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Neurorehabilitation in Multiple Sclerosis: insights into fatigue and motor function

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About this work

This doctoral project aims to improve the overall knowledge on the effects of neurorehabilitation in People with Multiple Sclerosis (PwMS), by providing more insights on fatigue and the relationship between fatigue and motor functional aspects.

The general introduction provides background information on the main topics of this doctoral project. In the first part, the specific disease characteristics of Multiple Sclerosis are described. In the second part, the current status of fatigue and motor impairment and a focus on the management are presented. Finally, the aims and outline thesis are reported.

Four studies were conducted and reported in 4 different chapters.

The first study provides information about the cardiac autonomic function during rest, postural changes and exercise and the relationship between autonomic modulation of heart rate and the perceived fatigue.

The second study investigates the effect of an experimental rehabilitation protocol which combines aerobic training and task oriented exercises aimed to reduce fatigue and improve upper limb impairments and function.

The third study provides information about preliminary effects of a high-intensity rehabilitative multimodal training protocol carried out on a treadmill aimed at improving mobility and balance.

The fourth study shows the effectiveness of functional electrical stimulation on reducing falls, improving gait kinematics and promoting energy recovery.

Lastly, general conclusions, including main findings and clinical implications, are provided at the end of the doctoral thesis.

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General introduction

Definition, pathogenesis and prevalence

Multiple Sclerosis is a chronic inflammatory and neurodegenerative disease of the Central Nervous System (CNS) and it is the leading cause of non-traumatic disability in young and middle-aged adults.[1] Even though the pathogenesis of MS is only partly understood, it is believed that lymphocytic infiltration through the blood-brain-barrier into CNS leads to damage of myelin.[1] In addition, it initiates a cascade of inflammatory reactions which also affect surrounding oligodendrocytes as well as microglia. This initial damage can be repaired as inflammation resides and remyelination of the affected axons occurs. However, whether remyelination is not suitable progressive and definitive damage of CNS occurs.[1]

According to the WHO/MSIF MS Atlas, the disease affects 2.3 million people worldwide, with more than 600,000 cases in Europe.[1] Since 1980, many epidemiological studies have classified Italy as a high-risk area for MS, with the highest rates in the island of Sardinia, and no evidences of a latitude gradient. According to the Italian MS patient society (AISM) estimates, there are 75,000 patients in Italy with an incidence of 2000 cases per year. Applying these mean prevalence rates to the Italian population as of 2015, we obtained an estimate of more than 109,000 MS patients in Italy.[2]

Diagnosis, sign, symptoms and progression

The diagnosis of MS is made clinically. There is not a single test that can determine if a person does or does not have the disease. MS is a disease defined by neurological symptoms separated (or disseminated) in time and space. MS diagnosis is primarily based on the Poser criteria[3] or the McDonald criteria.[4]

According to Poser criteria is based on (1) number of relapse, (2) clinical and paraclinical symptoms, (3) chronic inflammation of the CNS as determined by the analysis of the cerebrospinal fluid. According to McDonald criteria, (1) clinical evidence of two attacks at different times (i.e. disseminated in time), (2) evidence of at least two different areas of

the CNS affected (i.e. dissemination in space), (3) chronic inflammation of the CNS as determined by the analysis of the cerebrospinal fluid. In 2010, the revisions to the McDonald Criteria emphasizes the use of MRI of the brain to support and to confirm diagnosis of MS and rule out alternative explanations for the symptoms, such as stroke, brain tumors or infections.[5,6]

Clinically Isolated Syndrome (CIS) is now recognized as the first clinical presentation of a disease that shows characteristics of inflammatory demyelination that could be MS, but has yet to fulfill criteria of dissemination in time. MS phenotypes can be categorized as relapsing or progressive in the context of current medical status and history, but these categories do not provide temporal information about the ongoing disease process: relapsing remitting (RR), secondary progressive (SP), primary progressive (PP).[6]
All forms of MS, with the exception of PPMS, are initially characterized by a pattern of relapses and remissions over time. A relapse is defined as the appearance of new symptoms or worsening or reactivation of previously present symptoms. The appearance or change in symptoms must last at least 24h, be separated from a previous relapse by at least 30 days, and not be the consequence of a change in body temperature or an infection. The specific course of MS that a person has will influence disease progression.[6]
MS relapses are highly variable between individuals as well as in a given individual and over time. A person may experience a very mild relapse that allows him or her to continue to perform most daily activities.[7]

Onset of MS most often occurs in adults between the ages of 20 and 50 years, and is two to three times more common in women than men. The course of MS is heterogeneous, but generally evolves over 30–40 years, and is characterized by multiple neurologic deficits and significantly decreased quality of life (QOL), and leads to substantial disability in many patients.[8] In a population-based study, 33% of 1099 people with MS had difficulty walking and required assistance at 10 years from onset of MS. Symptoms are also heterogeneous and may include optic neuritis, fatigue, weakness, gait ataxia, spasticity, muscle spasms, pain, tremor, numbness,

paraesthesia, bladder and bowel dysfunction, and cognitive deficits, among other problems.[8]

Gait impairment is a clinical hallmark of MS, often resulting from the combination of multiple common symptoms and deficits such as fatigue, weakness, spasticity, ataxia, and balance problems.[9]

Accordingly, measurement of walking ability is a major component of instruments widely used for evaluation of disease severity and progression. Although EDSS has been criticized for over-reliance on ambulation and lack of sensitivity to other problem, it still remains the widely used scale to evaluate and describe progression in MS.[10]

The EDSS score is based on examination of eight body functions (called functional systems): pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and walking. Typically, the EDSS score is determined by a neurologist's clinical examination. The resulting score is an ordinal-level measure that extends from 0.0 (normal neurological exam) to 10.0 (death from MS), see Figure 1.

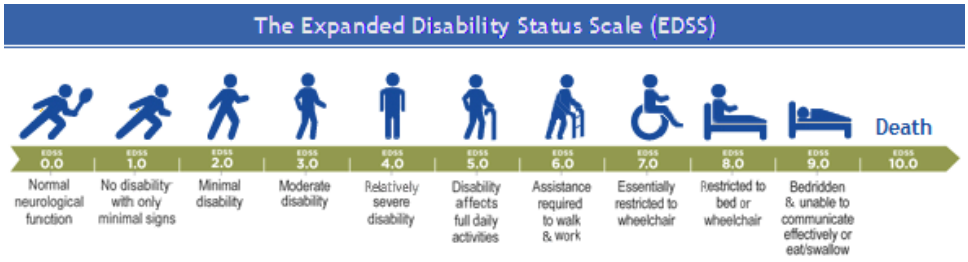

Figure 1: Expanded Disability Status Scale (EDSS)

Treatment

Pharmacological treatment of MS consists of treatment of relapse, disease-modifying therapies, and symptomatic therapy. The standard regimen in treating relapse leading to a faster recovery by restoring blood-brain barrier leakage, reducing edema and dampening the inflammatory processes in CNS is the use methylprednisolone at high dose. Relapse

treatment with steroids probably has no long-term benefit on disease progression while disease modifying therapies have been shown to decrease relapse rate and slow clinical progression.[11]

First-line disease-modifying drugs currently being used include beta-interferons (Avonex®, Betaferon®, Rebif®) and glatirameracetate (Copaxone®), whereas in those patients with very high disease activity or not responding to first-line agents, second-line treatment such as natalizumab (Tysabri®), mitoxantron (mitozantron), fingolimod (Gilenya®) has been introduce. These disease-modifying therapies are able only to decelerate disease progression, but cannot reverse existing lesions.[12]

Currently, there are not approved pharmacological therapies for people with PPMS.[13] Symptomatic pharmacological treatment may help to reduce the negative impact of MS symptoms (e.g. spasticity, pain, bladder and bowel dysfunction).[9]

Despite established advancement of pharmacological treatment, especially by disease-modifying therapies, MS continues to be the most common disabling neurological disease in young adults. While a growing number of medications can reduce the number of relapses and alter the course of the disease, PwMS continue to experience restrictions in their ability to participate in activities daily living. Therefore, there is a continuing need for comprehensive, multidisciplinary, long-term management, which constitutes the basic concept of rehabilitation.[12]

Rehabilitation is defined as a problem solving educational process aimed at reducing disabilities and handicaps (participation) experienced by someone as a result of a disease or injury.[13] The principal focus of rehabilitation is on reducing symptoms and limitations at the level of activity and participation, through interventions which include personal and environmental factors, to achieve the highest possible independence and the best Quality of Life (QoL) of PwMS within the limits of the disease.[14]

Multidisciplinary rehabilitation is designed to be patient-centered, time-based, functionally oriented and aims to maximize activity and participation. The activity of a person with MS can be affected from a combination of motor (weakness, spasticity), sensory (proprioception loss, ataxia), fatigue, psychological and visual impairments. Improving or

restoring physical and psychosocial abilities therefore is a key issue in rehabilitation of PwMS.[15]

Fatigue

Fatigue is the most common symptom reported by people with MS and contributes to reduced walking capacity[16] and experiencing problems in daily life, for example with grasping or lifting an object, due to upper limb dysfunction.[17]
In a recent study LaRocca et al. interviewed 1011 PwMS and documented the most commonly reported MS symptoms experienced at least twice a week were fatigue (76%), abnormal sensation (60%) and loss of balance (54%) (Figure 2).[11]

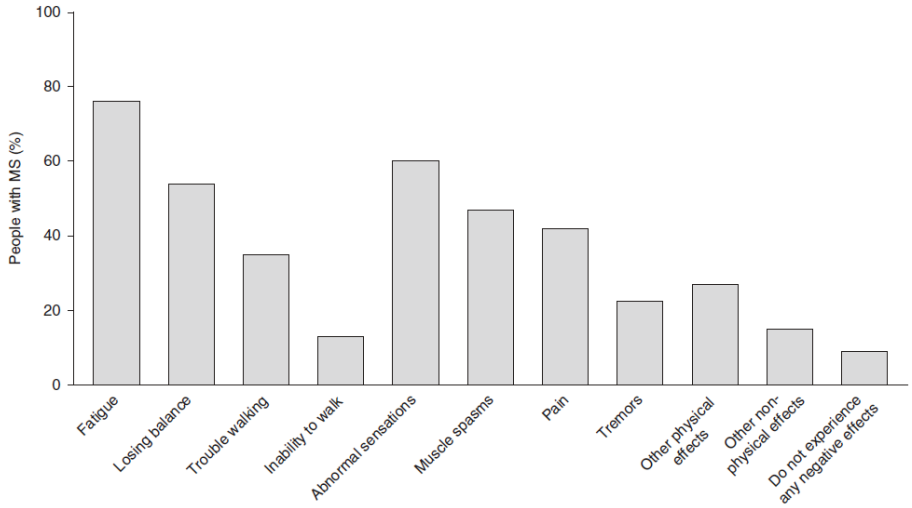

Figure 2: Multiple Sclerosis symptoms experienced at least twice a week by PwMS

Moreover, of all PwMS, 412 (41%) reported difficulty walking saying that this problem not only negatively affected their mobility but also restricted their activities and affected their emotional health.[11] (Figure 3 and 4)

