot Walk Test*.

Secondary Aims

2.1.1.3. To provide evidence that helps physicians classify patients attending to their postural control impairment.

2.1.1.4. To differentiate between clinically relevant changes in postural control and normal variability in individuals with MS.

2.1.1.5. To evaluate the relationship between postural control parameters, functional mobility and walking ability in individuals with MS.

2.1.2. Study 2

Principal Aims

2.1.2.1. To analyse the effect of a MST program on the perceived fatigue in individuals with MS.

2.1.2.2. To assess the effect of the MST on functional mobility in individuals with MS.

Secondary Aims

2.1.2.3. To improve strength outcomes in individuals with MS, especially of the lower limbs (knee flexors and extensors).

2.1.2.4. To improve walking performance in individuals with MS.

2.1.2.5. To provide evidence that helps physicians in the design of safe and effective training protocols to improve the QoL of individuals with MS.

2.2. Research Hypotheses

2.2.1. Study 1

2.2.1.1. Standing balance and trunk stability assessment through the analysis of center of pressure (CoP) excursion using a force platform will be a reliable methodology in individuals with MS.[87-89]

2.2.1.2. Standing balance and trunk stability will have a significant correlation, being suitable methods to evaluate postural control in inidividuals with MS.[96]

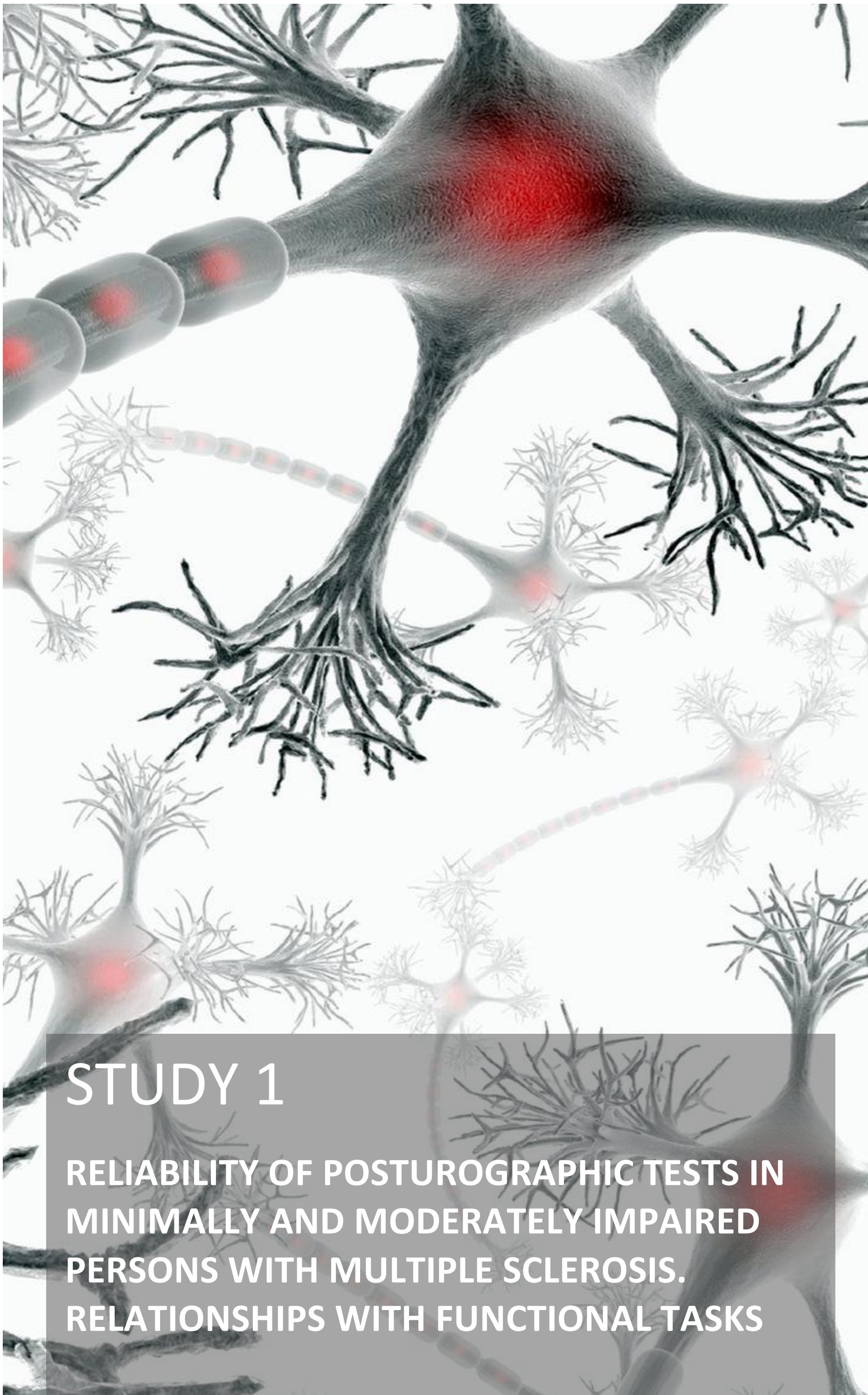
2.2.1.3. Postural control parameters will have significant correlations with functional mobility and walking performance.[96, 112]

2.2.2. Study 2

2.2.2.1. The MST program, owing to the neural improvements that this type of resistance training implies, will significantly reduce perceived fatigue in individuals with MS compared to a control group.[108]

2.2.2.2. The MST program will improve functional mobility in individuals with MS compared to a control group.[113]

2.2.2.3. Greater strength improvements after the MST will correlate with greater fatigue reductions in the participants of the MST program.[107, 113]



CHAPTER 3

STUDY 1

RELIABILITY OF POSTUROGRAPHIC TESTS IN MINIMALLY AND MODERATELY IMPAIRED PERSONS WITH MULTIPLE SCLEROSIS. RELATIONSHIPS WITH FUNCTIONAL TASKS

3. STUDY 1: RELIABILITY OF POSTUROGRAPHIC TEST IN MINIMALLY AND MODERATALY IMPAIRED PERSONS WITH MULTIPLE SCLROSIS. RELATIONSHIPS WITH FUNCTIONAL TASKS.

RELIABILITY OF POSTUROGRAPHIC TESTS IN MINIMALLY AND MODERATELY IMPAIRED PERSONS WITH MULTIPLE SCLEROSIS. RELATIONSHIPS WITH FUNCTIONAL TASKS.

Gomez-Illan, RJ., Moreno, P., Barbado, D., Reina, R., & Vera-Garcia, FJ.

3.1. Abstract

Background: Postural control has been associated with the functional degree of impairment and fall risk status in moderate-to-severe impaired persons with multiple sclerosis (pwMS). However, there is a need for accurate and reliable methods to assess postural control in standing and sitting conditions in pwMS with low Expanded Disability Status Scale (EDSS) scores. In addition, the relevance of standing and sitting postural control in minimally-impaired pwMS is unknown.

Objectives: To assess the absolute and relative reliability of two posturographic protocols in minimally (EDSS ≤ 2) and moderately (2.5 ≤ EDSS ≤ 4) impaired pwMS (i.e. a tandem stance balance test and an unstable sitting balance test), and to analyze the potential influence of standing and sitting postural control parameters on dynamic stability and walking performance in pwMS.

Methods: 14 minimally and 16 moderately impaired pwMS performed the postural control tests on a force platform. Specifically, to assess postural control in an upright stance, participants performed six 70-s trials in tandem position: 3 trials with the weaker leg behind (TW) and 3 trials with the stronger leg behind (TS). Additionally, participants carried out five 70-s trials of an unstable sitting protocol (US) to assess participant's trunk stability while minimizing lower-limb participation. Then, mean radial errors (MRE) of TW, TS and US were calculated as postural control measurements. Furthermore, participants performed the *Timed Up and Go Test* (TUG) and the *Timed 25-foot Walk Test* (T25FW) to determine their functional mobility and walking speed, respectively. The relative and absolute reliability of the measures were calculated using the intraclass correlation coefficient ($ICC_{3,1}$) and the typical error (TE), respectively. Pearson correlation analyses (*r*) were performed to explore the potential influence of upright and sitting postural control on TUG and T25FW scores.

Results: ICC values were high to excellent for minimally (TW_{MRE}: 0.87; TS_{MRE}: 0.92; US_{MRE}: 0.90) and moderately (TW_{MRE}: 0.83; TS_{MRE}: 0.80; US_{MRE}: 0.92) impaired pwMS. In addition, TE values were lower than most posturographic tests for minimally (TW_{MRE}: 11.76%; TS_{MRE}: 9.32%; US_{MRE}: 10.98%) and moderately (TW_{MRE}: 12.84; TS_{MRE}: 15.33%; US_{MRE}: 10.33%) impaired pwMS. All standing and sitting postural control parameters showed significant correlations with TUG scores ($0.419 \le r \le 0.604$), and TW_{MRE} also correlated with T25FW scores ($r = 0.534$). Furthermore, US_{MRE} correlated with both tandem stance parameters (TW_{MRE}: $r = 0.540$; TS_{MRE}: $r = 0.433$).

Conclusions: Tandem stance and unstable sitting balance tests are reliable posturographic protocols for pwMS, even for minimally impaired patients. Quality of gait and weaker leg status seem decisive in assessing the degree of activity limitation in pwMS. In addition, trunk stability performance seems to be decisive for both standing balance and functional capacity in pwMS.

Key words: postural control, functional mobility, reliability, multiple sclerosis.

3.2. Introduction

Multiple sclerosis (MS) is an immune-mediated neurodegenerative disease that affects the central nervous system, which frequently results in postural control impairments.[114] Postural control impairment is one of the main concerns of persons with MS (pwMS), as it has a severe impact on the ability to perform mobility-related activities during their daily life[13, 14] (e.g. manual activities while standing, rising from a chair, walking and turning) which in turn may increase the probability of falling.[15, 16] An accurate evaluation of this ability in pwMS is needed to obtain a better understanding of its impact on functional parameters and also to facilitate an early detection of postural control deficits, which may help to implement more aggressive therapeutic interventions.

Posturography is considered an objective and accurate technique to reveal subtle postural control reductions in pwMS, which would be usually untraceable using common clinical scales.[20, 83-86] Hence, posturography has been used to discriminate between pwMS and matched healthy individuals.[20, 83, 84, 87, 115-118] In addition, some reliability studies have shown that posturographic protocols have good relative consistency [intraclass correlation coefficient (ICC): 0.62 to 0.93], allowing a proper classification of pwMS according to their level of postural control.[87-89] However, the samples of pwMS in these studies were very heterogeneous [as participants showed a broad range of Expanded Disability Status Scale (EDSS) scores], which could have increased relative reliability scores and facilitated their classification. In these sense, future studies should analyse the relative reliability of posturographic protocols in pwMS with similar EDSS scores (i.e. in homogeneous samples).

Moreover, to the authors' best knowledge, there are no studies that have assessed the absolute reliability of these protocols (i.e. trial-to-trial variation); therefore, the ability of the posturographic tests to discriminate between clinically relevant differences in postural control (caused by the disease progression) and normal day-to-day variability remains unknown. Overall, these limitations hinder the postural control assessment in pwMS.

Most posturographic tests measure the stability of the whole body in upright stance.[86] However, although the stability of the core area of the body has sparked interest in physical medicine and rehabilitation in recent years due to its potential benefits for patients' balance[97-101], only two studies have used posturography in sitting positions (on unstable seats) to assess trunk postural control in ambulatory and non-ambulatory pwMS.[102, 119] In comparison to the protocols performed in upright stance, these posturographic tests reduce the influence of the lower limbs on test performance, while they increase the role of the upper-body in postural control[102, 119]. Although several studies have shown the reliability of these protocols in different populations,[97-101] only one study has analysed the reliability of an unstable sitting test in pwMS.[102] This study showed the relative reliability of the protocol, but the absolute reliability was not analysed.[102] Therefore, new reliable posturographic protocols should be developed to assess trunk postural control in pwMS, especially because this ability seems an important factor for balance and functional mobility in patients with different neurological disorders, as cerebral palsy,[93, 94] stroke[120, 121] and Parkinson disease.[122].

Based on these literature limitations, there is a need to develop accurate and reliable methods to assess postural control in standing and sitting conditions in pwMS. So, the first aim of this study was to assess the absolute and relative reliability of two posturographic protocols in minimally (EDSS ≤ 2) and moderately

(2.5 ≤ EDSS ≤ 4) impaired pwMS, i.e. a tandem stance balance test and a sitting balance test on an unstable seat. The second aim was to analyse the potential influence of standing and sitting postural control parameters on functional mobility and walking performance in pwMS, assessed by two of the most common clinical tests used in this population: *Timed Up and Go Test*[123] (TUG) and *Timed 25-foot Walk Test*[124] (T25FW), respectively.

3.3. Material and Methods

3.3.1. Participants

Thirty participants (Table 2) with MS were recruited for this study based on the following inclusion criteria: 1) medical diagnosis of MS; 2) EDSS ≤ 4; and 3) being able to stand in a tandem position without help. Participants were excluded if they needed an orthosis for stance control of the foot, ankle, and/or knee. After their recruitment, they were stratified according to their EDSS score as minimally (EDSS ≤ 2) or moderately impaired (2.5 ≤ EDSS ≤ 4) pwMS. Experimental procedures were in accordance with the Declaration of Helsinki and were approved by the University Office of Research Ethics (DPS.RRV.05.15). All participants provided informed consent prior to their participation. Demographic and clinical descriptive data were derived from medical records (Table 2).

Table 2. Demographic and clinical characteristics of the participants stratified according to their Expanded Disability Status Scale (EDSS).

	EDSS ≤ 2			2.5 ≤ EDSS ≤ 4			
	N	Mean	(SD)	N	Mean	(SD)	*p*
Women/Men	11/3			14/2			
EDSS	14	1.32	(0.69)	16	3.125	(0.59)	< 0.001
Age (years)	14	38.64	(7.66)	16	46.25	(8.86)	< 0.001
Height (m)	14	1.65	(0.09)	16	1.63	(0.06)	0.244
Body mass (kg)	14	68.25	(9.20)	16	59.92	(6.51)	0.004

SD: Standard deviation.

3.3.2. Experimental Procedures

Participants completed two assessment sessions separated by 15 days. In both sessions, to reduce the fatigue effect on postural control and clinical/functional tests, all participants were instructed to refrain from doing exercise on the day of the assessment.

During the testing session, participants firstly performed the protocols to evaluate postural control in tandem stance and sitting position. Secondly, they carried out the TUG and T25FW to assess the functional mobility and walking performance, respectively.

Tandem Stance Balance Test

To assess the participants' ability to control their body in an upright stance, they performed the tandem stance balance test, consisting in an anterior-posterior movement task while standing in the tandem position on a force-platform (9286AA, Kistler, Switzerland), sampling at 1000 Hz. During this test, feedback of the CoP displacement was provided to the participants in real time (Figure 6). In addition, a target point was presented to assess the participants' ability to adjust their CoP position to that point, which moved repeatedly over an anterior-posterior trajectory, comprising 20 s to complete a cycle (0.05 Hz). The displacement amplitude of the target point corresponded to an inclination angle of the whole-body centre of mass of 2°. Body centre of mass was established as 0.55 of body height.[125] The initial position of the target point was readjusted prior to each trial by averaging the CoP position during a 6 s static data collection without visual feedback. Participants performed 6 trials of 70 s with 1 min rest between trials: 3 trials with their stronger leg placed behind their weaker leg, and 3 trials with their weaker leg behind their stronger leg. The categorisation of stronger and weaker leg was based on their postural control performance during the tandem test.[126]

Figure 6. These pictures show a given participant performing the tandem stance balance test with feedback of the centre of pressure.

Unstable Sitting Balance Test

Participants performed a sitting balance test[97, 127] on an unstable seat placed over a force platform (sampling at 1000 Hz) to assess trunk postural control (Figure 7). The unstable seat was a wooden chair with a polyester-resin hemisphere (radius = 35 cm; height = 12 cm) attached to its bottom. Participants were placed in the unstable wooden chair with their arms crossed over the chest and their lower limbs strapped to the seat (90° knee flexion). Similarly to the tandem stance balance test, the feedback of the CoP and target point displacements was provided to the participants in real time (Figure 7). They were requested to adjust their CoP to the target point, which moved repeatedly over a circular trajectory, lasting 20 s to complete a cycle (0.05 Hz). The displacement amplitude of the target point corresponded to the upper body centre of mass inclination angle of 4°. Upper body centre of mass was calculated as 0.626 of the distance between the greater trochanter and the acromioclavicular joint.[125] As in the tandem stance balance test, the target point position was readjusted prior to each trial by averaging the CoP position during a 6 s static data collection without visual feedback. Participants performed 5 trials of 70 s with 1 min rest between trials. All participants were able to maintain the sitting position without grasping a support rail placed around them to prevent participants from falling.

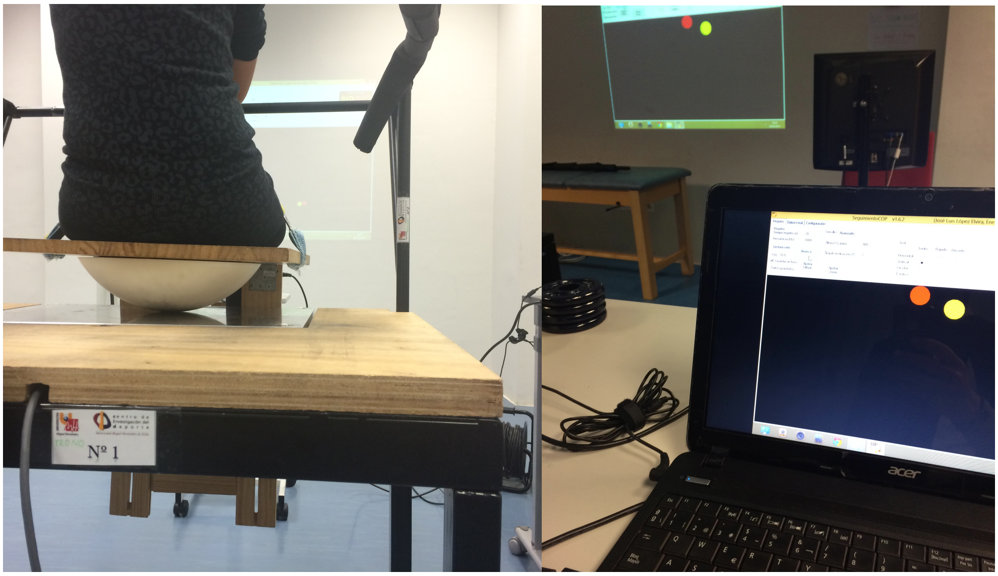


Figure 7. Circular trajectory feedback in real time while the participant is performing the unstable sitting balance test.

Functional mobility and gait speed

Participants carried out TUG[123] and T25FW[124] to obtain clinical scores of their functional mobility and gait speed respectively. TUG consisted of standing up from a chair, walking 3 m around a cone and sitting back down in the chair as fast as possible. Similarly, T25FW consisted of walking a 25 feet distance (7.62 m) in the shortest possible time. In both test, the time (in seconds) was recorded using a digital chronometer (CASIO HS-30W-N1V). Participants performed 3 consecutive repetitions of TUG and T25FW with 1 min rest between trials. The average of the two best trials of each test was used for statistical analyses.

3.3.3. CoP Data Reduction of Postural Control Tests

For the tandem stance and unstable sitting balance tests, the CoP signal was low-pass filtered (4th-order, zero-phase-lag, Butterworth, 5 Hz cut-off frequency)[128] and subsampled at 20 Hz.[129] The first 10 s of each 70 s trial were discarded to avoid non-stationarity related to the beginning of the trial.[100] In order to quantify postural control performance while standing and sitting, the mean radial error (MRE) was calculated as the average of the CoP vector distance magnitude (mm) from the target point[130]: TW_{MRE}, MRE in the tandem position performed with the weaker leg behind; TS_{MRE}, MRE in the tandem position performed with the stronger leg behind; and US_{MRE}, MRE in the *Unstable Sitting Test*. For both protocols, the average of the two best trials was used for subsequent statistical analyses.

3.3.4. Statistical analysis

Descriptive statistics (mean and standard deviation) were calculated for all variables and groups in both sessions. The normality of the data was examined using a Kolmogorov-Smirnov statistical test. To analyse the inter-session absolute reliability of each test, the typical error (TE) was calculated[131] as the standard deviation of the difference between trial 1 and 2 divided by √2.[132] This TE method was selected to avoid the influence of sample heterogeneity and to reduce the effect of systematic error (e.g. learning effect).[133] TE values were expressed as a percentage of the mean score, which facilitates the extrapolation of the results to other individuals and the reliability comparisons with other protocols.[133] Although TE is task-dependent,[131] TE values lower than 20% were considered acceptable for posturographic parameters.[134] The relative reliability of the different measures was analysed using the $ICC_{3,1}$, calculating 90% confidence limits (90% CL). The ICC values were categorized as follows: excellent (0.90 to 1.00), high (0.70 to 0.89), moderate (0.50 to 0.69) and low (< 0.50).[135] Reliability analyses were carried out using a spreadsheet designed by Hopkins.[136]

One-way repeated-measures ANOVAs were performed to assess repetition effect, being *session* the within-subject factor (2 levels: session 1, session 2). Moreover, one-way independent-measures ANOVAs were performed to assess between-group differences, being *group* the between-subject factor (2 levels: EDSS ≤ 2, 2.5 ≤ EDSS ≤ 4). To estimate the effect size of within and between-group differences, Hedges' *g* index (d_g) was used.[137] This index is based on Cohen's *d* index, but it provides an effect size estimation reducing the bias caused by small samples (n < 20). Effect sizes were interpreted as trivial ($d_g < 0.2$), small ($0.2 < d_g < 0.5$), moderate ($0.5 < d_g < 0.8$) and large ($d_g > 0.8$). Finally, the Pearson correlation coefficient (*r*) was used to analyse the relationship among measurements. To reduce the potential influence of learning effect in the results, ANOVA and correlational analyses were performed using the participants' scores obtained in the second session. ANOVA and correlational analyses were performed with the Statistical Package for Social Sciences (version 22.0, SPSS Inc., Chicago, IL, USA), establishing significance at $p < 0.05$.