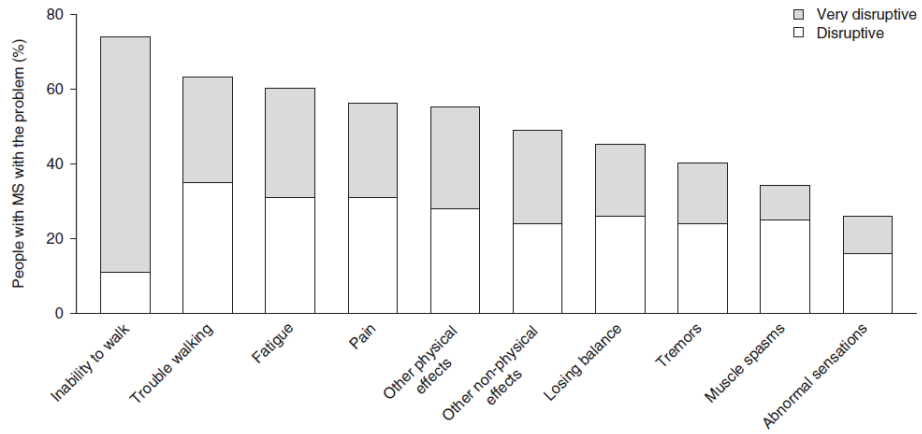

Figure 3: Multiple Sclerosis symptoms experienced by PwMS

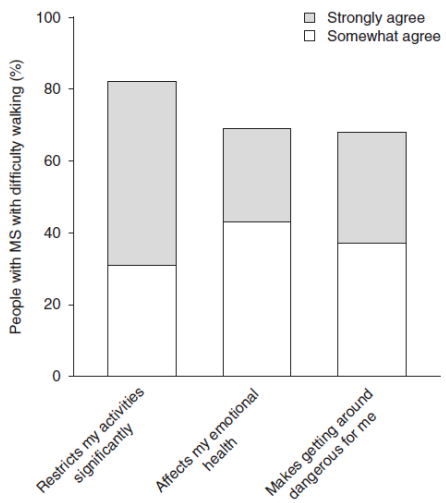

Figure 4: Negative impact of difficulty walking on PwMS

Approximately 70-90% of PwMS experience fatigue and up to 40% of them describe it as their most disabling symptom. Even though the importance and clinical relevance of fatigue is evident, there is a lack of consensus regarding its definition and underlying theoretical construct. Multiple Sclerosis for Clinical Practice Guidelines defines fatigue as a subjective lack of mental or physical energy as perceived by the individual (or caregiver) to interfere with usual or desired activities.[18]

Fatigue can be of sensory, motor, cognitive or subjective origin. MS fatigue can occur as a consequence of the disease process itself defined as primary fatigue. Current knowledge suggests there are three potential mechanisms for primary MS fatigue that are changes in the central nervous system (including axonal loss and cortical reorganization), changes in immune system and endocrine influences. Fatigue can be a consequence of other factors not directly related to the disease, secondary fatigue. Examples include sleep problems, medications, deconditioning, depression, stress and anxiety.[19]

Chadhuri and Behan introduced a clinical approach to fatigue distinguishing central fatigue from peripheral fatigue, where central fatigue is defined as the inability to initiate and/or sustain attentional tasks (cognitive fatigue) and physical activities (physical fatigue). It is consistently seen with lesions in pathways associated with arousal, attention, reticular and limbic system and the basal ganglia. On the contrary, peripheral fatigue is defined as muscle fatigability due to abnormalities of muscle and neuromuscular junctions with an objective reduction in muscle strength measured as the rate of decline in peak force generated during maximal voluntary muscle contraction.[20]

The lack of a uniform definition for MS-related fatigue, can be contributed to the multifaceted and complex pathophysiological mechanism. Therefore, fatigue is a critical symptom to address during rehabilitation because it may worsen other symptoms (e.g. cognition) or it may increase as a consequence of others (e.g. spasticity).[21,22]

Managing fatigue and motor impairment: Role of exercise

The underlying mechanisms regarding the effects of exercise therapy on fatigue in MS are still poorly understood. Exercise therapy may increase the energy reserves available for physical work and alleviate the detrimental effects of physical inactivity. In addition, exercise therapy and/or physical activity in itself may enhance neurobiological processes that could promote neuroprotection and neuroplasticity and reduce long-term disability. Exercise therapy has the ability to induce changes in this neurobiological processes. Compared to pharmacological and non-pharmacological interventions such as energy conservation management and cognitive behavioral therapy, exercise may affect both primary mechanisms (e.g. neuroprotection or dysfunction), as well as secondary factors related to fatigue (e.g. inactivity or co-morbidity).[23]

Level of physical activity is a key issue in the management of fatigue. Patients are likely to be sedentary because of associated disabilities (e.g. weakness and pain), reduced levels of physical endurance and deterioration of symptoms that could follow physical exertion. However, physical inactivity imposed by fatigue leads to chronic cardiovascular and muscle deconditioning and raised health risks. Input from therapists can help in assessment of the level of disability and to identify an acceptable range of daily physical activity to prevent physical deconditioning and resulting weakness and muscle atrophy.[23]

It has been reported in a recent review by Heine et al. that exercise can be safely prescribed and is moderately effective in the treatment of fatigue in PwMS without increasing the number of relapses. He has also shown that these effects vary between studies and between participants. This review suggested that endurance training, mixed training, or 'other' types of training (e.g. yoga) may be more effective compared to muscle strength training and task-oriented training but it is too premature to consider a certain type of training superior to any other.[22]

Aim and thesis outline

Aim

The main topic of the present dissertation consists of the investigation into the effects of neurorehabilitation in individuals with multiple sclerosis (MS), focusing on fatigue and motor function.

The main aim of this thesis is to investigate physiological and rehabilitative outcomes in order to identify whether there is any difference in physiological outcomes between healthy subjects and people with multiple sclerosis and the impact of exercise.

Moreover, a second objective of this thesis is to find new rehabilitative strategies able to mitigate fatigue symptoms and motor dysfunctions in MS. Towards this goal, we evaluated the role of exercise.

Thesis outline

Here, we are presenting four studies focused on different aspects of neurorehabilitation concerning fatigue and motor function.

Chapter 1 provides evidence about the differences in basal cardiac autonomic tone between healthy subjects and PwMS and its modulations while standing, during submaximal exercise and during the recovery phase after exercise. Moreover, the relationship between autonomic modulations of heart rate and the perceived fatigue in PwMS without clinically overt autonomic dysfunction was provided.

Chapter 2 describes a crossover study investigating the effects of an intensive period of rehabilitation comprising a combination of endurance training and task-oriented training on fatigue and upper limb impairment in people with MS. The main result of this pilot study is that 8 weeks of neurorehabilitation can reduce fatigue and upper limb impairments without any improvement in manual dexterity.

Chapter 3 extends the results of Chapter 2 to the impact of neurorehabilitation using endurance training and task oriented approaches. The present study examined the response of moderately to

severely affected PwMS to an in clinic intensive multimodal training on a treadmill and compared it to a control group that received a strengthening program of similar intensity. The main result of this study is that many more people in the treadmill group improved their gait resistance than in the strength training group and as a whole the group improved much more in gait resistance, speed and mobility.

Chapter 4 describes prospective longitudinal study investigating the role of using functional electrical stimulation on improving gait parameters and walking endurance in neurological conditions. We found a period of 8 weeks of walking training with the use of a functional electrical stimulation device had an impact on gait, reducing the number of falls and improving walking. Moreover, we observed a specific effect at the ankle joint, increasing foot clearance during the swing phase of gait without a concomitant reduction in the energetic expenditure during walking in subjects with neurological conditions.

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Chapter 1

CARDIAC AUTONOMIC FUNCTION DURING POSTURAL CHANGES AND EXERCISE IN PEOPLE WITH MULTIPLE SCLEROSIS: A CROSS-SECTIONAL STUDY

Abstract

Background. People with multiple sclerosis (PwMS) often develop an autonomic dysfunction (AD), which onset should be assessed early at a sub-clinical level, as it may interfere with pharmacological treatments and exercise.
Objective. To evaluate basal cardiac autonomic tone, its modulations during sit-to-stand, sub-maximal exercise and recovery in PwMS without clinical overt AD and its relationships with fatigue perception.
Methods. Twenty-three PwMS (55±8 yrs [mean±SD]; EDSS score 5.7±1.3) and 20 age-matched healthy controls (HC; 55±8yrs) were enrolled. ECG was digitally acquired at baseline (sitting and standing), during a light upper-limb cyclic exercise and during sitting recovery. Parasympathetic and sympatho-vagal parameters of heart rate (HR) variability in time and frequency domains were calculated from beat series.
Results. HR was slightly higher but not significantly different in PwMS compared to HC in all experimental conditions. Parasympathetic indexes were significantly lower ($P<0.05$) in PwMS compared to HC during baseline sitting and exercise recovery, whereas sympatho-vagal parameters were similar in both groups. No correlation between autonomic tone and perceived fatigue was observed.
Conclusion. Parasympathetic tone appears to be impaired in PwMS basal and post-exercise conditions, but not during postural challenge and exercise. In addition, subclinical AD doesn't seem to affect perceived fatigue.

Introduction

Multiple Sclerosis (MS) is a chronic central nervous system disease that may affect autonomic function. The demyelination of specific structures causes bladder, bowel and sexual dysfunction, leading to disability in 45-84% of PwMS and dramatically impacts quality of life.[1]

The effects of sympathetic and parasympathetic disturbances on hearth function in PwMS are not fully understood. A cardiovascular autonomic dysfunction (AD) has been demonstrated in variable proportions of patients,[1, 2] ranging from 7 to 60%,[1] and appears to correlate with the severity and the duration of the disease. However, it is not clear when AD arises in the course of MS development. Therefore, the importance of autonomic function testing in detecting early subclinical changes in PwMS has been highlighted[2] to set an adequate prevention therapy, based on drug interventions or exercise.
A validated method to study cardiac autonomic activity is the analysis of spontaneous Heart Rate Variability (HRV), which can be easily used to evaluate the cardiovascular autonomic reactions to common everyday motor tasks, such as light exercise and postural challenges. So far, the studies evaluating autonomic HRV modulations in PwMS have used classic clinical autonomic tests in supine position and during sleep[3, 4] or long-term heart activity recording based on 24-h ECG monitoring.[5] However, no studies investigated vagal or sympathetic modulations of HR during orthostatic challenges and continuous exercise in PwMS.

Moreover, an altered cardiac autonomic response might be one of the reasons for an impaired tolerance to exercise or everyday life activities: however little information is available on the relationship between subjective fatigue perception and the autonomic modulation of HR in functional situations in PwMS.
Finally, the assessment of autonomic responses is of particular interest for patients undergoing pharmacological treatments (e.g. fingolimod) 6 potentially interfering with cardiovascular function and may help to optimize physical activity prescription for PwMS, with important implications in terms of clinical outcomes.

The aims of this study were therefore to evaluate basal cardiac autonomic tone and its modulations during standing, continuous submaximal exercise and recovery and assess whether a relationship exists between autonomic modulation of HR and the perceived fatigue in PwMS without clinical overt AD.

Materials and Methods

Study design and participants

Our cross-sectional study conducted from January 1 2016 to July 30 2017 recruited Healthy Control (HC) subjects and PwMS from the hospital and ambulatory services of [masked]. The study involved PwMS meeting the following inclusion criteria: having a confirmed MS diagnosis (according to revised McDonald criteria)7, age>18 years, free from relapses or relapse-related treatments for three month before the study and from any medical conditions that could interfere with the autonomic cardiovascular control.
The study was conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committee of the Don Gnocchi Foundation. Each subject gave an informed consent to participate.

Experimental protocol

All subjects underwent clinical examination, including measurements of resting blood pressure and a standard 12-lead ECG. Co-morbidities, medications, disease severity and disease duration were documented.
Participants were asked to stop alcohol, coffee and smoking 2 hours before testing.
ECG was digitally acquired by a wearable sensor[1], in a clinical rehabilitation setting, during the following conditions: 1) baseline: 5 minutes, sitting at rest in a comfortable position; 2) standing: 2 minutes, using a hand support to maintain balance; 3) exercise: 4 minutes, performing submaximal upper limb cyclic aerobic exercise at 5-10 watt power, in sitting position4 using an arm ergometer2 ; 4) recovery: 2 minutes, sitting.

[1] Faros 180, Finland
[2] Monark 881E, Sweden

At the end of each experimental phase the rate of perceived exertion (RPE) was recorded using the Borg scoring system, ranging from 6 to 20, where 6 means 'no exertion at all' and 20 means 'maximal exertion'. This scale is validated for healthy individuals[8] and has also been used to assess exertion in PwMS.[9] In particular, participants were asked about the RPE of breath (Breath_RPE) and upper limb (UL_RPE) at the end of each experimental phase.