3.4. Results

As Table 3 shows, all the parameters assessed in this study showed high to excellent ICC scores (always above 0.80) and good TE values (postural control tests: TE ≤ 15.33%; functional tests: TE ≤ 6.56%) in both minimally and moderately impaired pwMS. Nevertheless, it should be noted that moderately impaired pwMS presented worse TE values for tandem stance balance test and TUG scores (TW_{MRE}: 12.84%; TS_{MRE}: 15.33%; TUG: 6.56%) than minimally impaired pwMS (TW_{MRE}: 11.76%; TS_{MRE}: 9.32%; TUG: 3.43%). Regarding ANOVA results, only TW_{MRE} and US_{MRE} showed a significant decrease (i.e. higher postural control) from session 1 to session 2 in both MS groups.

Concerning the between-group comparison (Table 4), minimally impaired MS group showed better performance in TUG, T25FW and TW_{MRE} than moderately impaired MS group ($p < 0.05$). Nevertheless, no statistical differences were found for TS_{MRE} and US_{MRE} variables.

Table 3. Reliability scores for the different parameters obtained from the posturographic and functional tests in minimally (EDSS ≤ 2) and moderately (2.5 ≤ EDSS ≤ 4) impaired individuals with multiple sclerosis (MS).

		Session 1		Session 2						TE (%)	$ICC_{(3,1)}$
Task	**n**	**Mean**	**(SD)**	**Mean**	**(SD)**	***F***	***p***	d_g	**TE (units)**	**(mean - 90% CL)**	**(mean - 90% CL)**
Minimally impaired MS individuals											
TW_{MRE}	14	10.80	(3.51)	9.20	(2.98)	11.15	0.005	0.43	1.27	11.76 (8.97 – 17.47)	0.87 (0.70 – 0.95)
TS_{MRE}	14	9.25	(2.36)	9.18	(2.66)	0.05	0.826	0.03	0.86	9.32 (7.10 – 13.84)	0.90 (0.76 – 0.96)
US_{MRE}	14	11.46	(4.00)	9.66	(4.00)	14.33	0.002	0.42	1.26	10.98 (8.37 – 16.31)	0.92 (0.80 – 0.97)
TUG	14	5.29	(0.63)	5.25	(0.68)	0.28	0.608	0.06	0.18	3.43 (2.62 – 5.10)	0.94 (0.84 – 0.97)
T25FW	14	2.83	(0.41)	2.82	(0.42)	0.01	0.830	0.02	0.15	5.17 (3.94 – 7.68)	0.89 (0.74 – 0.96)
Moderately impaired MS individuals											
TW_{MRE}	16	13.97	(3.57)	12.57	(4.50)	4.84	0.044	0.37	1.79	12.84 (9.94 – 18.45)	0.83 (0.63 – 0.92)
TS_{MRE}	16	13.10	(3.09)	11.67	(5.08)	4.06	0.062	0.44	2.01	15.33 (11.88 – 22.03)	0.80 (0.57 – 0.91)
US_{MRE}	16	13.48	(5.02)	11.13	(4.00)	22.90	0.000	0.44	1.39	10.33 (8.00 – 14.85)	0.92 (0.81 – 0.97)
TUG	16	5.90	(0.95)	6.11	(0.94)	2.36	0.145	-0.21	0.39	6.56 (5.08 – 9.42)	0.85 (0.68 – 0.94)
T25FW	16	3.37	(0.66)	3.42	(0.70)	0.52	0.483	-0.07	0.19	5.57 (4.31 – 8.00)	0.93 (0.85 – 0.97)

Repeated measures ANOVA. TE: Typical error; ICC: Intraclass correlation coefficient; CL: confidence limits; EDSS: Expanded Disability Status Scale; TW_{MRE}: Tandem stance balance test with the weaker leg behind (mm); TS_{MRE}: Tandem stance balance test with the stronger leg behind (mm); US_{MRE}: Unstable sitting balance test (mm); TUG: *Timed Up and Go Test* (s); T25FW: *Timed 25 foot-Walk* (s).

Table 4. Comparison of postural control parameters and functional scores between minimally (EDSS ≤ 2) and moderately (2.5 ≤ EDSS ≤ 4) impaired multiple sclerosis individuals.

Test	Minimally Impaired			Moderately Impaired			*F*	*p*	d_g
	n	mean	(SD)	n	mean	(SD)			
TW_{MRE}	14	9.20	(2.98)	16	12.57	(4.50)	5.66	0.024	-0.85
TS_{MRE}	14	9.18	(2.66)	16	11.67	(5.08)	2.70	0.111	-0.59
US_{MRE}	14	9.66	(4.00)	16	11.13	(4.00)	1.00	0.326	-0.36
TUG	14	5.25	(0.68)	16	6.11	(0.94)	7.97	0.009	-1,00
T25FW	14	2.82	(0.42)	16	3.42	(0.70)	7.99	0.009	-0,99

EDSS: Expanded Disability Status Scale; TW_{MRE}: Tandem postural control test with the weaker leg behind (mm); TS_{MRE}: Tandem postural control test with the stronger leg behind (mm); US_{MRE}: Unstable sitting balance test (mm); TUG: *Timed Up and Go Test* (s); T25FW: *Timed 25-foot Walk Test* (s).

As shown in Table 5, with the exception of US_{MRE}, all parameters significantly correlated with EDSS scores; mainly the TUG scores, which showed the highest correlation ($r = 0.691$; $p < 0.001$). Standing and sitting postural control parameters showed significant correlations with TUG scores ($0.419 \leq r \leq 0.604$; $p < 0.05$), nonetheless, only TW_{MRE} correlated with T25FW scores ($r = 0.534$; $p < 0.001$). Although, US_{MRE} correlated with both tandem stance parameters, the correlation was higher for TW_{MRE} ($r = 0.540$; $p < 0.001$) than for TS_{MRE} ($r = 0.433$; $p < 0.05$).

Table 5. Pearson correlations between EDSS scores, postural control parameters and functional scores in individuals with multiple sclerosis.

	EDSS	TW_{MRE}	TS_{MRE}	US_{MRE}	TUG	T25FW
EDSS		.574**	.527**	.354	.691**	.606**
TW_{MRE}			.862**	.540**	.604**	.534**
TS_{MRE}				.433*	.511**	.361
US_{MRE}					.419*	.240
TUG						.849**
T25FW						

* Significant Pearson correlation at $p < 0.05$, ** Significant Pearson correlation at $p < 0.01$. TW_{MRE}: Tandem postural control test with the weaker leg behind; TS_{MRE}: Tandem postural control test with the stronger leg behind; US_{MRE}: Unstable sitting balance test; TUG: *Timed Up and Go Test*; T25FW: *Timed 25-foot Walk Test*.

3.5. Discussion

The absolute and relative reliability of the tandem stance and the unstable sitting balance tests were analysed with the intention to provide clinicians and researchers with useful posturographic protocols to detect clinically relevant changes in postural control caused by the MS progression, as well as to classify minimally and moderately impaired pwMS based on their postural control impairment. In addition, a correlation analysis was performed to assess the potential influence of postural control parameters on functional mobility (TUG) and walking performance (T25FW) in this population.

Tandem stance and unstable sitting tests showed high-to-excellent relative reliability in both groups, minimally (0.87 ≤ ICC ≤ 0.92) and moderately (0.80 ≤ ICC ≤ 0.92) impaired pwMS. These results support previous findings which showed a high relative reliability of posturographic tests performed in standing[87-89] and in sitting positions.[119] Nevertheless, this study confirmed that posturography is a consistent tool to classify MS individuals according to their postural control, even in homogeneous MS samples (i.e. pwMS with similar EDSS scores).

Regarding absolute reliability, TE values obtained in tandem stance and unstable sitting tests (≤ 15.33%) were lower than the reference value of 20%.[134] Consequently, TW_{MRE}, TS_{MRE} and US_{MRE} could be considered reliable parameters to identify subtle changes in postural control produced by the disease progression (variations higher than 1 and 2 mm in minimally and moderately impaired pwMS, respectively; see Table 3). Although future studies should confirm this hypothesis, posturographic protocols may play an important role in quantifying postural control deterioration and in verifying treatment effectiveness, especially in minimally impaired pwMS who showed lower session-to-session variability in the tandem stance balance test (TW_{MRE}: 11.76%; TS_{MRE}: 9.32%) than in moderately impaired pwMS (TW_{MRE}: 12.84%; TS_{MRE}: 15.33%). These differences between MS groups confirm that patients' postural control varies in higher extent between days with disease progression.[20, 138] Also, based on ANOVA results (Table 3), only TW_{MRE} and US_{MRE} reduced significantly between sessions, suggesting those parameters are largely susceptible of improving due to learning. Thus, a longer familiarization period seems necessary to diminish the learning effect of these posturographic tests.

Regarding between group differences, ANOVAs revealed that only TW_{MRE}, TUG and T25FW were able to discriminate between minimally and moderately impaired pwMS (Table 4). These results suggest they are more sensitive or relevant parameters than US_{MRE} and TS_{MRE} for classifying the degree of disability in pwMS using EDSS. These findings were confirmed by the correlational analysis, where TUG, T25FW and TW_{MRE} reached the highest correlations with EDSS scores (Table 5). Considering these and previous results,[20, 139] impairment of the standing balance on the weaker leg, of the functional mobility and of the walking speed seem to be the very relevant symptoms to determine the activity limitation caused by MS disease progression. In the same way, the correlations found between TW_{MRE} and both clinical tests support previous findings on lower limb strength, which highlighted that the degree of impairment of the weaker leg seems to be more relevant for walking and functional mobility than the impairment of the stronger leg.[126, 140, 141] However, this is a cross-sectional survey, and longitudinal studies should assess the extent in which all the analysed parameters are affected by the MS disease progression.

The reliability scores obtained by the posturographic and functional tests in this study allow the analysis of the influence of trunk postural control on functional mobility and gait performance. Based on the correlational analysis, trunk postural control positively correlated with functional mobility (US_{MRE} – TUG: $r = 0.419$, $p < 0.05$), but it did not correlate with gait speed (US_{MRE} – T25FW: $r = 0.240$, $p > 0.05$). The correlational analysis also shows a significant relationship between US_{MRE} and both tandem conditions (US_{MRE} – TW_{MRE}: $r = 0.540$, $p < 0.001$; US_{MRE} – TS_{MRE}: $r = 0.433$, $p < 0.05$). These data could support the influence of trunk stability on standing postural control, in concordance with Freeman and colleagues,[96] who analysed the influence of trunk muscles in standing balance in pwMS, obtaining improvements both in balance and mobility after an 8-week trunk stability training. Under the authors' point of view, the lack of correlation between trunk control and T25FW could be related to the low balance demands of walking (in a straight line) for our MS sample (EDSS ≤ 4). Nevertheless, the task balance demands were higher during the TUG (i.e. standing with a small base of support, rising, turning, etc.) and consequently, trunk control could play a more important role in the performance of this test.[142] These results support Freeman et al.'s pilot study,[96] which analysed the effects of a trunk stability training program on functional mobility and gait performance in pwMS. However, they do not fully agree with the results obtained by Fox et al.,[112] who did not observe positive effects of a trunk stability exercise program neither on gait speed nor on functional mobility. Although further research is needed to explore the effects of increasing trunk postural control on pwMS's functional capabilities, trunk stability exercise programs may be useful to improve pwMS's balance and performance during the most demanding daily life activities, in which pwMS have the highest risk of falling.