Outcome measures

ECG recorded signals were firstly visually inspected, in search for artifacts or premature beats, which were manually removed. HRV parameters were then calculated by Kubios HRV 2.2 software (Kuopio, Finland), using validated methods in the time and frequencies domains.[10]

Autonomic function was assessed as follows:

- The Root Mean Square of Successive Differences between consecutive beats (RMSSD, ms) and the percentage of consecutive beats differing>50 ms (pNN50, %) from each other were assessed as indexes of parasympathetic activity;[10] 10
- The High Frequency (0.15–0.4 Hz) band of heart rate power spectrum, expressed in absolute units (HF, ms2) was evaluated as an index of parasympathetic activity;[10]

- The Low Frequency (LF, 0,04-0,15 Hz) band, expressed in normalized units (LFnu = Total power/LF power) was used as an index of modulation of the sympathetic branch of the autonomic nervous system.[10]
- The Low to high frequency ratio (LF/HF) was calculated as a marker of the sympatho-vagal balance.[10]

Finally, the ECG derived respiratory frequency (EDR, Hz) was used to estimate the respiratory frequency.[11]

Statistical analysis

Descriptive statistics were provided on the demographic and baseline clinical variables in the entire sample and for each group separately and were used to detect the presence of outliers. Data were not normally distributed according to the Shapiro–Wilks test; thus, Box Cox

transformations were applied,[12] to improve the normality of the following transformed (t) variables: RMSSD, HF, pNN50, LFnu, LF/HF and EDR. T-test or Chi-squared test or Mann-Whitney U test were used when appropriate to detect differences between groups.
Repeated measures ANOVA and planned comparisons were used to determine differences between groups in different experimental conditions.
Spearman's correlation coefficients were computed between RMSSDt,, EDSS and disease duration at baseline and between RMSSDt and UL_RPE, EDR and Breath_RPE t during exercise in PwMS. All analyses were performed using Statistica software (ver. 9.0, Tulssa, USA) and the P level was set at 0.05.

Results

Demographic, clinical and baseline parameters
The study included a total of 43 subjects, i.e. 20 healthy control (HC) subjects and 23 PwMS. At the time of the study, 3 HC subjects were receiving anti-hypertensive drugs (other than ß-blockers, which could interfere with HRV analysis), 2 HC subjects were under pharmacological treatment for hypercholesterolemia and other 2 HC individuals were receiving thyroid medications (and were in documented euthyroidism); 7 PwMS were under disease modifying drugs, 1 subject was receiving anticonvulsant treatment and 1 subject was being treated with antidepressants.
None of the subjects was presenting clinical signs of overt AD (postural intolerance, tachycardia, etc.).
One HC subject was removed from the subsequent analysis as outlier, due to unstable hypertensive values of blood pressure at the baseline evaluation, and 1 subject with MS was removed from the analysis due to the presence of complex and frequent cardiac arrhythmias at the basal ECG recording. Descriptive demographic and clinical characteristics of the remaining enrolled subjects (n=41), along with the baseline values of HR and blood pressure are reported in Table 1. No statistically significant difference was found between HC and PwMS groups.

Table 1. Clinical and demographic characteristics of the samples (mean±SD).

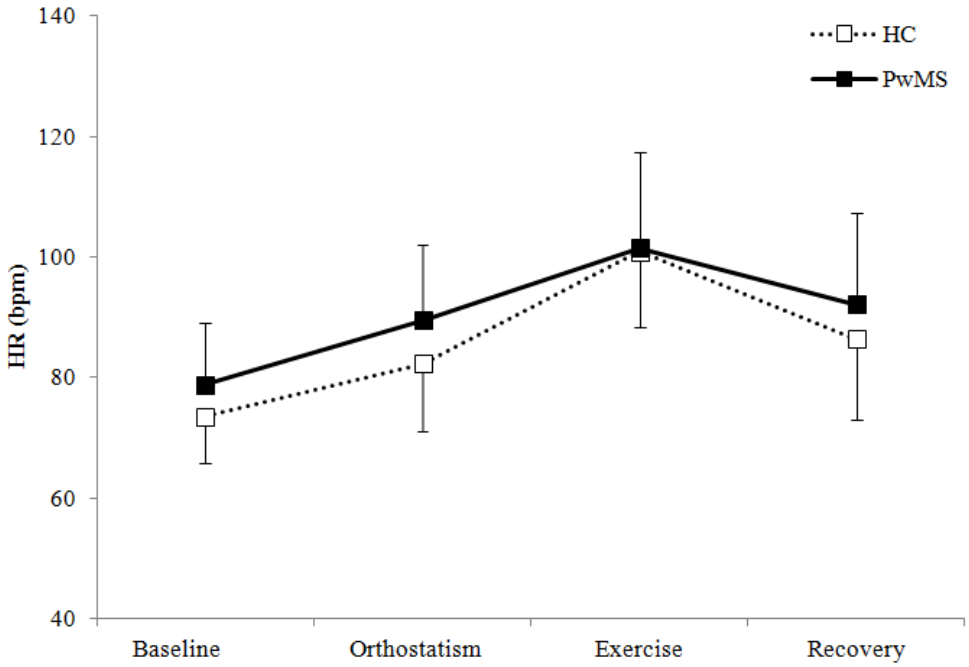
	HC (n=19)	PwMS (n=22)	P value
Age (years)	54.5 ± 7.9	55.4 ± 9.4	n.s.
Sex (F/tot)	14/19	14/22	n.s.
EDSS	/	5.7 ± 1.3	-
Disease duration (years)	/	15.1 ± 10.3	-
Mean resting HR (bpm)	73 ± 8	79 ± 10	n.s.
Systolic Blood Pressure (mmHg)	125 ± 16	118 ± 14	n.s.
Diastolic Blood Pressure (mmHg)	80 ± 11	80 ± 8	n.s.

EDSS: Expanded Disability Status Scale; HR: Heart Rate; HC: Healthy Control subjects; PwMS: People with Multiple Sclerosis; n.s.: not statistically significant.

HR and HRV assessment: comparing HC and PwMS

Figure 1 shows baseline HR values and HR responses to standing, exercise and recovery in both groups. Two-way repeated measure analysis of variance (ANOVA) reported slightly higher but not significantly different HR in PwMS in all experimental conditions (Group: $p=0.17$; Condition: $p<0.01$; Interaction: $p=0.29$).

Figure 1. Heart rate (mean ± SD) at baseline and during standing, exercise and recovery in Healthy Control subjects and in People with Multiple Sclerosis.



HR: Heart Rate; HC: Healthy Control subjects; PwMS: People with Multiple Sclerosis. Whiskers represent standard deviations.

Absolute values of HRV variables at baseline are reported in Table 2. Basal values of the parasympathetic indexes (RMSSD, pNN50 and HF power) were significantly lower ($p<0.01$ for all comparisons) in PwMS. Conversely, the indexes of sympathetic activity (LFnu), sympatho-vagal balance (LF/HF) and baseline EDR values did not differ between groups.

Table 2. Absolute values (mean±SD) of Heart Rate Variability parameters and ECG Derived Respiration estimate in Healthy Control subjects and in People with Multiple Sclerosis at baseline.

	HC (n=19)	PwMS (n=22)	P value
RMSSD (ms)	24.1 ± 9.6	17 ± 6.4	<0.01
pNN50 (%)	5.2 ± 5.0	1.2 ± 2.4	<0.01
HF (ms2)	222 ± 184	87 ± 81	<0.01
LFnu	69.7 ± 15.1	72.5 ± 16.1	n.s.
LF/HF	3.3 ± 2.4	4.0 ± 2.7	n.s.
EDR (Hz)	0.23 ± 0.1	0.23 ± 0.1	n.s.

RMSSD: Root Mean Squared Difference between adjacent R-R intervals; pNN50: percentage of normal beats differing for >50 ms from the preceding normal beat; HF: Absolute HF (High Frequency [0.15-0.40 Hz]) power of HR power spectrum; LFnu: LF (Low Frequency [0.04-0.15 Hz]) in normalized units; LF/HF: Ratio between LF and HF powers; EDR: ECG derived respiratory frequency (Hz); HC: Healthy Control subjects; PwMS: People with Multiple Sclerosis; n.s.: not statistically significant.

Table 3 shows the results of a 2-way repeated measures ANOVA on HRV transformed variables in each experimental condition with clinical conditions (HC, PwMS) as group factors and experimental conditions as repeated factors: significant overall interactions were found for RMSSDt, pNN50t and HFt.

Table 3. Two-way analysis of variance (ANOVA) for repeated measures on Heart Rate Variability (HRV) parameters and ECG Derived Respiration (EDR) estimate, with clinical conditions as levels and experimental conditions as factors. Significant values are reported in bold.

	Group	Condition	Interaction
RMSSDt	0.01	<0.01	0.01
pNN50t	<0.01	<0.01	0.01
LFnut	0.31	<0.01	0.67
HFt	0.02	<0.01	0.04
LF/HFt	0.36	<0.01	0.78
EDRt	0.50	<0.01	0.45

RMSSDt: transformed values of Root Mean Squared Difference between adjacent R-R intervals ; pNN50%t: transformed values of the percentage of normal beats differing for >50 ms from the preceding normal beat >50; HFt: transformed values of absolute HF power (High [0.15-0.40 Hz] Frequencies) of HR power spectrum; LFnut: transformed values of LF (Low [0.04-0.15 Hz] Frequencies) power in normalized units; LF/HFt: transformed values of ratio between LF and HF powers; EDRt: transformed values of ECG derived respiration.

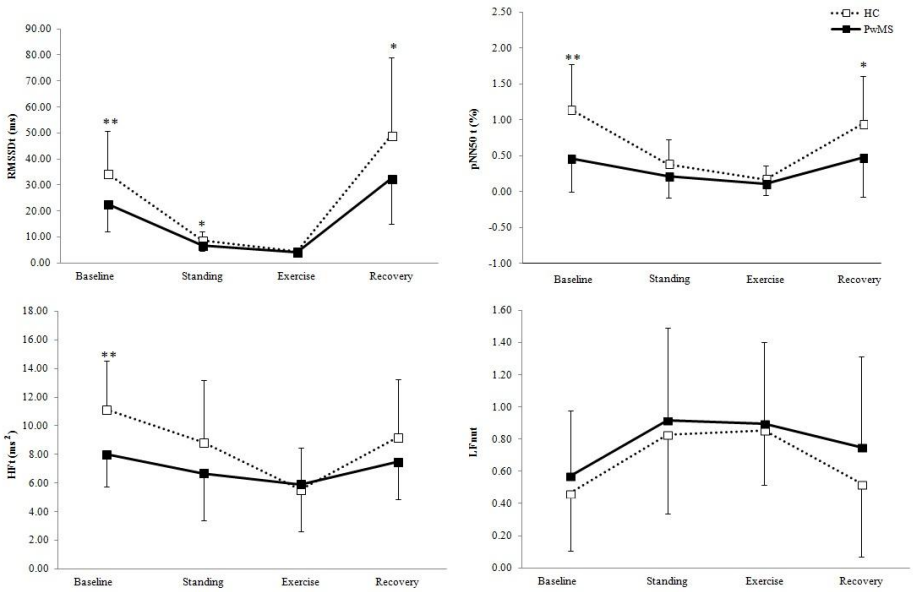
Figure 2 shows HRV transformed variables (RMSSDt, pNN50t, HFt, LFnut) in HC subjects and in PwMS at baseline and during standing, exercise and recovery. Basal values of the parasympathetic indexes (RMSSDt, pNN50t and HFt power) remained significantly lower (P<0.01 for all planned comparisons) in PwMS compared to HC, whereas the indexes of sympathetic activity (LFnut) were similar in both groups.

Surprisingly, during standing and exercise none of the HRV parameters significantly differed between PwMS and HC subjects, with the only exception of RMSSDt, which was significantly lower (P<0.05) in PwMS during standing only.

Similar to the baseline values, post-exercise recovery of the parasympathetic indexes RMSSDt and pNN50t were significantly lower

(p<0.05 for all comparisons) in PwMS with no differences between groups in LFnut.

Figure 2. Heart Rate Variability variables (m ± SD) in Healthy Control subjects and in People with Multiple Sclerosis at baseline and during standing, exercise and recovery.



RMSSDt: transformed values of Root Mean Squared Difference between adjacent R-R intervals; pNN50t: transformed values of the percentage of normal beats differing for >50 ms from the preceding normal beat; HFt: transformed values of absolute HF (High [0.15-0.40 Hz] Frequencies) power of HR power spectrum; LFnut: transformed values of LF (Low [0.04-0.15 Hz] Frequencies) power in normalized units. Whiskers represent standard deviations. *: P<0.05; **: P<0.01 between groups comparisons.

RPE assessment

Table 4 shows the results of UL_RPE and Breath_RPE measured in baseline, orthostatism, exercise and recovery for HC and PwMS. We found

statistically significant differences between groups in all conditions with the exception of Breath_RPE during the exercise.

Table 4. Rate of Perceived Exertion (mean ± SD) parameters related to upper limbs and breath in Healthy Control subjects and in People with Multiple Sclerosis in each condition.

	Score	HC	PwMS	P value
Baseline	UL_RPE	6.0 ± 0.0	7.4 ± 2.1	<0.01
	Breath_RPE	6.0 ± 0.2	7.1 ± 1.8	<0.01
Orthostatism	UL_RPE	6.4 ± 1.6	8.1 ± 2.5	<0.01
	Breath_RPE	6.0 ± 0.2	9.1 ± 2.9	<0.01
Exercise	UL_RPE	10.3 ± 3	14.5 ± 3.0	<0.05
	Breath_RPE	12.7 ± 2.8	11.6 ± 3.4	n.s.
Recovery	UL_RPE	8.4 ± 2.4	11.6 ± 3.1	<0.01
	Breath_RPE	7.4 ± 1.6	9.8 ± 2.7	<0.01

HC: Healthy Control subjects; PwMS: People with Multiple Sclerosis; UL_RPE: Rate of Perceived Exertion of Upper Limbs; Breath_RPE: Rate of Perceived Exertion of Breath; n.s.: not statistically significant.

Relationship between clinical features and HRV parameter in PwMS

No correlations were found between baseline RMSSDt and EDSS (r=0.23, p=0.30) nor between baseline RMSSDt and disease duration (r= -0.28, p=0.24). Similarly, no correlations were observed during exercise between

RMSSDt and UL_RPE (r=0.02, p=0.91) nor EDRt and Breath_RPE (r= -0.03, p=0.87).

Discussion

The main findings of our study are the following: 1) basal HR and its modulation during submaximal exercise and postural challenges did not differ between PwMS and HC subjects, although it tended to be higher in PwMS; 2) the parasympathetic cardiac autonomic tone appears to be affected at rest and during post-exercise recovery in PwMS, though in absence of clinical signs of overt AD; 3) although the upper limbs and breath perceived fatigue were significantly higher in PwMS in almost all conditions, no correlation was found between parasympathetic modulations of HR and fatigue during exercise.

HR data showed slightly higher but not significantly different values (about 5-10 bpm, on average) in PwMS in comparison to HC in all experimental conditions. We chose a submaximal exercise, along with the postural challenges of the sit-to-stand movement, because it mimics the usual exertion observed in everyday activities (light house works, stair climbing, rising from a chair, using the wheelchair, etc.). Higher HR values during submaximal efforts may suggest a reduced efficiency of cardiac pump in adapting cardiac output to a required task and are generally due to the cardiovascular deconditioning, which is known to affect PwMS. Since cardiac autonomic dysfunction was observed in this study in resting and recovery conditions only, it is unlikely that it could have affected the cardiovascular response to exercise and postural changes. Our data seems therefore to confirm what was found by Feltham, who demonstrated that the submaximal adaptation of HR to exercise is more affected by deconditioning rather than by autonomic dysfunction in PwMS.[13]

At baseline, we found lower values of the parasympathetic indexes in PwMS compared to HC subjects, whereas the indexes of sympathetic and sympatho-vagal balance did not differ between groups: this suggests a subclinical impairment of the cardio-vagal system in long lasting PwMS,

confirming previously published results.[14,15,16,17] The appraisal of existing literature and our results suggest that subclinical AD involvement may vary during the course of the disease, at the beginning involving the sympathetic system and chronically evolving in a prevalent parasympathetic deficiency. The lack of correlation between the vagal indexes and the EDSS score, in accordance with the results by Videira,[18] suggests that parasympathetic AD in PwMS is more related to disease duration rather than to disability.

Interestingly, during orthostatic challenge and exercise, the difference in parasympathetic indexes of HRV between PwMS and controls completely disappeared. During sit-to-stand transition and during exercise the cardio-vagal system needs to be inhibited, in order to sustain the necessary increase in HR. Therefore, the capacity of inhibition of the vagal tone in PwMS seems to be preserved. It is noteworthy that, although not significantly, the sympathetic activation due to postural change and exercise, as reported by the HRV index LFnu, showed a trend towards an increase in each condition in PwMS with respect to HC subjects (Figure 4). Further studies are needed to infer whether a compensatory increase in the tone of sympathetic system occurred in our PwMS. However, Heesen et al. did not find any difference in norepinephrine concentration during exercise in PwMS.[19]

The reduced post-exercise HR recovery is currently considered a cardiovascular risk factor: our data suggests a blunted post-exercise HR recovery in PwMS (although not significant compared to HC), this impaired recovery is probably not linked to impairment in HR adaptation to exercise since both groups reached similar values of HR at the end of the exercise (about 100 bpm), but it seems more associated with an impaired recovery of parasympathetic indexes in PwMS, as demonstrated by the significantly reduced values of RMSSD and pNN50. A different HR adaptation during the first 2 minutes of post-exercise recovery has been observed in PwMS also by Collett and coworkers,[20] especially after a sub-maximal effort (45% of Watt peak), like the one used in our study. This is of particular clinical relevance, considering the high number of submaximal efforts required by everyday life activities (e.g. orthostatic challenges, light manual works etc.), which may enhance fatigue accumulation in PwMS.

Finally, upper limb fatigue perception was significantly higher in PwMS in all experimental conditions. However, the lack of relationship during exercise between the autonomic parameters and perceived fatigue may suggest that fatigue is due to central factors more than cardiovascular activation. These results agree with those of Merkelbach et al., who found no relationship between fatigue perception and autonomic function.[21]
Similarly, the perception of respiratory fatigue differed between groups in all conditions except exercise, although the respiratory frequency both at rest and during orthostatic and exercise challenge, as estimated by EDR, was similar between groups. This deserves further examination of pulmonary function adaptation to exercise in PwMS.

Finally, we acknowledge some limitations of our study. Firstly, the relatively small number of participants makes it difficult to generalize results. Secondly, the period of post-exercise analysis was very short, and therefore was not suitable to study long-term adaptation of HR or a possible carry-over effect of fatigue on cardiovascular recovery. Thirdly, the HRV method to investigate the autonomic control of HR does not represent the gold standard in evaluating the sympathetic tone, which is based on the micro-neurographic assessment of the peripheral autonomic nervous traffic. However, some parameters as LFnu and LF/HF are known to change when the interplay between parasympathetic and sympathetic system changes, therefore producing an estimate of the relative activation of the adrenergic system.
Fourthly, no typical clinical testing of AD was performed on our patients, as these data was already reported in each clinical record. Finally, no plasma catecholamine concentration measure was performed in this study.

Conclusions

To the best of our knowledge, this is the first study integrating basal and functional measures of cardiac autonomic tone to evaluate the presence of subclinical AD in PwMS and evaluating how this may have an impact on cardiovascular responses to everyday life activities, as light exercise and

postural challenges. Parasympathetic basal tone and post-exercise reactivation appear to be impaired in PwMS, but HR modulation during postural challenge and exercise seems to be preserved. Furthermore, subclinical AD doesn't seem to affect perceived fatigue.

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Chapter 2

EFFFECT OF NEUROREHABILITATION ON FATIGUE AND UPPER LIMB PERFORMANCE IN MULTIPLE SCLEROSIS: RANDOMIZED CROSS-OVER STUDY

Abstract

Background. People with multiple sclerosis (PwMS) exhibit fatigue and sensory-motor upper limb impairments even in the early stages of the disease. Rehabilitation is a viable way to reduce fatigue and sensory-motor impairments.
Objective. We designed an experimental rehabilitation protocol which combines aerobic training and task oriented exercises aimed to reduce fatigue and improve upper limb function.
Study Design. Randomized Crossover Study
Methods. Twenty PwMS received 20 treatment sessions lasting one our comprising of 30min of Aerobic Training and 30min of Task-oriented exercises for upper limbs. Fatigue was measured by Modified Fatigue Impact Scale (MFIS) and Rate of finger tapping at Maximum velocity during a fatiguing task (RATE-MV). Manual dexterity was measured with Nine Hole Peg Test (NHPT). The differences between treatment effects was assessed by a standard T-test, for continuous variables and Mann Whitney Test (MW) for independent samples using the intra-individual differences between the outcomes at the end of both periods as dependent variables. We checked for carryover effects summing up the values measured at the end of both periods for each subject and comparing the two groups by means of another T or MW test.
Results. After protocol subjects showed a statistically significant reduction ($p<0.05$) in MFIS (-5 points) and RATE-MV (+0.17 HZ) without any carryover effect (respectively, $p=0.63$ and $p=0.86$). Manual dexterity (NHPT) showed no statistically significant treatment effect (+3.6s, $p=0.63$) after the rehabilitation period without any carryover effect ($p=0.67$).
Conclusion. A combined aerobic and task oriented training positively reduces fatigue without improving manual dexterity. This suggests to clinicians a beneficial role of rehabilitation on fatigue on upper limb but tailored and more intensive interventions are needed to reduce manual dexterity disorders.

Introduction

Multiple Sclerosis (MS) is a neurodegenerative, demyelinating disease that affects mostly young and middle-aged people. The multiplicity of physical and psychological dysfunctions has been shown to exhibit a high number of impairments such as fatigue, weakness, alteration of upper extremity and lower fine motor coordination, affecting activities of daily life and participation.[1, 2]

Approximately 70-90% of People with Multiple Sclerosis (PwMS) experience fatigue defined as a "subjective lack of mental or physical energy as perceived by the individual (or caregiver) to interfere with usual or desired activities".[3] Moreover, approximately 70% of PwMS exhibit sensory-motor upper limb impairments such as reduced manual dexterity and sensitivity, muscle weakness, slowness of movements and tremor involving either one or both limbs even in the early stages of the disease.[4,5]

Rehabilitation is a viable way to reduce fatigue and sensory-motor impairments. Studies on rehabilitation interventions and exercise therapy have proven to be safe and effective to reduce fatigue, with potential effects on cardiorespiratory fitness, promoting brain plasticity in PwMS.[6] Aerobic exercise may reduce the effects of deconditioning increasing physical fitness, general health lowering the incidence of comorbidity[7] and it may positively affect neuroprotection, normalize hypothalamic-pituitary-adrenal axis imbalances, and reduce inflammation.[8] In addition, it has been recently suggested that aerobic exercise can be used as a priming technique to enhance cortical activation promoting motor relearning.[9] It has been reported that a single bout of aerobic exercise on brain function improves functional connectivity[10,11] enhancing the ability to learn and that these positive effects can persist after 30 minutes after the exercise suggesting that physical activity could promote brain plasticity in healthy subjects in motor and non-motor areas.[12]

Priming the motor system before rehabilitation to improve upper limb function has been supported by Stinear in stroke population.[13] However, the use of these strategies to prime the motor system is under explored in

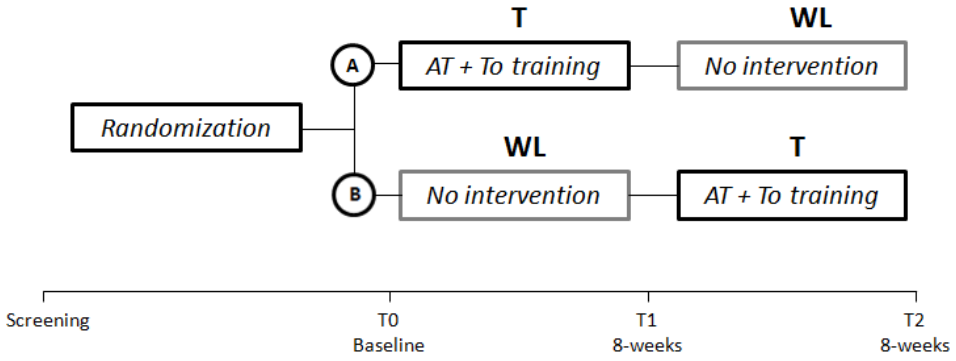
PwMS since it is well known that aerobic training can have beneficial effect on cognition and brain function in this population.[14]
Aerobic exercise can be used in rehabilitation to reduce fatigue and to prime the brain and to warm up upper limbs by performing task oriented exercises. However, the combination of aerobic training and upper functional exercises has not yet been explored. Recently, a review reported that motor rehabilitation can have a small but clinically relevant impact on upper limb function.[15] Further, it has been demonstrated that task-oriented exercises seem to be more efficient than passive mobilization preserving white matter microstructure and potentially induce a slight improvement in the activation of areas in the brain.[16]
Despite current evidences supporting the positive effects of aerobic training, no studies have investigated the impact of a combination of aerobic and task-oriented exercises to boost the effect of upper limb rehabilitation in disable PwMS. Thus, in the present crossover study we designed a 8-weeks experimental rehabilitation protocol which combines aerobic training and task oriented exercises aimed to reduce fatigue and improve upper limb function.