Finally, it must be pointed out that this study has some limitations that must be considered to apply its results to clinical settings. For example, the dynamic tasks performed in tandem and in sitting position on the unstable seat seem too difficult to be able to evaluate the stability of patients with EDSS > 6. Therefore, it may be necessary to assess postural control using easier posturographic tests for those individuals with severe forms of MS, for example, assessing stability in upright stance with both feet together instead of in tandem position, or changing the circular task of the unstable sitting balance test for one in which subjects simply have to maintain the initial position during the test.

3.6. Conclusions

The reliability data showed that the posturographic tests performed in tandem stance and sitting positions are reliable protocols to measure postural control in pwMS with a homogeneous disease profile, even in minimally impaired individuals (i.e. EDSS ≤ 2). Therefore, these tests could be used to take individual decisions in these patients. In addition, both test scores showed significant correlations, which seem to indicate that an increase of trunk stability could improve standing balance in pwMS.

Based on the comparison between minimally and moderately impaired groups, the impairment of functional mobility, gait performance and weaker leg condition are relevant symptoms to evaluate the activity limitation caused by the disease progression. Trunk stability, although it doesn´t seem so affected by the course of the disease, remains relevant for postural control and functional capacity.

CHAPTER 4

STUDY 2
Effects of a Maximal Strength Training on Perceived Fatigue in Persons with Multiple Sclerosis

4. STUDY 2: EFFECTS OF A MAXIMAL STRENGTH TRAINING ON PERCEIVED FATIGUE AND FUNCTIONAL MOBILITY IN PERSONS WITH MULTIPLE SCLEROSIS.

EFFECTS OF A MAXIMAL STRENGTH TRAINING ON PERCEIVED FATIGUE AND FUNCTIONAL MOBILITY IN PERSONS WITH MULTIPLE SCLEROSIS.

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4.1. Abstract

Background: Fatigue is one of the symptoms which most limits daily life activities in persons with Multiple Sclerosis (pwMS).

Objective: To evaluate the effects of a maximal strength training (MST) on perceived fatigue and functional mobility in pwMS.

Methods: 26 participants with MS were balanced according to their fatigue scores before the study, and distributed into a MST group (n = 13) and a control group (CG; n = 13). The MST group completed 4 weeks of resistance/conditioning training and 8 weeks using high loads, evaluating detraining after 10 weeks. Quadriceps and hamstring isokinetic (QPT_{IK}; HPT_{IK}) and isometric (QPT_{IM}; HPT_{IM}) peak torque were assessed using an isokinetic dynamometer. Fatigue was evaluated through the *Fatigue Severity Scale* (FSS) and the *Modified Fatigue Impact Scale* (MFIS), while functional mobility was assessed via the *Timed Up and Go Test* (TUG).

Results: The MST significantly improved the QPT_{IK} (+16.22%) and the QPT_{IM} (+16.90%), as well as the HPT_{IK} (+29.55%) and the HPT_{IM} (+7.02%). Fatigue

diminished in FSS (-39.53%) and MFIS (-58.68%). Participants of MST group reduced the TUG time (-19.83%). Improvements in strength correlated with the reduction of the perceived fatigue ($0.50 \leq r \leq 0.62$). Intervention improvements significantly remained after a 10-week follow up.

Conclusion: Strength training using high loads (up to 90% 1RM) seems to be a feasible and useful way to obtain clinically relevant improvements of the perceived fatigue symptoms, even after a 10-week detraining period. This study also shows that MST improves functional mobility in pwMS.

Key words: maximal strength training, perceived fatigue, functional mobility, multiple sclerosis

4.2. Introduction

Fatigue is one of the most important and frequent symptoms which affect the quality of life (QoL) of people with multiple sclerosis (pwMS).[26] At least 3 in every 4 pwMS indicate experiencing symptoms of fatigue at least once per week.[27] Furthermore, increase in fatigue is usually accompanied by other symptoms such as depression, pain, anxiety or cognitive dysfunction.[27]

Although the exact causes of fatigue in MS has not been clearly determined, there are some links with the neurodegeneration process of the pathology (central fatigue) and/or with physical inactivity.[9] Several researchers have confirmed that physical training programs can be safe[44] and effective tools[39, 104] to reduce fatigue and other symptoms (balance impairments, strength deficits, etc.) in pwMS.[45, 143] Among the different physical activity therapies, resistance training has been shown as one of the most successful therapies to reduce the MS disease symptoms.[45, 48, 126] Resistance training produces improvements in neural drive[144] as well as in the efferent motor output of spinal motor neurons in pwMS,[107] which, in turn, enhance balance[145] and functional mobility[75], related factors to the QoL of this population.[113] Unlike endurance exercises, resistance training seems to be better tolerated by this population (especially the most sedentary individuals), as their body temperature does not increase so much, which is very relevant for pwMS, as this increase is related to loss of physical performance and low states of mood.[146]

It has been indicated that resistance training may reduce perceived fatigue in pwMS by enhancing functional mobility, which would make the activities of the daily living less fatiguing.[113] Despite this statement, the resistance-training effect on fatigue symptom does not seem so clear. On the one hand, a recent Cochrane meta-analysis[104] assessing randomized controlled trials (RCTs) did not find a significant effect of resistance training programs on fatigue. On the other hand, although a meta-analysis[39] found evidence that general exercise programs, including resistance exercises, may be a positive way to reduce perceived fatigue, the effect sizes displayed in the majority of studies were low or even trivial (0.10 < ES < 0.65).

The evidence of resistance training benefits upon fatigue may be limited because the majority of the studies have conducted progressive programs up to sub-maximum loads (<80% of 1RM).[48] Among the types of resistance training, it is known that maximal strength training (MST), which uses loads higher than 80% 1RM, requires the complete use of the neuromuscular system, enhancing the recruitment of muscle fibers and neural drive in a higher extent than other resistance training.[110] Based on this feature, as it was confirmed by Fimland et al.,[107] MST seems to be the best resistance training regime to cope with the decreased central neural drive associated with MS, which, in turn, could alleviate some of the disease symptoms. Accordingly, high-intensity resistance training (80% of 1RM) on this population has also been shown as a useful methodology to reduce peripheral pro-inflammatory cytokine levels,[108] which seems related to fatigue symptoms during the disease.[109] Based on these preliminary findings, high loads seem to be a key component of resistance training to reduce fatigue in pwMS. However, a recent pilot study applying high loads (85–95% of 1RM) did not find a significant reduction of perceived fatigue after the intervention, questioning the effectiveness of MST to reduce fatigue.[108, 111]

In order to clarify the current controversy, the aim of this study was to analyse the effect of a MST program on perceived fatigue in pwMS. Additionally, due to the fact that functional mobility improvements are considered an important factor to reduce fatigue caused by daily life physical activities,[75, 113] the potential benefits of the MST on this parameter were also explored. We hypothesized: 1) the MST program, owing to the neural improvements that this type of resistance training implies, will reduce perceived fatigue in pwMS compared to a control group;[108] 2) the MST program will improve functional mobility compared to a control group;[113] and 3) greater strength improvements after MST will correlate with greater fatigue reductions in the participants of the MST program.[107, 113]

4.3. Material and Methods

4.3.1. Participants

Twenty-six participants, 6 men and 20 women (43.73 ± 10.12 years old; EDSS = 2.58 ± 1.19), were selected from patients of the Neurology Department of a Spanish Public Hospital, participating voluntarily in the study if they complied with the following inclusion criteria: 1) to be a patient with relapsing remitting MS diagnosed by a neurologist; 2) to have symptoms of severe perceived fatigue [>36 points on the *Fatigue Severity Scale* (FSS)]; and 3) to possess <6.5 points on the EDSS. The present study was approved by the Hospital's Ethics Committee. All the participants signed a written consent to participate in this study. Patients were randomly and balanced assigned to two groups: an intervention group which performed the MST program; and a control group (CG), that did not perform any specific training (Table 6).

Table 6. Participant characteristics.

	MST group	Control group
Women/Men	9/4	12/1
Age (years)	45.31 (11.06)	41.31 (9.58)
Body mass (kg)	66.02 (15.21)	58.82 (11.31)
EDSS (unitless)	2.38 (0.98)	2.81 (1.33)
FSS (unitless)	56.23 (6.57)	52.08 (7.35)
TUG (s)	7.06 (1.40)	7.35 (2.10)

MST: Maximum strength training; EDSS: Expanded Disability Status Scale; FSS: *Fatigue Severity Scale*; TUG: *Timed Up and Go Test*. Data are presented as mean (standard deviation).

4.3.2. Experimental Procedures

Isokinetic and Isometric Strength Measurements

An isokinetic dynamometer (Biodex System 4 PRO, Biodex Medical Systems, Shirley, NY) was used to evaluate lower limb isokinetic and isometric strength, both knee extensors (i.e. quadriceps) and flexors (i.e. hamstrings). The dynamometer seat was adjusted to each participant, strapping chest, waist and the involved leg, in order to isolate the joint action and impeding the movement of the rest of the body during testing. The dynamometer torque was positioned 2 cm from the axis of the knee and the leg of the involved joint was held together by the torque, using the articulated arm provided by the manufacturer. The participant's arms remained crossed over the chest throughout the test, and the data regarding the adjustments were recorded for the following test sessions of measurement. Before each test, participants underwent a 5-min warm up on a stationary bicycle.

For the isokinetic evaluation, starting from an anatomical position of the knee bent at 90°, the subjects carried out two sets of 5 repetitions of knee extension and flexion at a speed of 60°/s in a range of movement of 80° (from 90° to 170°), with rests of 3 min between sets. The Isokinetic Peak Torque (PT_{IK}) was taken to be the maximum value in Newton x meter (N*m) reached, both in extension and in flexion in any of the two sets (Figures 8A and 8B).

For the isometric protocol, starting from an anatomical reference position with the knee bent at 90°, the arm supplied by the manufacturer was fixed at 70°. The subjects carried out three sets of voluntary maximum contractions of the quadriceps (attempt of extension) for 5 s, followed by another three sets of the hamstrings (attempt of flexion) for 5 s, with 15 s rest between contractions. The rest period between sets was 60 s. The Isometric Peak Torque (PT_{IM}) was taken to be the maximum value in Newton x meter (N*m) reached, both in extension and in flexion in either of the three sets (Figure 8C).

Figure 8. Isokinetic protocol, with start (maximal flexion: 90°) (A) and final (maximal extension: 10°) (B) positions; Isometric protocol (70° position) (C).

Perceived Fatigue

Two questionnaires were used to evaluate perceived fatigue, investigating its impact on functional performance and daily activities of pwMS. The *Modified Fatigue Impact Scale*[147] (MFIS) measures perceived fatigue in pwMS in monthly periods, asking about 21 daily-life situations in which the participant answers if he/she *never, rarely, sometimes, often or almost never* perceived fatigue*;* providing a total value (overall score) and three dimensions: physical, cognitive, and psychosocial. The *FSS*[148] measures perceived fatigue in weekly periods, asking about 9 situations in which the participant responds on a 1-to-7 Likert scale (where 1 means *strongly disagree* and 7 means *strongly agree*). Both scales have shown good reliability, with Cronbach's alpha of 0.88 and 0.81, respectively. Greater FSS and MFIS scores mean a greater perceived fatigue.

Evaluation of Functional Mobility

The *Timed Up and Go Test* (TUG) was used to evaluate the functional mobility of the participants.[123] TUG has good inter-rater and intra-rater reliability (ICC = 0.99) in pwMS[149], and it has been presented in the previous chapter. Participants performed three repetitions with 1 min rest between trials, and the average of the two best trials was used for analysis.

Intervention

Assessments were carried out at the Sport Research Center of the Miguel Hernandez University of Elche. Labs were conditioned at 23°C and participants were required not to exercise 48 h prior to the evaluation days. Participants carried out three testing sessions: pre-test, post-test (12-weeks after pre-test), and follow-up test (10 weeks after the intervention finished to evaluate detraining). In those three temporal moments, participants performed, in this order, the isokinetic and isometric strength tests, the perception scales of fatigue (FSS and MFIS), and the TUG. The time required to complete perceived fatigue tests was used as rest period between strength and functional tests.

Participants were randomized and balanced according to their FSS scores prior to the intervention, and they were distributed into two groups of 13 participants: MST and CG. The MST group followed a 12-week training program based on 3 weekly sessions. Weeks 1 to 4 served as prior preparation (conditioning period) to the MST program, carried out throughout weeks 7 to 12 (Table 7). During this intervention, none of the participants undertook any physical activity other than the programmed for this study. Two days before the beginning of the intervention, and after week 4, a Repetition Maximum (RM) test was carried out employing the Brzycki protocol,[150] personalizing the load of the exercises included in training, expressed as a percentage of that RM.

The structure of the sessions began with 5 min of cardiovascular exercises (treadmill, static bicycle or walking) followed by the prescribed exercises for that day. Stretching was carried out on the worked muscle groups after each exercise and just at the end of each session as a cooldown. Sets, repetitions, rest intervals and %1RM are described in Table 7.

Table 7. Weekly Training.

	Weeks	%1RM	Sets	Repetitions	Rest Interval (Min)
Conditioning Period	**1-2**	50	2	8-10	3
	3-4	60	2	12-14	3
Training Period	**5-6**	75	3	7	5
	7-8	80	4	6	5
	9-10	85	4	4	5
	11-12	90	5	4	5

1RM = 1 repetition maximum.

During weeks 1 to 4, all the participants carried out the same exercises each day (Table 8). During weeks 5 to 12, participants were divided into 3 groups, and each group carried out one of the three weekly workouts each day (Table 8). No adverse events occurred during the training period and data collection.

Table 8. Training schedule and exercises.

Week	Day	Exercise
1 – 4	Monday Tuesday Thursday	Dumbbell Shoulder Press Cable Standing Biceps Curl Cable Triceps Pushdown Chest Press Machine Wide-Grip Lat Pulldown Leg Extension Leg Curl Multipower Standing Calf Raises
5 – 12	1ST	Chest Press Machine Barbell Incline Bench Press Leg Curl Leg Extension Multipower Standing Calf Raises
	2nd	Alternate Hammer Curl Cable Triceps Pushdown Front Dumbell Raise Saide Lateral Raise
	3rd	Wide-Grip Lat Pulldown Seated Cable Rows Leg Press Thigh Adductor Half Stance Multipower Squat

1st: First training day of the week. 2nd: Second training day of the week. 3rd: Third training day of the week.

4.3.3. Statistical Analysis

To simplify the analysis of strength variables (PT_{IK} and PT_{IM}), results from the left and right legs were averaged and normalized by the body weight [(right leg + left leg) / body mass].[64] Percentages of improvement (%) of each variable were also calculated as follows: intervention improvement (pre- to post-test) and detraining (re-test to follow-up test).

Descriptive statistics (mean and standard deviation) were used to present data. All the variables showed a normal distribution according to the Kolmogorov-Smirnov test with a Lilliefors correction. ANOVAs for repeated measures were performed for all variables to test differences between groups, being *intervention* the between-group factor (2 levels: MST, CG) and *moment of evaluation* the within-group factor (3 levels: pre-test, post-test and follow-up test). Hedges' *g* effect size index (d_g)[137] was calculated to assess the practical signification of within and between-group differences. This index is based on *Cohen's d* index[151] but it provides an effect size estimation reducing the bias caused by small samples (n < 20), interpreted as follows: large ($d_g > 0.8$), moderate ($0.5 < d_g < 0.8$), small ($0.2 < d_g < 0.5$) and trivial ($d_g < 0.2$). Pearson correlation moment (r) was used to assess the relationship between the possible improvement in strength parameters caused by the intervention, reduction of perceived fatigue and TUG time. For all variables, improvements (post-pre differences) were calculated for the correlational analysis. Correlations were interpreted according to the following values[152]: low ($r \leq 0.3$), moderate ($0.3 < r \leq 0.7$) and high ($r > 0.7$). The statistical analysis was conducted with the Statistical Package for Social Sciences (version 22.0, SPSS Inc., Chicago, IL, USA), with a significance level chosen at $p < 0.05$.

4.4. Results

4.4.1. Strength

After finalizing the intervention, the MST group significantly improved their knee extension and flexion strength in isokinetic and isometric exertions compared to the CG (Table 9). In the follow-up test, strength benefits were still observed in knee extensors and flexors isokinetic values (QPT_{IK} and HPT_{IK}) compared with the values obtained before MST. However, isometric knee strength of both, extensor (QPT_{IM}) and flexor (HPT_{IM}) muscles, decreased practically to those values displayed in the pre-test ($p > 0.05$) (Table 9).

4.4.2. Fatigue

The MST group significantly reduced perceived fatigue ($p < 0.01$, ES = large) in both the FSS and the MFIS (overall, physical, cognitive and psychosocial scores) (Table 10). In the follow up test, all fatigue scores showed by the MST group were significantly lower compared to the pre-test.

4.4.3. Timed Up and Go Test.

After the intervention, the MST group significantly reduced the TUG time (p = 0.002; ES = large). In the follow up, a significant reduction (p = 0.005) was also observed in TUG time with respect to the pre-test values, but the ES was small (Table 10).

Table 9. Strength parameters of the knee extensor and flexor muscles obtained from the isokinetic dynamometer in 60°/s isokinetic and isometric conditions at pre-test, post-test and follow-up test for the maximal strength training (MST) and control group (CG).

		Pre-test (1)		Post-test (2)		Follow up (3)		*Dif_{1-2} (%)*	*d_{1-2}*	*Dif_{1-3} (%)*	*d_{1-3}*
QPT_{IK}	**MST**	2.96	(0.71)	3.44	(0.85)	3.11	(0.81)	16.22**	1.07	5.07*	0.61
	CG	3.09	(1.06)	2.60	(1.23)	2.61	(1.24)	-15.86		-15.53	
HPT_{IK}	**MST**	1.31	(0.36)	1.70	(0.32)	1.62	(0.45)	29.55**	1.00	22.73*	0.83
	CG	1.57	(0.56)	1.59	(0.62)	1.55	(0.53)	1.27		-1.27	
QPT_{IM}	**MST**	4.25	(1.01)	4.97	(1.16)	4.28	(1.20)	16.90**	0.86	0.70	0.25
	CG	4.08	(1.68)	3.76	(1.45)	3.70	(1.59)	-7.84		-9.31	
HPT_{IM}	**MST**	1.71	(0.36)	1.83	(0.31)	1.75	(0.26)	7.02*	0.45	2.34	0.19
	CG	1.91	(0.80)	1.79	(0.88)	1.84	(0.80)	-6.28		-3.6	

Data are presented as mean (standard deviation). * $p < 0.05$, ** $p < 0.01$.

QPT_{IK} (Nm/kg): Quadriceps Isokinetic Peak Torque normalized by the body mass; HPT_{IK} (Nm/kg): Hamstring Isokinetic Peak Torque normalized by the body mass; QPT_{IM} (Nm/kg): Quadriceps Isometric Peak Torque normalized by the body mass; HPT_{IM} (Nm/kg): Hamstring Isometric Peak Torque normalized by the body mass; Dif. (%): percentage of difference; *d:* standardized mean differences between groups calculated with Hedge's correction.

Table 10. Results of perceived fatigue and functional mobility at pre-test, post-test and follow-up test for the maximal strength training (MST) and control group (CG).

		Pre-test (1)		Post-test (2)		Follow-up (3)		*Dif₁₋₂ (%)*	*d₁₋₂*	*Dif₁₋₃ (%)*	*d₁₋₃*
$MFIS_{Ov}$	**MST**	66.46	(15.33)	27.46	(16.30)	37.85	(15.95)	-58.68**	2.56	-43.12**	1.03
	CG	47.08	(18.09)	48.90	(16.50)	45.46	(19.21)	3.87		-3.44	
$MFIS_{Ph}$	**MST**	32.69	(10.21)	12.15	(7.22)	18.39	(7.31)	-62,83**	1.93	-43.74**	1.07
	CG	25.23	(7.63)	25.08	(6.32)	23.00	(8.38)	-0.59		-8.84	
$MFIS_{Cg}$	**MST**	27.31	(10.24)	13.00	(9.02)	15.62	(9.26)	-52.40**	2.17	-42.88**	1.31
	CG	17.15	(11.01)	26.46	(6.05)	19.46	(11.11)	54.29		13.47	
$MFIS_{Ps}$	**MST**	6.46	(1.76)	2.31	(1.49)	3.85	(1.68)	-64.24**	2.21	-40.40**	1.47
	CG	4.69	(2.18)	4.54	(1.85)	4.77	(2.31)	-3.20		1.71	
FSS	**MST**	56.23	(6.57)	34.00	(16.16)	48.77	(8.41)	-39.53**	2.92	-13.27**	0.47
	CG	52.08	(7.35)	49.39	(8.80)	47.31	(11.04)	-5.17		-9.16	
TUG	**MST**	7.06	(1.40)	5.66	(0.83)	6.63	(1.12)	-19.83*	0.87	-6.09*	0.29
	CG	7.35	(2.15)	7.15	(1.99)	7.34	(2.10)	-2.72		-0.14	

Data are presented as mean (standard deviation). * $p < 0.05$, ** $p < 0.01$.
$MFIS_{Ov}$: Overall score of the Modified Fatigue Impact Scale; $MFIS_{Ph}$: Physical score of the Modified Fatigue Impact Scale; $MFIS_{Cg}$: Cognitive score of the Modified Fatigue Impact Scale; $MFIS_{Ps}$: Psychosocial score of the Modified Fatigue Impact Scale; FSS: *Fatigue Severity Scale*; TUG: *Timed Up and Go Test*; Dif. (%): percentage of difference; *d*: standardized mean differences between groups calculated with Hedge's correction.

As shown in Table 11 the improvement in strength parameters correlated significantly with the reduction in perceived fatigue. The TUG changes also correlated significantly with the PT_{IM} values of the knee extensors.

Table 11. Correlations among the improvements (%) observed in strength, perceived fatigue and functional parameters displayed by the participants of the maximal strength training group.