Materials and method

Study design and Participants
Our cross-over study included a total of 22 People with Multiple Sclerosis (PwMS). The eligible population included all PwMS residing in the centers' catchment areas requiring rehabilitation. We recruited PwMS meeting the following inclusion criteria: having a confirmed MS diagnosis (by a neurologist), age >18 years old, free from relapses or relapse-related treatments for three month before the study, Expanded Disability Status Scale (EDSS) > 8. We excluded individuals unable to follow test instructions (e.g. with cognitive impairment or language barrier), having other diseases interfering with the execution of tests (e.g. psychiatric or orthopedic disorders), or affected by cardiovascular diseases.
The study was approved by the Ethics Committee of the Don Gnocchi Foundation and each subject gave the informed consent to participate.

Subjects who met all the eligibility criteria underwent study assessment and were randomly assigned in a 1:1 ratio to counterbalanced groups (group A and B) by computer-generated random numbers. In agreement with a previous study on rehabilitation in MS[17] Group A started a 8-week period of rehabilitation (intervention period, T), followed by a 8-week period without any intervention or specific training (waiting list period, WL). Group B was given the treatment in reverse order. (Figure 1)

Figure 1: Flow chart shows the study protocol



AT: Aerobic Training; To: Task-oriented training; T0: baseline assessment; T1: assessment after 8 weeks; T2: assessment after 8 weeks; T: Treatment period; WL: Waiting list period.

Assessment procedures

Participants were assessed with clinical evaluation at baseline (T0), at the end of the first 8-week period (T1) and at the end of the 8-week period (T2). (Figure 1)

Each assessment was performed by a blind physical therapist.

Clinical assessment

Fatigue

Modified Fatigue Impact Scale (MFIS) is our primary outcome. Trait fatigue has been defined as a more stable state in an individual that is not likely to change over time[18] measured by Modified Fatigue Impact Scale (MFIS) that is a structured, self-report questionnaire designed to assess physical and mental fatigue. This tool contains 21 items, which were scored from 0 (never) to 4 (almost always), thus ranging from 0 (indicates no fatigue) to 84 (indicates higher fatigue).[19]

To understand whether a reduction in reported fatigue is accompanied with a reduction of motor fatigue we assessed finger movement rate in a fatiguing task. The assessment was performed using an engineered glove[3] to quantify finger motor performance accuracy; this simple and objective method has been recently demonstrated to be able to discriminate healthy controls and PwMS even with very low disability.[20] Specifically, subjects were asked to perform with their eyes closed repetitive finger opposition movements of thumb to index, medium, ring and little fingers, with the affected hand at their maximal velocity. From the raw data recorded by the glove system, the movement rate [Hz] at maximum velocity (RATE-MV) has been extracted.

Upper limb function

Our primary outcome for manual dexterity was measured with the Nine Hole Peg Test (NHPT).[21]

Secondary outcomes:

Heart rate (HR) was used to assess the physiological aspects and adaptations related to the effort. HR was monitored at the end of arm ergometer exercise (HR). Participants performed 4 minutes of submaximal exercise at 10w intensity. Exercise was performed in sitting position using an arm ergometer[4]. State fatigue that is defined as a transient condition which can change with time and can fluctuate based on internal and

[3] Peregrine ETT

[4] Monark 881E

external factor.18 The Borg scale was used to monitor the rate of perceived exertion (RPE) during the exercise testing. RPE is defined as subjective effort intensity and fatigue during physical exercise. RPE of breath (Breath_RPE) and upper limb (UL_RPE) were monitored at rest (baseline) and at the end of the submaximal exercise. The Borg Scale ranges from 6 to 20, where 6 means "no exertion at all" and 20 means "maximal exertion".[22]
The Action Research Arm Test (ARAT) was performed to rate individual ability to grasp and lift objects of various sizes. It consists of 19 items organized into Grasp, Grip, Pinch and Gross Motor subsections. The Score ranges from 0 (bad upper limb function) to 57 (normal upper limb function).[21]
Maximal isometric handgrip strength was measured in Newton using an hand-held CITEC5 digital dynamometer. [21]

Hospital Anxiety and Depression Scale (HADS) is a 14-item tool to measure the anxiety (7 items) and depression (7 items). A higher score represents higher levels of anxiety and depression: a domain score of 11or greater indicates anxiety or depression and 7 or lower indicates no signs of anxiety or depression.[23]

Intervention
PwMS received 15-20 one hour treatment sessions comprising of 30min of Aerobic Training and 30min of Task-oriented rehabilitation for upper limbs.
Aerobic Training was performed in sitting position using an arm ergometer following the recommendations for PwMS in which subjects were encouraged to maintain an intensity of 11 and 12 points of RPE during aerobic exercise.[24]
Task-oriented training comprised an active protocol based on voluntary unimanual and bimanual exercises for neuromuscular control to improve proprioceptive sensibility, muscle strength, stability and coordination of the upper limbs, mainly including task-oriented exercises with the goal to improve activities of daily living.[25] The treatment dealt with such as manipulating and grasping wooden cubes or balls of different sizes,

[5] http://www.citec.nu/frm/uk.htm.

pinching objects with unimanual and bimanual exercises (e.g. grab a bottle, fill a glass of water, hang out clothes).

Statistical analysis

Descriptive statistics were provided on the demographic and clinical variables in the entire sample and for each group separately. Means (with standard deviations), medians (with interquartile ranges, IQR) and Percentage were used as appropriate. Parametric and non parametric tests were used to assess baseline differences between Group A and Group B.

We checked for data distribution and logarithmic transformation was used for the NHPT to get normal distribution. Then the analysis of covariance was used to check statistically significant between group differences taking into account baseline values and depression (HADS) at T0. Since these two confounders were not statistically associated with the outcome we used a more parsimonious model as described in Wellek et al.[26] In short the differences between treatment effects was assessed by a standard T-test, for continuous variables and Mann Whitney Test (MW) for independent samples using the intra-individual differences between the outcomes at the end of both periods (T1 and T2) as dependent variables. Similarly, we checked for carryover effects summing up the values measured at the end of both periods for each subject and comparing the two groups by means of another T or MW test.

An intention to treat approach was used and drop outs were excluded from the analysis. All analyses were performed using Statistica software and the p-level was set at 0.05.

Results

Overall, 22 participants were recruited and were randomized in two groups: Group A and Group B (Figure 2). Two people in the Group B dropped out during the execution of the study: one due to a relapse and one for lack of motivation to participate. The baseline characteristics of the participants were reported in Table 1 depicting a sample with moderate to

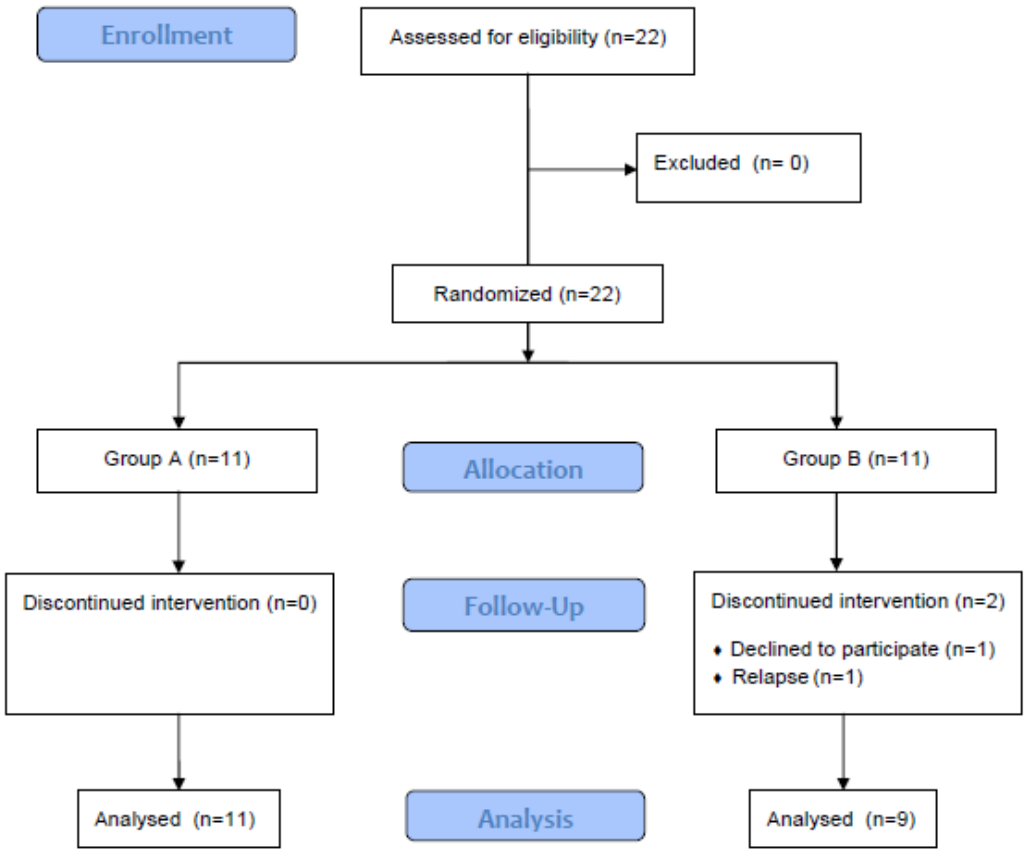
severe mobility impairments. No baseline significant statistically differences were found between Group A and B.

Table 1: Baseline clinical and demographic characteristics of the sample

	Total sample (n=22)	Group A (n=11)	Group B (n=11)	P value
Age (years)	56.7 ± 9.8	54.5 ± 7.9	55.8 ± 9.2	0.7
Female (n, %)	14, 63%	6, 54%	8, 73%	0.37¥
EDSSł (score)	6 (2)	6.5 (0.75)	6 (1.5)	0.37
Disease duration (years)	20.27 ± 10.7	18.18 ± 6.57	22.36 ± 13.7	0.23
Dominant hand (R/L)	21/1	11/0	10/1	0.26¥
Affected hand (R/L)	12/10	5/6	7/4	0.19¥
HADS ł (points)	8.5 (6)	10 (9.5)	8 (3.5)	0.30

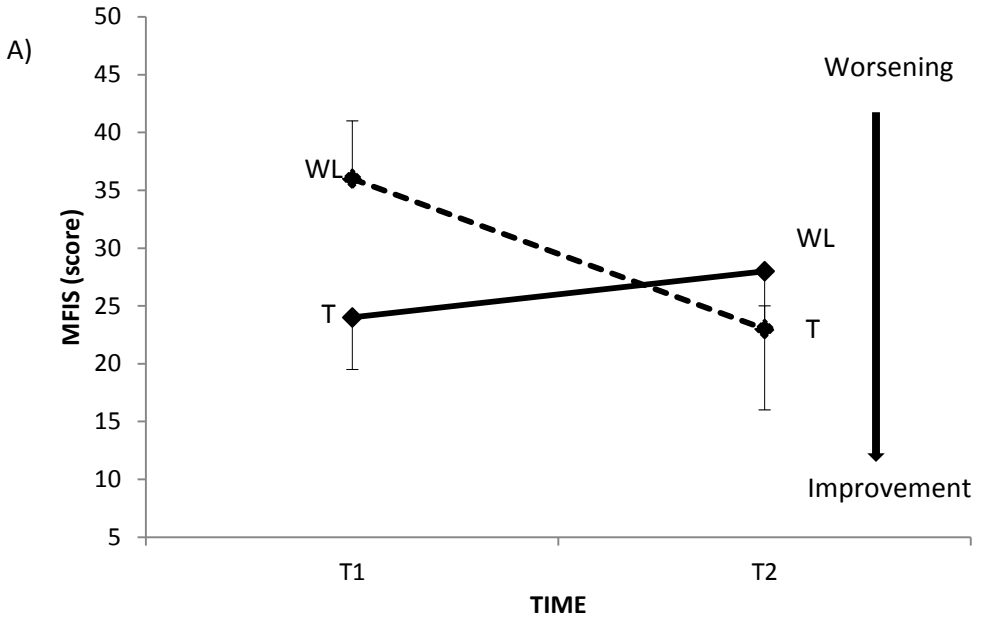
Note. Unless otherwise indicated, values are means ± standard deviation ł Data are medians (Interquartile range), ¥Chi-Square test.
EDSS: Expanded Disability Status Scale; R: right; L: left; HADS: Hospital Anxiety Depression Scale

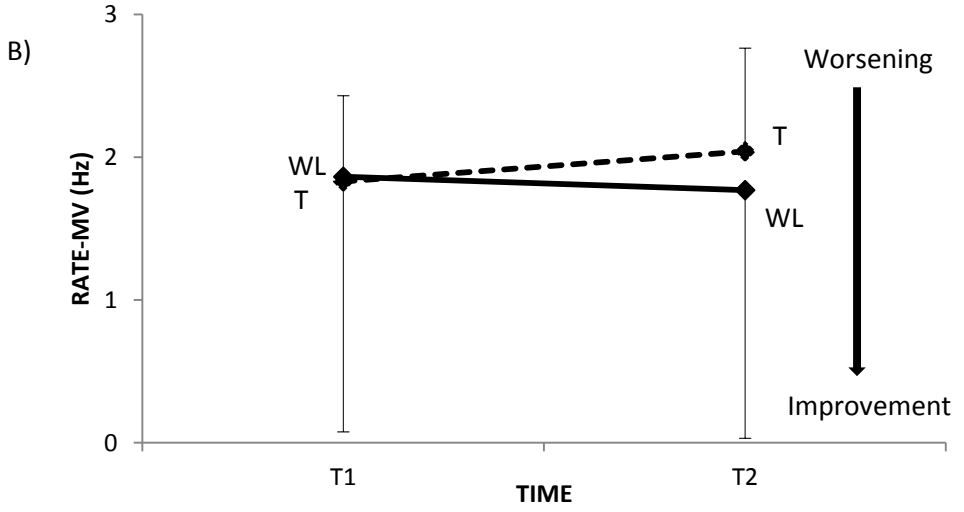
Figure 2: Consort flow chart of the study and subject selection



Analysis of our primary outcome for fatigue (MFIS, Figure 3A) shows a statistically significant treatment effect (p=0.05) after the rehabilitation periods without any carry over effect (p=0.63). MFIS was lower after the treatment periods (T) compared to the WL periods (WL) with a median (IQR) MFIS between periods (WL –T) difference of 5.15 (10.67) points.
The second primary outcome for fatigue (Rate-MV, Figure 3B) shows a statistically significant treatment effect (p=0.05) after the rehabilitation period without any carry over effect (p=0.86). Rate-MV was higher after the treatment periods (T) compared to the waiting list periods (WL) with a mean (SD) Rate-MV between periods (WL –T) difference of 0.15 (0.36) Hz.

Figure 3: Effect of rehabilitation on Fatigue

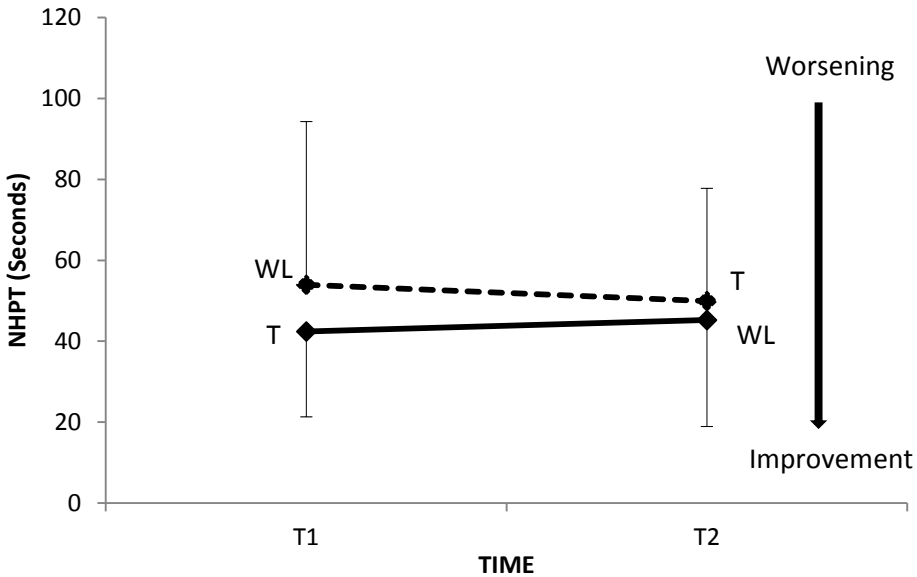




MFIS: Modified Fatigue Impact Scale; RATE- MV: Rate at maximum velocity; T1: assessment after 8 weeks from T0; T2: assessment after 8 weeks from T1; Group A: T-WL; Group B: WL-T

The analysis of the first primary outcome for manual dexterity (NHPT, Figure 4) shows no statistically significant treatment effect (p=0.63) after the rehabilitation period without any carry over effect (p=0.67) with a mean (SD) between periods (WL –T) difference of 3.58 (25.02) seconds.

Figure 4: Effect of rehabilitation on manual dexterity



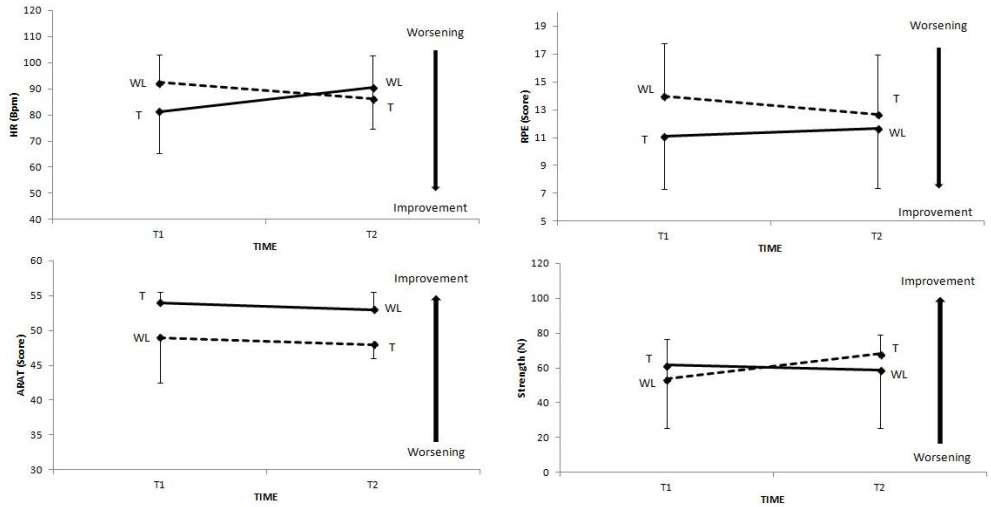
NHPT: Nine Hole Peg Test; T1: assessment after 8 weeks from T0; T2: assessment after 8 weeks from T1; Group A: T-WL; Group B: WL-T

The analysis of the first primary outcome for manual dexterity (NHPT, Figure 4) shows no statistically significant treatment effect (p=0.63) after

the rehabilitation period without any carry over effect (p=0.67) with a mean (SD) between periods (WL –T) difference of 3.58 (25.02) seconds.

Finally, Figure 5 reports the results for the remaining secondary outcomes for fatigue and manual dexterity. No statistically between group differences (P>0.05) were found at the end of the T and WL periods.

Figure 5: Effect of rehabilitation on secondary outcomes



ARAT: Action Reaching Arm Test; HR: Heart Rate; RPE: Rate of Perceived Exertion; T1: assessment after 8 weeks from T0; T2: assessment after 8 weeks from T1; Group A: T-WL; Group B: WL-T

Discussion

The present crossover study aimed to investigate the effect of a combination of aerobic and task oriented exercises on improving fatigue and upper limb function. Our main result is that eight weeks of exercise reduces subjective fatigue and increases fingers movement rate. Conversely, we found any improvement in upper limbs strength and

dexterity indicating that a more effective treatment for upper limbs function is needed.

Several studies have investigated the effect of rehabilitation on fatigue[6] and on upper limb function[15], however, no studies investigated the effects of combined treatments on fatigue and functional interventions. Our hypothesis was the use of combining treatments could be a new viable way to optimize well know effects of separated treatments, specifically the role of aerobic training as priming before functional rehabilitation. The comparison of our results with other published reports is difficult due to the lack of studies combining fatigue and task oriented exercises therefore, in the following paragraphs, we compare our findings with previous studies treating separately fatigue and upper limb function.

Fatigue was present in our sample having a median MFIS baseline score of 32 out of 84 points. At the end of the treatment we observed a median change score of 5 points with 70% of PwMS in the treatment phase and 30% of PwMS in the waiting list phase that reduce fatigue after rehabilitation. 30% of PwMS in the treatment phase and 10% of PwMS in the waiting list phase have reached the cut-off score of 10 points defined by Kos et al. as a clinically relevant improvement.[19] Other studies reporting the effects of rehabilitation on fatigue have shown heterogeneous results. Rampello et al.[27] and Petajan et al.[28] failed to demonstrate a change in this outcome. Conversely, in line with our results, Surakka et al. found that aerobic 6-months period comprising aerobic and strength exercises can reduce motor fatigue in PwMS.[29] Similarly, Heine et al. found a reduced but not clinically relevant fatigue measured by the Check Individual Strength Fatigue after a rehabilitation period of 8 weeks of aerobic training with any impact on social participation.[7]

The reduction in subjective fatigue was accompanied with improvement in the ability to sustain long motor task. Finger movement opposition rate at maximal velocity significantly increased (+0.17 Hz) in all patients meaning that the time to pass from a finger to the next one decreased from 610 to 590 milliseconds. This result is in agreement with the previous study by Bonzano et al. in which movement frequency increased of 0.2 Hz after

rehabilitation in the same assessment.[16] This improvement to perform higher number of movements suggests that PwMS were less deconditioned and more coordinated after rehabilitation, better sustaining long motor task at maximum velocity.
The beneficial role of rehabilitation on reducing fatigue has been already known to be important on improving deconditioning, on reducing secondary health risks and potentially disease progression.6 Moreover a higher velocity in an endurance fingers tasks can imply less fatigue in PwMS in everyday repetitive hand activities such as writing[30] or using a mobile phone.[31]
Although not statistically significant both Rate of Perceived Exertion (P=0.12) and Heart Rate (P=0.22) showed a trend towards improvements. Half of the sample showed 10 beats per minute reduction right after the end of the exercise while only 15% of the sample showed similar improvement after the waiting list period suggesting that the change in general fatigue (MFIS) is associated to better cardiovascular health after exercise, as it has known that lower heart rate decreases risk for coronary artery disease and sudden death.[32]
Our results are in line with previous studies.[27,33, 34] Specifically, Skjerbaek reported that upper body exercise is tolerable for disable people with MS and an improvement on maximal oxygen consumption is associated with an improved health, increased physical activity and a lower disability level in MS.[34]

With respect to our first primary outcome for manual dexterity, we found no changes in NHPT (Figure 4) after rehabilitation. Our results are in contrast with those of two previously published studies on upper limb rehabilitation.[16,35] Carpinella et al. found an intervention involving robot rehabilitation led to 13 seconds improvement in the execution of the NHPT[35] while Bonzano et al. found both task-oriented rehabilitation and passive rehabilitation resulted in 4 seconds improvement.[16] Lack of functional improvements in proximal and distal components of the upper limb was confirmed by results from ARAT and hand grip test measuring whole arm function and hand strength. These results are in line with previous studies[16, 35, 36] showing small and not statistically significant improvement in ARAT and hand grip test[37,38,39] after rehabilitation.