	$IQPT_{IK}$	**$IHPT_{IK}$**	**$IQPT_{IM}$**	**$IHPT_{IM}$**	**IFSS**	**$IMFIS_{OV}$**	**$IMFIS_{Ph}$**	**$IMFIS_{Cg}$**	**$IMFIS_{Ps}$**	**ITUG**
$IQPT_{IK}$		.60**	.77**	.69**	-.50*	-.62**	-.60**	-.55*	-.60**	-.33
$IHPT_{IK}$			.35	.61**	-.51*	-.55*	-.46*	-.35	-.43	-.39
$IQPT_{IM}$				.59**	-.32	-.45	-.49*	-.35	-.43	-.60**
$IHPT_{IM}$					-.31	-.33	-.31	-.32	-.28	-.32
IFSS						-.72**	-.58**	-.79**	-.59**	.05
$IMFIS_{OV}$							.95**	.94**	.86**	.33
$IMFIS_{Ph}$								.81**	.83**	.36
$IMFIS_{Cg}$									.75*	.24
$IMFIS_{Ps}$										.44
ITUG										

IQPTIK.: Improvement of Quadriceps isokinetic Peak Torque; $IHPT_{IK}$: Improvement of Harmstring Isokinetic Peak Torque; $IQPT_{IM}$: Improvement of Quadriceps Isometric Peak Torque; $IHPT_{IM}$: Improvement of Hamstring Isometric Peak Torque; IFSS. *Fatigue Severity Scale Improvement*; $MFIS_{Ov}$: Overall *Modified Fatigue Impact Scale* Improvement; $IMFIS_{Ph}$: Physical *Modified Fatigue Impact Scale* Improvement; $IMFIS_{Cg}$: Cognitive *Modified Fatigue Impact Scale* Improvement; $IMFIS_{Ps}$: Psychosocial *Modified Fatigue Impact Scale* Improvement; ITUG: *Timed Up And Go Test* Improvement (ITUG); $*p < 0.05$; $**p < 0.01$.

4.5. Discussion

Perceived fatigue is one of the most limiting symptoms in pwMS and currently there is no treatment which is able to reduce it in a significant way.[39] The aim of this study was to evaluate the effects of a resistance-training program, increasing working loads progressively until 90% of RM scores, on perceived fatigue and functional mobility. Our results confirmed the study hypotheses, demonstrating that a resistance-training program up to maximal loads, ending in an MST zone to maximize strength gains, caused a reduction of perceived fatigue and an enhancement of functional mobility in pwMS. Additionally, it was also confirmed that the magnitude of perceived fatigue reduction was highly related to the strength gains.

The most important finding of the present study supports the utility of MST to reduce perceived fatigue,[108] showing a great reduction of the FSS and MFIS scores in the MST group (39.53 to 64.24%) compared to CG, with very large ES ($1.92 < d_g < 2.93$). These results confirmed Kirkergard and colleagues' findings,[108] who found a similar perceived fatigue improvement (64%) after an 80% RM training, although their intervention lacked a CG, hindering the results generalization. As the afforementioned authors[108] observed, fatigue reduction could be related to the peripheral inflammatory response to the MST program in pwMS. In that study, high-intensity resistance training reduced pro-inflammatory cytokine levels which could lead to an improvement of fatigue symptoms.[109] However, it must be noted that the fatigue improvements found in our study were notably greater than those observed in other resistance intervention programs, which oscillated between low-to-moderate ES (0.10 - 0.65).[39] The high fatigue reduction could also be associated with an increase in neural drive,[107] as well as with the great improvements in lower limb strength enhancement after the MST, which is fundamental to reduce the effort needed to perform numerous daily life activities (i.e. going up stairs, walking, etc.). This is, maximizing strength gains after a physical intervention could be the key to counteract the loss of functional capacity, and, in consequence, to reduce fatigue in pwMS.[45, 65, 126] The relevance of strength gains on fatigue in pwMS seem to be confirmed by the correlational analysis (Table 11) which, unlike a previous study,[66] showed that the greater the strength improvement after the intervention was (in particular isokinetic strength), the greater the reduction in perceived fatigue was. Likewise, the MST program also improved functional mobility in pwMS, confirming not only the relevance of resistance training as a fundamental tool for facilitating the performance of those daily life actions which require getting up, walking and turning,[45, 65] but it would also be related to fatigue reductions (where strength gains would make the daily living activities less demanding for this population).[113] It must be noted that our intervention improves the TUG score in a higher extent than others physical interventions,[75] highlighting the potential benefits of MST to improve the QoL in pwMS.

A relevant finding of this study is that the significant fatigue reduction ($0.47 < d_g < 1.07$; 13.27 to 43.74%) was maintained after the detraining period compared to pre-test evaluation. This fatigue reduction was also accompanied by the preservation of the knee isokinetic strength ($0.61 < d_g < 0.83$; 5.07 to 22.73%). These results are in agreement with Dalgas and colleagues,[66] who found fatigue reductions and knee strength improvements at a 12-week follow-up after a progressive resistance training. Conversely, Dodd and collegues[82] found that the benefits on fatigue and strength after a progressive resistance program declined once the intervention was finished.

Although our findings seem to highlight the relevance of MST to maximize strength and fatigue improvements, the sample characteristics could have modulated our results in some way. On one hand, before the intervention, participants in this study were fully sedentary, making them more susceptible to the potential benefits of the training program. On the other hand, in the same way as Dalgas and colleagues,[66] our main outcome was the perceived fatigue, and thus, our sample presented high and homogeneous FSS (MST group = 56.23 ± 6.57) and MFIS (MST group = 66.46 ±

15.33) values, categorized as severe fatigue. Conversely than previous resistance training, which included individuals who did not suffer this level of fatigue, all our participants were a specific target of the therapy, which could reveal the real MST effectiveness on fatigue. Therefore, to obtain a more comprehensive knowledge of the efficacy of resistance training programs, future studies should use them with individuals of different degrees of perceived fatigue.[104]

This study has some limitations that should be considered to interpret our findings. The major one was the small sample size, hindering the results generalization, so larger studies should be performed to confirm the effectiveness of MST on perceived fatigue symptoms. In addition, participants were only relapsing remitting MS patients presenting a relatively low-to-mild impairment (1.0 < EDSS < 4.5). Hence, the results observed herein cannot be extended to more impaired pwMS, or other disease sub-types. Another limitation is that MST only took place in half of the intervention period, during weeks 7 to 12, because it was considered unsuitable to start training in week 1 with loads of 80% RM with sedentary individuals. Finally, although MS patients were asked about the medication they were using to control their pathology, it is unknown if any of them could have side-effects that affect for better or for worse the sense of fatigue.

4.6. Conclusions

Resistance training increasing working loads progressively up to 90% 1RM seems to be a feasible way to obtain clinically relevant improvements in perceived fatigue, knee strength and functional mobility, even after a 10-week detraining period. Additionally, our results suggest maximizing strength gains is a key factor to take full advantage of fatigue improvements. Under the authors' point of view, considering the benefits of MST upon functional mobility and fatigue, added to those previously indicated in the literature (such as lower elevation of body temperature), resistance trainings with high loads seem to be more suitable to improve QoL in pwMS than other types of training (such as endurance trainings).

CHAPTER 5

Epilogue

5. EPILOGUE

5.1. Discussion and Conclusions

This Doctoral Thesis presents the first two studies of a research line developed at the Sport Research Center of the Miguel Hernández University of Elche, aiming to improve the QoL of pwMS.

The Study 1 analysed the reliability of two protocols for measuring stability in individuals with MS in tandem and in a sitting position, through the use of posturographic analysis. This study also analysed the relationship between the posturographic tests and two of the most used field test in clinical assessment. In the Study 2, 13 patients with Relapsing-Remitting MS and severe fatigue underwent 12 weeks of high-intensity strength training to reduce their perceived fatigue, one of the most disabling symptoms this pathology entails.

The main conclusions of the aforementioned studies are presented below, based on the hypotheses presented in Chapter II of this Doctoral Thesis. So, the hypotheses will be accepted or rejected based on the achieved results.

Hypothesis 1: Standing balance and trunk stability assessment through the analysis of CoP using a force platform will be a reliable test in pwMS (Study 1).

This hypothesis is confirmed. The reliability values of the tandem and sitting tests achieved a high to excellent relative reliability. In minimally impaired patients (i.e. EDSS < 2) the reliability was 0.87 and 0.90 for the TW_{MRE} / TS_{MRE} respectively, and 0.92 for the sitting test. In patients with EDSS > 2 the reliability was 0.83 and 0.80 for affected/non affected leg respectively, and 0.92 for the sitting test.

Having an accurate and feasible tool to evaluate stability is fundamental, both to classify patients according to their ability to remain stable and to analyse the relationships of stability with other functional measures. Moreover, this tool will allow physicians to evaluate the benefits of different interventions that aim to improve the stability of individuals with MS.

Hypothesis 2: Standing balance and trunk stability will have a significant correlation, being suitable methods to evaluate postural control in pwMS (Study 1).

This hypothesis is also confirmed. The correlation analysis between the tandem stance balance test and the sitting balance test showed significant correlations (US_{MRE} – TW_{MRE}: $r = 0.540$, $p < 0.01$; US_{MRE} – TS_{MRE}: $r = 0.433$, $p < 0.05$).

These results show that trunk stability may affect the general stability of pwMS, becoming a variable to be trained within the rehabilitation programs prescribed to pwMS.

Hypothesis 3: Postural control parameters will have significant correlations with functional mobility and walking performance (Study 1).

This hypothesis is partially confirmed. Based on the correlational analysis, trunk postural control positively correlated with functional mobility (US_{MRE} – TUG: $r = 0.419$, $p < 0.05$), but it did not correlate with gait speed (US_{MRE} – T25FW: $r = 0.240$, $p > 0.05$). Postural control in tandem stance positively correlated with functional mobility (TW_{MRE} – TUG: $r = 0.604$, $p < 0.05$; TS_{MRE} – TUG: $r = 0.511$, $p < 0.05$; TW_{MRE} – TUG: $r = 0.604$, $p < 0.05$) and also with walking speed (TW_{MRE} – T25FW: $r = 0.534$, p

< 0.05). The lack of correlation between trunk control and gait performance could be related to the low balance demands of walking (in a straight line) during the T25FW for our MS sample (EDSS ≤ 4). Nevertheless, the balance task demands were higher during the TUG (i.e. standing with a small base of support, rising, turning, etc.) and, consequently, trunk control could play a more important role in the performance of this test.

Hypothesis 4: The MST program, owing to the neural improvements that this type of resistance training implies, will significantly reduce perceived fatigue in pwMS compared to a control group (Study 2).

This hypothesis is confirmed. Unlike the CG, the MST group showed a significant reduction in perceived fatigue after the intervention (FSS = -39.53%, $MFIS_o$ = -58.68%, $MFIS_{ph}$ = -62.83%, $MFIS_{cg}$ = -52.40%, $MFIS_{ps}$ = -64.24%). It seems to be confirmed that high-intensity strength training, reaching RM values considered as a maximum strength, is a treatment to be considered to reduce perceived fatigue in individuals with Relapsing-Remitting MS and severe perceived fatigue.

Hypothesis 5: The MST program will improve functional mobility compared to a control group (Study 2).

This hypothesis is partially confirmed. Only the improvement in the isometric strength of the knee extensor muscles correlated significantly with the decrease in TUG time, which seems to indicate that improvements in the power production capacity of this musculature could improve functional mobility in pwMS.

Hypothesis 6: Greater strength improvements after MST will correlate with greater fatigue reductions in the participants of the MST program (Study 2).

This hypothesis is confirmed. The correlational analysis showed that the greater the strength improvement after the intervention was, in particular in isokinetic strength, the greater the reduction in perceived fatigue was ($IQPT_{IK}$ – IFSS: $r = 0.50$, $p < 0.05$; $IHPT_{IK}$ – IFSS: $r = 0.51$, $p < 0.05$; $IQPT_{IK}$ – $IMFIS_{ov}$: $r = 0.62$, $p < 0.01$; $IHPT_{IK}$ – $IMFIS_{ov}$: $r = 0.55$, $p < 0.05$).