One of the reason for the lack of effect is that the intervention was not intensive enough to improve manual dexterity and function. The frequency and the intensity of training reported in the studies by Carpinella et al. and Bonzano et al. ranged from 3 to 5 days per week with a duration of the training sessions ranging from 45 to 60 minutes. This is supported by a review reporting a more intensive therapy (>15 hours) can improve recovery in activities of daily living in people with stroke.[40,41] It is possible that in our study subjects received a too small amount of practice to improve manual dexterity, this issue should be closely considered when planning combined therapies because this may lead to unsatisfactory outcomes. A second reason is that more disabled PwMS may have been excessively fatigued after the aerobic training interfering with the task oriented training. Thus, the effects of fatigue on functional recovery should be carefully considered when planning tailored intervention.

Study limitations

We finally acknowledge some limitations of our study. Firstly, the small sample size may have affected the generalizability of the results and reduced the power of the study. Secondly, there was no "washout" between treatments, although we did not find statistically significant carry-over effects a larger sample size may reveal bias in the analysis since treatment performed in one period may have a residual effect that persists into the subsequent period. Thirdly, patients with a higher level of fatigue need to be considered in further studies in order to better describe the impact of rehabilitation in a more fatigued population.

Conclusion

The present study reports that a combined aerobic and task oriented training positively reduces fatigue without improving manual dexterity and strength. This suggests to clinicians a beneficial role of rehabilitation on fatigue on upper limb but tailored and more intensive interventions are needed to reduce manual dexterity disorders.

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Chapter 3

INTENSIVE MULTIMODAL TRAINING FOR PERSONS WITH MULTIPLE SCLEROSIS: RANDOMIZED CONTROLLED TRIAL

Abstract

Persons with multiple sclerosis (MS) have deficits in many aspects of physical and cognitive functioning that can impact on mobility and participation in daily life. The effect of a 4-week intensive multimodal treadmill training on functional mobility, balance, executive function and participation in persons with MS with moderate to severe disability was investigated.

Methods. Thirty-eight persons with MS recovered for rehabilitation participated in a two-arm randomized 2:1 controlled trial. Participants in the experimental group received supervised dual task treadmill training (DT-group), 4-5 sessions per week and a control group received the same amount of supervised resistance training (R-group). The participants were assessed before and after the rehabilitation period with the 2 Minutes Walking Test (2MWT), static and dynamic balance measures, the Frontal Assessment Battery and the Short Form-12 questionnaire. A logistic regression was used to test the main hypothesis related to the superiority of the treadmill intervention based on a greater proportion of people making a clinically relevant gain (15% increase on 2MWT) in gait resistance following treatment. ANCOVA (Analysis of covariance) models adjusting for baseline measurement of the respective outcome variable, as well as sex, age and EDSS, were used to evaluate differences in efficacy for all variables. P was set at 0.05.

Results. Being in the DT-group was highly predictive (OR 0.0017 (0.0017 to 0.4154), $p<0.001$) of having a clinical improvement underscoring the efficacy of the intervention. The DT-group improved more in gait resistance, speed and mobility ($P< 0.05$). Factors to do with static and dynamic balance instead improved moderately in both groups following training while executive control and perception of health remained similar in both groups.

Conclusion. A four to five week aerobic and multimodal training was more effective in augmenting gait resistance and mobility in moderately to severely affected persons with MS than resistance training.

Introduction

Persons with multiple sclerosis (MS) can have various deficits, affecting many aspects of physical and cognitive functioning, frequently leading to low levels of physical activity in daily life which further impacts on mobility difficulties through deconditioning of muscles and reduced cardiorespiratory fitness.[1,2,3] Physical inactivity, is particularly common in persons with MS with moderate to severe walking disability and can be due to many factors, such as, inability to maintain steady gait, balance deficits, inability to adapt to environmental demands, fatigue, as well as, cognitive factors.[4] Physical activity, in terms of mobility, requires a balance between various interacting systems, locomotion, balance and the central nervous system (CNS) as the coordinating part, where, in particular, executive functions of the frontal cortex appear to be important for mobility.[5] In fact, persons with moderate and severe MS disability often have difficulty walking while simultaneously doing motor or cognitive tasks leading to a higher risk of falls during everyday activities.[6]

There are some indications in the literature that aerobic and strengthening exercises can change aspects of physical and cognitive performance of PwMS, with a potentially bigger benefit associated with supervised exercise training.[7, 8, 9, 10, 11]
In particular it is suggested that high-intensity repetitive task-specific practice may be an effective principle when trying to promote motor recovery in neurological diseases.[12] For elderly multimodal interventional strategies have been suggested to promote secure mobility by improving attention, dual task performance and executive functions.[13] In spite of various studies suggesting a multimodal approach to rehabilitation to increase its general effect and augment physical activity, the effect of intense mobility rehabilitation paradigms including additive cognitive tasks has not been investigated in the MS population. However, there are preliminary indications that 20 minutes of treadmill training can momentarily influence cognitive aspects such as executive control.[14]
Given the importance of exercise and physical activity for persons with multiple sclerosis that are already moderately to severely hampered by their locomotor ability and balance, the setting up of intense functional

mobility training that targets the main deficits and under close supervision, may be a viable way of increasing the level of physiological health and give a basis for the persons to start their own activity pursuit outside of the rehabilitation clinic. Treadmill walking has several benefits for mobility rehabilitation. First, it is an everyday task, walking. Second it lends itself well to a dual task paradigm where other aspects of mobility, such as equilibrium and cognitive factors can be addressed during walking. Third, even persons with severe walking limitations can train walking at various speeds when on treadmill, holding onto handrails and using safety harnesses that minimizes the possibility of adverse events during training. Further, the treadmill paradigm lends itself well to training with progressive task difficulty, numerous rhythmic repetitions, and importantly it can include an aerobic component to improve cardiorespiratory fitness. All of which should lead to improved submaximal exercise tolerance and endurance, more functional mobility and consequently increased ability to carry out activities of daily living.

The aim of this study was to evaluate the safety, feasibility and preliminary effects of a high-intensity rehabilitative multimodal training protocol carried out on treadmill on walking efficacy, mobility, balance, executive function and health-related quality of life in a sample of persons with moderate to severe MS mobility compared it to a control group that received a strengthening program of similar intensity.

Methods

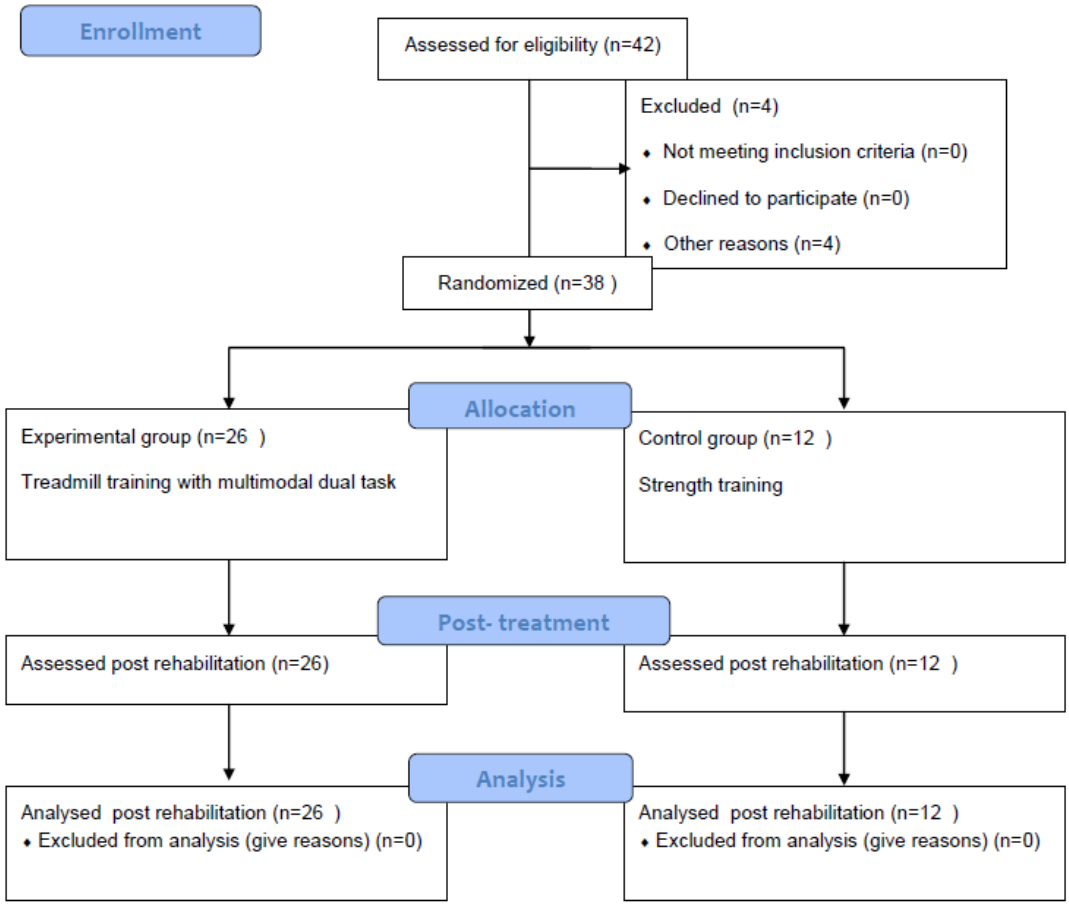
A consecutive sample of 42 People with Multiple Sclerosis (PwMS) was recruited from the inpatient rehabilitation service of the Don Gnocchi Foundation. Subjects were included in this study if they met the following inclusion criteria: diagnosis of multiple sclerosis according to McDonald's criteria,[15] EDSS score ≤ 7, free from relapses and steroid treatment for at least 3 months) able to stand 30 seconds, able to walk at least 10 meters independently or with a cane, aged between 18 and 80 years, able to understand and follow instructions, stable neurological conditions and willingness to participate in the study. Subjects were excluded if they had a cardiac pacemaker, any heart condition that their medical doctor

considered risky for intense aerobic activity, any pre-existing conditions that affected walking function, diagnosis of depression or psychotic disorder.
The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Don Gnocchi Foundation. Subjects signed an informed consent form before the beginning of the study.

Experimental Procedures
The study design is a two arm randomized 2:1 controlled trial (see study flow chart in Figure 1).

The participants were assessed before and after the rehabilitation period by researchers blinded to group assignment. Primary outcome measures were 2 Minutes Walking Test (2MWT),[16] Timed Up and Go (TUG),[17] and Frontal Assessment Battery (FAB).[18]
The secondary outcome measures were: Berg Balance Scale (BBS),[19] 10 Meter Walking Test (10MWT),[20] Dynamic Gait Index (DGI),[21] Short Form-12 questionnaire (SF-12).[22]

Figure 1: Flow chart of the study



Randomization

Patients were consecutively randomized to the experimental or control group in a 2:1 ratio, using a computerized automated algorithm. To ensure a concealed allocation randomization was done after determining eligibility.

Intervention protocols

Participants in both groups received 15- 20 treatments sessions lasting 30 minutes 5 times per week by experienced physical therapists trained for

the study. All participants also followed their usual rehabilitation care protocols as planned.