5.2. Study Limitations and Future Research

While carrying out the present Doctoral Thesis some limitations were found, which should be useful as a starting points for further research on stability and strength training in pwMS:

I. One of the main limitations found in Studies 1 and 2 was the number of participants. Study 1 included 30 participants, but after dividing the sample into two groups, the subgroups were not entirely equal: 14 participants with EDSS ≤ 2 and 16 participants with EDSS between 2.5 and 4. Future research to explore the relative and absolute reliability should consider that to achieve greater statistical power, a larger sample would be required. In addition, in order to explore possible differences between women and men, samples should be sex-balanced. Although it is a limitation to bear in mind, it should be pointed out that the very epidemiology of the population that suffers the disease makes it difficult to recruit the same number of men than women for the study because the number of diagnoses has a 3:1 ratio women/men.

Regarding Study 2, it included 26 participants, 13 of which were part of the MST group and 13 of the CG. Thus, although the results about the decrease in perceived fatigue are promising, it is necessary to carry out new interventions with larger groups to be able to state emphatically that MST reduces fatigue perceived by this kind of participants. Moreover, groups in Study 2 could not be sex-balanced either. Of the 26 participants, 20 were women and 6 men. After dividing the sample into groups, the MST group had 8 women and 5 men, while in the CG there were 12 women and 1 man.

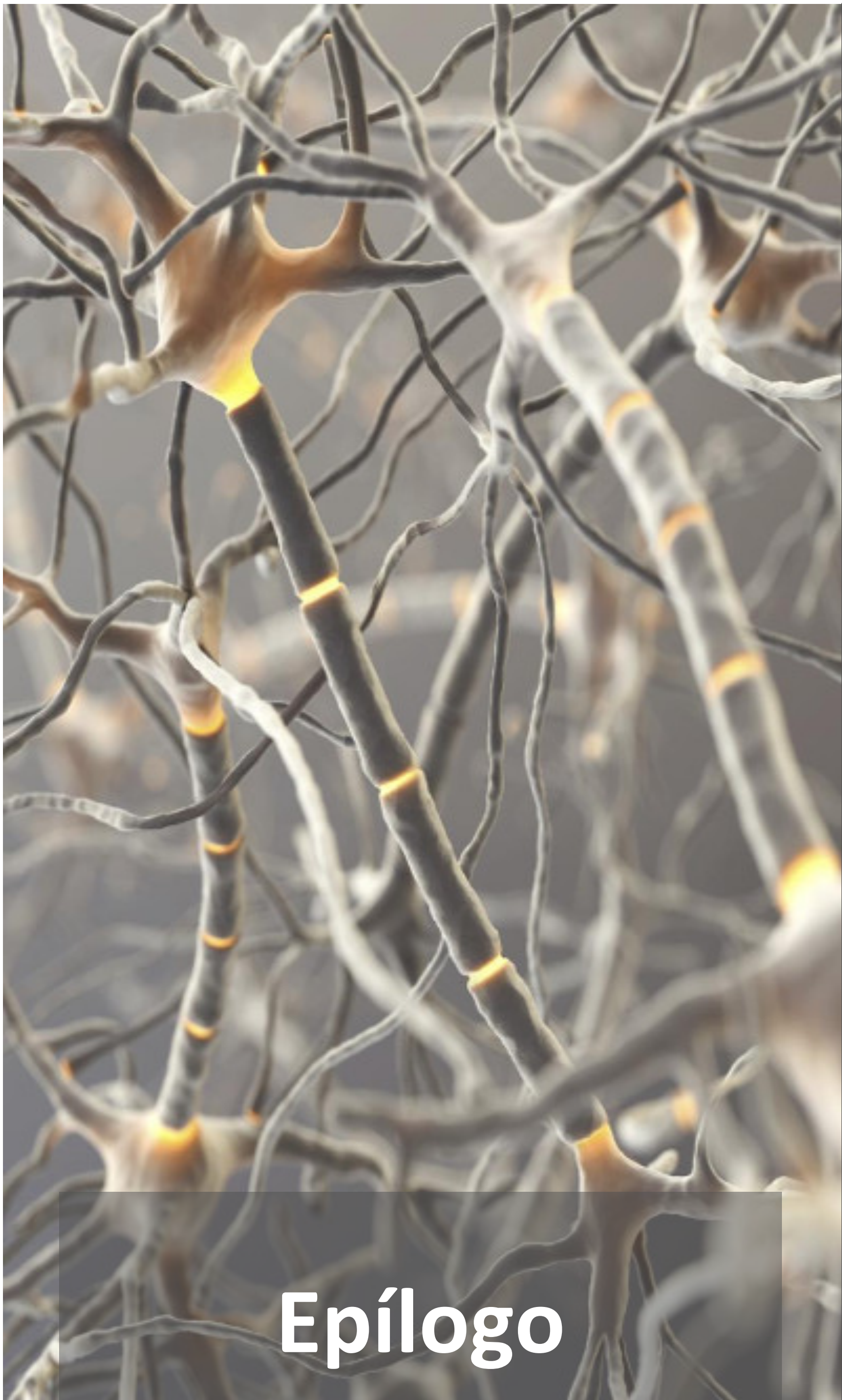
II. The difficulty of the posturographic tests, both in tandem stance and sitting on the unstable seat, preventing the evaluation of the stability of patients with EDSS > 6. This EDSS marks the limit which indicates that patients may begin to need the help of a cane or similar technical help to prevent falls. In this way, it is necessary to modify these posturographic protocols for the most affected patients, as for example: i) measuring standing balance with both feet together instead of in tandem position; or ii) changing the circular task of the unstable seat for one in which subjects simply have to maintain the initial position of the test (i.e. quiet sitting). It is also possible that individuals with poor trunk stability might need to perform the sitting tasks on the force platform but without the unstable seat.

III. In Study 2, MST truly took place only in half of the intervention, during weeks 7 to 12. This was so because it was considered unsuitable to start training in week 1 with loads of 80% RM bearing in mind that the subjects were sedentary. For this reason, it was decided to undergo a period of adjustment that would allow participants to mobilize the higher loads at the end of the intervention with more security. Future interventions should check if MST in already trained pwMS obtains similar results to Study 2 of this thesis.

IV. Although the intervention carried out in the Study 2 involved the major muscle groups of the participants, isometric and isokinetic strength could only be measured in knee flexion-extension muscles due to lack of the necessary staff to evaluate more muscle groups. Therefore, the results of correlations between the increase in muscle strength and the reduction of the perceived fatigue must be interpreted with caution, because, actually, only the increase in muscle strength of certain muscle groups was evaluated. In this sense, it cannot be assured that the decrease in perceived fatigue of the patients was actually due to the strength increase of those muscle groups and not other, as for example muscles of the upper limbs or trunk.

V. The participants in Study 2 did not take any medication to reduce fatigue during the time this study was carried out so that this fact was not a pollutant variable of the intervention. There wasn't a change in the participants' medication either. However, it should be noted that although patients were asked about the medication they were using to control their pathology, it is unknown if any of them could have side-effects that affect for better or for worse the sense of fatigue. In future interventions in which the perceived fatigue is the main output, there must be the effective participation of a neurologist who certifies that medication that participants used does not influence the results of the aforementioned intervention.

CHAPTER 6



Epílogo

6. EPÍLOGO.

6.1. Discusión y Conclusiones

En esta Tesis Doctoral se han presentado dos estudios que son el germen de una línea de investigación desarrollada en el Centro de Investigación del Deporte de la Universidad Miguel Hernández de Elche, encaminada a mejorar la calidad de vida de las personas con EM.

En el Estudio 1 se analizó la fiabilidad de dos protocolos de medición de la estabilidad en sujetos con EM en posición tándem y en posición sedante mediante el uso de la posturografía. Este estudio analizó también la relación entre los test posturográficos y dos de los test funcionales de campo más usados en el ámbito clínico. En el Estudio 2, 13 pacientes con EM Remitente Recurrente y fatiga severa participaron en un programa de entrenamiento de fuerza de alta intensidad de 12 semanas con el fin de reducir su fatiga percibida, uno de los síntomas más incapacitantes que esta patología acarrea.

A continuación se presentan las principales conclusiones de los citados estudios en base a las hipótesis presentadas en el Capítulo II de la presente Tesis Doctoral. Para ello se aceptarán o rechazarán las hipótesis a tenor de los resultados obtenidos.

Hipótesis 1: La evaluación del equilibrio general y la estabilidad del tronco a través del análisis del Centro de Presiones usando una plataforma de fuerza será un test fiable en personas con EM (Estudio 1).

Esta hipótesis se confirma. Los valores de fiabilidad de las pruebas tándem y sedente alcanzaron una fiabilidad relativa de alta a excelente. En pacientes con daño mínimo (EDSS < 2) la fiabilidad fue de 0.87 y 0.90 para la pierna afectada / no afectada, respectivamente, y 0.92 para el test en sedestación. En pacientes con EDSS > 2 la fiabilidad fue de 0.83 y 0.80 para TW_{MRE} / TS_{MRE}, respectivamente, y de 0.92 para la prueba en sedestación.

Tener una herramienta precisa y fiable para evaluar la estabilidad se torna fundamental, tanto para clasificar a los pacientes de acuerdo a su capacidad de permanecer estable como para analizar las relaciones de la estabilidad con otras medidas funcionales. Además, esta herramienta podría permitir a personal médico evaluar los beneficios de las diferentes intervenciones que pretenden mejorar la estabilidad en personas con EM.

Hipótesis 2: El equilibrio general y la estabilidad del tronco tendrán una correlación significativa, siendo métodos adecuados para evaluar el control postural (Estudio 1).

Esta hipótesis también se confirma. El análisis de correlación entre el test de equilibrio en posición tándem y el test de equilibrio en sedestación mostraron correlaciones significativas (US_{MRE} – TW_{MRE}: $r = 0.540$, $p < 0.01$; US_{MRE} – TS_{MRE}: $r = 0.433$, $p < 0.05$).

Estos resultados demuestran que la estabilidad del tronco puede afectar la estabilidad general de las personas con EM, convirtiéndose en una variable a ser entrenada dentro de programas de rehabilitación prescritos para este colectivo.

Hipótesis 3: Las variables de control postural correlacionanarán significativamente con las de movilidad funcional y rendimiento de la marcha (Estudio 1).

Esta hipótesis se confirma parcialmente. Basándonos en el análisis correlacional, el control postural del tronco correlacionó positivamente con la movilidad funcional (US_{MRE} – TUG: $r = 0.419$, $p < 0.05$), pero no con la velocidad de la marcha (US_{MRE} – T25FW: $r = 0.240$, $p > 0.05$). Por otro lado, el control postural en posición tándem correlacionó positivamente tanto con la movilidad funcional (TW_{MRE} – TUG: $r = 0.604$, $p < 0.05$; TS_{MRE} – TUG: $r = 0.511$, $p < 0.05$; TW_{MRE} – TUG: $r = 0.604$, $p < 0.05$) como con la velocidad de la marcha (TW_{MRE} – T25FW: $r = 0.534$, $p < 0.05$). La ausencia de correlaciones entre el control de tronco y el test de velocidad de la marcha puede ser debido a la escasa demanda de equilibrio a la hora de caminar (en línea recta) durante el T25FW para nuestra muestra (EDSS ≤ 4). Sin embargo, la exigencia de equilibrio fue mayor en el TUG (es decir, levantarse con poca superficie de apoyo, girar, etc.), por lo que el control de tronco pudo desempeñar un rol más importante para el rendimiento en este test.

Hipótesis 4: Un programa de entrenamiento de fuerza máxima, debido a las mejoras neurales que acarrea, reducirá significativamente la fatiga percibida en pacientes de EM en comparación con un grupo control (Estudio 2).

Esta hipótesis se confirma. A diferencia del grupo control, el entrenamiento de fuerza máxima mostró una reducción significativa de la fatiga percibida tras el periodo de intervención (FSS = -39.53%, MFISo = -58.68%, MFISph = -62.83%, MFIScg = -52.40%, MFISps = -64.24%). Por lo tanto, parece confirmarse que el entrenamiento de fuerza de alta intensidad, alcanzando los valores de RM considerados como de fuerza máxima, es una metodología a considerar para reducir la fatiga percibida en individuos con EM Remitente Recurrente y fatiga percibida severa.

Hipótesis 5: Un programa de entrenamiento de fuerza máxima mejorará la movilidad funcional en comparación con un grupo control (Estudio 2).

Esta hipótesis se confirma parcialmente. Sólo las mejoras en la fuerza isométrica de los músculos extensores de rodilla correlacionaron significativamente con la reducción en el tiempo que los pacientes necesitaron para realizar el TUG ($IQPT_{IM}$ – ITUG: $r = 0.60$, $p < 0.01$). Esto que parece indicar que las mejoras en la capacidad de producción de fuerza de esta musculatura podrían mejorar la movilidad funcional en personas con EM.

Hipótesis 6: Mayores mejoras en fuerza después del entrenamiento de fuerza máxima correlacionarán con mayores reducciones de fatiga en el grupo MST (Estudio 2).

Esta hipótesis se confirma. El análisis correlacional muestra como las mayores ganancias en producción de fuerza, especialmente en las variables isocinéticas, correlacionaron con mayores reducciones en fatiga percibida ($IQPT_{IK}$ – IFSS: $r = 0.50$, $p < 0.05$; $IHPT_{IK}$ – IFSS: $r = 0.51$, $p < 0.05$; $IQPT_{IK}$ – $IMFIS_{ov}$: $r = 0.62$, $p < 0.01$; $IHPT_{IK}$ – $IMFIS_{ov}$: $r = 0.55$, $p < 0.05$).

6.2. Limitaciones y Prospectivas de Investigación

Durante el desarrollo de la presente Tesis Doctoral se encontraron algunas limitaciones que deben servir de punto de partida para futuras investigaciones sobre estabilidad y entrenamiento de fuerza en personas con EM:

I. Una de las principales limitaciones encontradas, tanto en el Estudio 1 como en el Estudio 2, ha sido el número de participantes. En el Estudio 1 se contó con 30 participantes, si bien al dividir la muestra en dos grupos respecto a sus valores de EDSS los subgrupos no fueron del todo iguales: 14 personas con EDSS ≤ 2 y 16 con EDSS > 2.5. Futuras investigaciones sobre la fiabilidad relativa y absoluta deberán tener en cuenta que para conseguir mayor potencia estadística se necesario un tamaño muestral mayor.

   Tampoco se pudo equilibrar en este estudio la población respecto al sexo. Si bien es una limitación a tener en cuenta, se ha de apuntar que la propia epidemiología de la población que sufre la patología hace difícil reclutar al mismo número de hombres que de mujeres para el estudio, pues el número de diagnósticos tiene una ratio mujeres/hombres de 3:1.

   En el Estudio 2 se contó con 26 participantes, 13 de los cuales formaron parte del grupo de intervención (MST) y 13 del grupo control. De este modo, aunque los resultados respecto a la disminución de fatiga percibida resultan prometedores, es necesario realizar intervenciones con grupos más numerosos para poder afirmar con mayor rotundidad que el entrenamiento de fuerza máxima reduce la fatiga percibida por este tipo de personas.

En el Estudio 2 tampoco se pudo equilibrar a los grupos respecto al sexo. De los 26 participantes, 20 eran mujeres y 6 hombres. Al dividir la muestra en grupos, el grupo MST contó con 8 mujeres y 5 hombres, mientras que en el grupo control fueron 12 mujeres y 1 hombre.

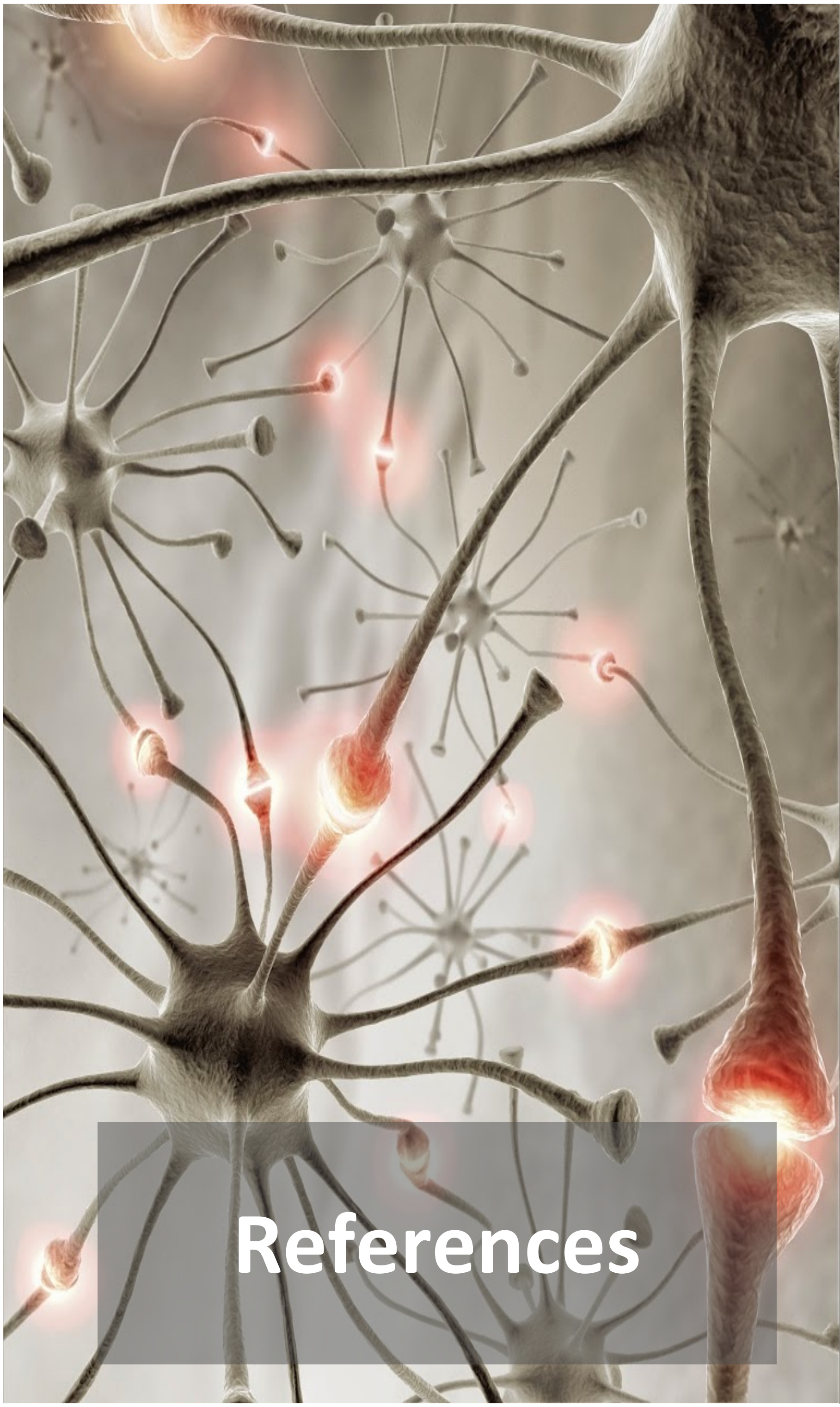
II. La dificultad de los test posturográficos, tanto en posición tándem como en sedestación sobre el asiento inestable, impiden evaluar la estabilidad de pacientes con EDSS > 6, límite de la escala de evaluación de la discapacidad de la patología que indica que los sujetos pueden empezar a necesitar de ayuda de bastón o ayuda técnica similar para evitar caídas. De este modo, es preciso modificar estos test posturográficos para aquellos pacientes más afectados, como por ejemplo: i) evaluando la estabilidad corporal general con los pies juntos en vez de en posición tándem; o ii) cambiando la tarea circular del asiento inestable por una en la que los pacientes simplemente tengan que mantener la posición de sedestación con la menos oscilación posible. También es posible que para sujetos con un bajo nivel de estabilidad del tronco sea necesario realizar el test de control postural en sedestación sobre la plataforma de fuerzas, pero prescindiendo del asiento inestable.

III. En el Estudio 2, el entrenamiento de fuerza máxima verdaderamente sólo se desarrolló en la mitad de la intervención, de la semana 7 a la 12. Esto fue así porque se consideró poco apropiado empezar a entrenar en la semana 1 con cargas del 80% de 1RM teniendo en cuenta que los participantes eran sedentarios. Por ese motivo se decidió realizar un periodo de adaptación que permitiera movilizar cargas superiores al final de la intervención con más seguridad. Futuras intervenciones deberán comprobar si el entrenamiento de fuerza máxima en personas con EM ya entrenadas previamente obtiene resultados similares a los del Estudio 2 de la presente Tesis Doctoral.

IV. Aunque la intervención realizada en el Estudio 2 implicó los principales grupos musculares de los participantes, las evaluaciones de fuerza isométrica e isocinética sólo pudieron realizarse en la musculatura flexo-extensora de la rodilla debido a que no se pudo disponer de personal necesario para evaluar más grupos musculares. Por lo tanto, los resultados de las correlaciones entre el aumento de fuerza muscular y la reducción de la fatiga percibida deben ser analizados con cautela, porque en realidad sólo se evaluó el aumento de fuerza muscular de determinados grupos musculares. Así, no se puede asegurar que la disminución de la fatiga percibida de los pacientes sea efectivamente debida al incremento en la fuerza de esos grupos musculares y no de otros, como por ejemplo a los de los miembros superiores o el tronco.

V. Los pacientes que participaron en el Estudio 2 no tomaron durante el tiempo en el que se desarrolló el mismo ninguna medicación para reducir la fatiga, con la finalidad de que este hecho no fuera una variable contaminante de la intervención. Tampoco se produjeron cambios en la medicación de los sujetos participantes. No obstante, cabe señalar que si bien se preguntó a los pacientes la medicación que estaban usando para el control de su patología, se desconoce si algún fármaco pudiera tener efectos secundarios que afecten, para bien o para mal, a la sensación de fatiga de los mismos. En futuras intervenciones en que la fatiga percibida sea el principal aspecto a evaluar se deberá contar con la participación de un neurólogo que certifique que las medicaciones que los participantes utilizan no influyen en los resultados de la intervención.

CHAPTER 7



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Para algunos la vida es galopar

un camino empedrado

de horas, minutos y segundos.

Yo, más humilde soy,

y solo quiero que la ola que urge del ultimo suspiro de un segundo

me transporte mecido hasta el siguiente.

Santos Isidro Seseña