Treadmill dual task training (DT)

Participants in the experimental group received supervised treadmill training, 4-5 sessions per week. The treatment protocol was aimed at improving participants' resistance, walking velocity, balance and cognitive functions during motor and cognitive (dual) tasks. The treadmill training was carried out without body weight support but if needed the participants were attached to a safety harness. They were also allowed to use the handrails for balance support as needed. Exercise intensity was decided according to the participants scoring of the Rate of Perceived Exertion (RPE) on the Borg Scale (6-20)[23], the training aim was to keep the participants in the 14-16 range of their RPE and treadmill parameters, speed and slope, were decided based on that. Throughout the treadmill session participants were monitored for heart rate. The thirty-minute training session consisted of three different walking bouts:

1) An aerobic phase (0-12/30 minutes): preferred walking speed for the first three minutes, to be increased to taxing walking speed and an increased slope until 12 minutes, aiming at keeping the RPE at about 14-16 and heart rate near 70-80% of age predicted maximum heart rate;

2) Dual task phase (12-22/30 minutes): preferred walking speed with dual task activities comprising motor activities (e.g. change in velocity, walking without holding onto handrails, use of arms in solving motor tasks, changes in walking motions (long steps, walking on toes, with knee lifts), purposeful head rotations, walking with closed eyes) and cognitive activities (e.g. talking, counting, counting backward, solving memory and recalling tasks);

3) An aerobic phase 2 (22-30/30 minutes): increase in walking speed and slope arriving at RPE 14-16, with the last 3 minutes at preferred speed.

Done in this way the intervention was characterized by high intensity interval aerobic training.

During the 4-week intervention, walking speed and slope was increased according to RPE of the participants with, however, with regard for the heart rate that was always kept within 80% maximum exertion. For those participants that could not do the whole 30 minutes initially, walking duration was gradually increased during the training period as tolerated,

with short rest periods allowed if absolutely necessary. If perceived exertion went to 17 or more on the Borg, the training intensity was first reduced slightly in order to have the participant continue at a level 14-16, and only if they felt they could not continue was the exercise interrupted.

Resistance group (R)

Participants in the control group were treated with Resistance exercises aimed at reducing improving strength in muscles involved in walking (hip abductors, quadriceps, plantar flexors, dorsal flexors) according to current guidelines from the American College of Sports Medicine.[24] Given these recommendations three sets of 10 repetitions were performed bilaterally with appropriate weights for each exercise. Exercise progression was set by increasing the resistance of Therabands and/or weights used in the exercises once the participants were able to perform two sets of six repetitions.[25]

Outcome measures

The primary outcomes were gait resistance assessed with the 2 Minutes Walking Test (2MWT).[16] The subjects were instructed to walk at their usual speed while the distance they covered in 2 minutes was recorded in meters. A change of 15% in meters walked from baseline measures to post intervention was considered clinically important improvement and subjects achieving that were termed responders while those not achieving 15% change were considered non-responders.

All other outcomes were considered secondary. The 10 meters timed test was used to test gait speed and the Timed Up and Go (TUG) to assess functional mobility.

In the 10 meters timed test the subjects were instructed to walk 10 meters at their comfortable speed, parting from a 0 meters and arriving at 10 meters. The time taken to walk from 2 meters to 8 meters was taken.[26,20] In the Timed Up & Go test (TUG) the subjects had to stand up from a chair (without armrests), walk 3m, turn back, and sit down again while being timed. Time taken to complete the test has been shown to be correlated to levels of functional mobility and with scores on the BBS as well as with scores on the DGI for PwMS.[27, 28]

Executive function was assessed with the Frontal Assessment Battery (FAB), a short cognitive and behavioral six-subtest battery used for bedside screening of global executive dysfunction. Total score is a maximum of 18 with higher scores indicating better performance. The six subtests of the FAB explore various functions of the frontal lobes, including similarities, mental flexibility, motor series, sensitivity to interference, inhibitory control, and environmental autonomy. The FAB has been used in studies of persons with MS as a measure of executive function and has been validated for the Italian population.[29]

Static balance performance was assessed with the Berg Balance Scale (BBS), a 14-item scale widely used to assess balance disorders in PwMS. BBS provides information about patient's balance-related abilities rating performance from 0 (worse) to 4 (best) on 14 items with a maximum total score of 56.27 Dynamic balance was assessed with the Dynamic Gait Index (DGI). The eight tasks of this scale include walking, walking with head turns, pivoting, walking over objects, walking around objects, and going upstairs. The maximum score is 24, indicating good dynamic balance.[27]

Quality of life was assessed with the Short Form-12 questionnaire (SF-12), a shorter version of the commonly used Medical Outcomes Study SF-36. The SF12 is comprised of two domains, physical and mental and gives two composite scores that reflect the perceived health of the participant. Both scores range from 0 and 100, with a higher score indicating better health. These SF12-based summaries have been shown to reproduce accurately both scores derived from the full SF36.[22]

Statistical analysis

Descriptive statistics were used to detect the presence of outliers. No subjects were removed from the analysis. The normality of distributions and the homogeneity of variances were assessed by Shapiro–Wilks and Levene tests. Berg Balance Scale cubed scores and Timed up and go logarithm scores were computed to improve the normality of distribution. Parametric tests and non-parametric tests were used when appropriate.

A primary statistical analysis for all outcomes was done using ANCOVA (Analysis of covariance) models adjusting for baseline measurement of the respective outcome variable, to evaluate treatment effects (measured as change from baseline) adjusting for baseline as well as sex, age, EDSS.

ANCOVAs were computed for the primary endpoint (2MWT) and for each of the secondary endpoints.
Logistic regression was used to test the main hypothesis related to the superiority of the treadmill intervention based on a greater proportion of people making a clinically relevant gain in gait resistance following treatment. We used 15% of improvement on the 2 Minutes walking test as dependent variable and FAB, DGI, BBS cubed, TUG, Type of treatment as independent variables.
Effect sizes expressed as Cohen's d and r were calculated for the primary outcomes.
All analyses were performed using Statistica software and the p-level was set at 0.05.

Results

The flow of participants in the study is shown in Figure 1. Of the 42 participants that started the study 38 finished the programs, 26 in the DT-group and 12 in the R-group (Figure 1). Reasons for not completing the trial was anticipated dismissal from the clinic in all four cases, for reasons not related to the study protocol. On average, subjects in both groups completed 18 sessions. There were no adverse events reported during or following either treatment except muscle and general fatigue that was resolved in a couple of hours after the session. After the first couple of sessions some participants complained of muscle soreness and increased stiffness but once ascertained that they were natural consequences of beginning a new intensive motor activity they continued the training without further complaints.
Baseline characteristics of the two groups are shown in Table 1. There were no differences between groups in any demographic, disability or ability parameter at baseline.

Table 1: Demographic and clinical features of experimental and control groups.

	DT-group (N=26)		R-group (N=12)		
Variable	n	Mean ± SD	n	Mean ± SD	P-value
Age (years)	26	51.4 ± 10.7	12	56.7 ± 5.7	0.07
(years)	26	16.3 ± 7.1	12	21.4 ± 10.0	0.11
EDSS	26	5.5 ± 1.1	12	5.6 ± 0.7	0.88
2MWT (m)	26	89.1 ± 35.5	12	84.5 ± 34.7	0.79
TUG (s)	26	16.1 ± 7.8	9	17.4 ± 13.5	0.98
Gait speed (m/s)	26	0.9 ± 0.3	12	0.7 ± 0.3	0.24
2MWT (m)	26	89.1 ± 35.5	12	84.5 ± 34.7	0.79
BBS	26	42.9 ± 10.3	12	44.8 ± 9.4	0.46
DGI	24	15.2 ± 4.4	10	15 ± 5.22	0.75
FAB	26	14.8+4	12	15.9+1.7	0.72
SF12_Mental	24	39.3 ± 8	12	42.0 ± 10.2	0.56
SF12_Physical	24	33.8 ± 7.4	12	37.4 ± 11.3	0.77
	n	%	n	%	
Sex					0.75
Female	17	44.7	11	28.9	
Male	9	23.7	1	2.6	
MS type					0.64
PP	22	57.9	7	18.4	
RR	2	5.3	2	5.3	
SP	2	5.3	3	7.9	

EDSS: Expanded Disability Status Scale; BBS: Berg Balance Scale, TUG: Timed Up and Go; 2MWT: 2 minutes walking test; DGI: Dynamic Gait Index; SF12_Mental: Short Form-12_ Mental Health Questionnaire; SF12_Physical: Short Form-12_ Physical Health Questionnaire; PP: Primary Progressive; SP: Secondary Progressive; RR: Relapsing Remitting

Primary outcome

Number of persons improved in gait resistance versus not improved.

The baseline value of the primary outcome, gait resistance measured by the 2MWT did not differ between groups at baseline. Following intervention 19 out of 26 persons (73%) in the DT-group improved clinically in gait resistance (>15%) whereas 2 out of 12 persons (16,7%) improved in the R-Group. The DT-group improved significantly more (d=1.31, p<0.001) than the R-group in gait resistance, with a 29.9 meters (33.3%) increase in meters walked during the 2MWT while the resistance group did not change (0.2 meters, change of 0.3%). The mean difference in change between the two groups was 28.3 ± 7.5 and was statistically significant (p<0.001) (Table 2).

Table 2: Outcomes of the ANCOVA in the DT-group and R-group post intervention and effect sizes with confidence intervals.

Post treatment

	DT-group		R-group				
Outcome measures	n	Mean ± SD	n	Mean ± SD	Between group differences (DT-R)* Mean ± SE	p	Cohen's D Mean (95%CI)
Primary							
2MWT (m)[Λ]	26	117.6 ± 43.3	12	84.8± 34.6	28.3 ± 7.5	0.0006[£]	1.31 (0.5-2.0)
Secondary							
Gait Speed(m/s) [Λ]	26	1.1 ± 0.36	12	0.8 ± 0.35	0.2 ±0.63	0.01[£]	0.95 (0.2-1.7)
TUG (s)ł ¥	26	13.3 ± 7.6	9	20.0± 23.3	-5.09 ±1.05	0.009[£]	-1.06 (-1.8-(-0.2))
BBS (points)[Ψ]	26	46.9 ± 8.42	12	46.75±6.90	1.55 ± 1.31	0.28	0.38 (-0.3-1.1)
DGI[Λ]	24	17.4 ± 3.8	10	17.1 ± 4.8	0.2±1.03	0.9	0.05 (-0.7-0.8)
FAB[Λ]	26	16.5 ± 5	12	16.7 ±1.6	0.6 ± 0.62	0.36	0.32 (-0.4-1)
SF12_Mental[Λ]	24	41.2 ± 8.3	11	45.6± 12.5	-3.2 ± 3.28	0.33	-0.35 (-1.1-0.4)
SF12_Physical[Λ]	24	34.2 ± 8.73	11	34.0 ± 9.42	2.0 ±1.93	0.31	0.37 (-0.3-1.1)

Abbreviations: n: number; SD: standard deviation; DT: Treadmill Dual Task Group; R: Resistance Group; 2MWT: Two-minutes walking test; BBS: Berg Balance Scale; TUG: Timed up &Go; DGI: Dynamic Gait Index; FAB: Frontal Assessment Battery; SF12_Mental: Short Form-12_ Mental Health Questionnaire; SF12_Physical: Short Form-12_ Physical Health Questionnaire. * Adjusted for pretreatment score (T0) by analysis of covariance; ł These variables did not meet assumptions of data normality

and/or homogeneity of variances. In this cases, statistical tests and Cohen d computation were performed on transformed data. Reported between-group differences were estimated from back-transformed results to facilitate interpretation; ʎ Higher scores indicate better performance; ƨ P<.05 (DT vs R, contrast analysis using independent sample t test); ¥ Lower scores indicate better performance

A logistic regression including type of treatment (DT-group or R-Group), age, MS type, EDSS and disease duration was run with predicted outcomes improved versus not-improved (see table 3). The model was significant (p<0.01) for type of treatment Persons in the DT-group has 0,0017 OR (0.0017 to 0.4154) more to be improved following treadmill dual task treatment; while age, MS type, EDSS and disease duration were not significant predictors of improved persons in the model.

Table 3: Logistic regression analysis between demographic, clinical variables, type of treatment and number of improved patients at 2MWT (Δ2MWTpost-pre ≥15%)

	Const.B0	AGE	MS type	EDSS	Disease duration	Type of treatment
Estimate	-60.49	-0.10	0.65	0.19	0.03	-3.62
Standard Error	74.92	0.06	0.76	0.54	0.07	1.34
t(30)	-0.81	-1.60	0.86	0.36	0.39	-2.70
p-level	0.43	0.12	0.40	0.72	0.70	0.01

Logistic regression (logit) N of 0 (improved): 29 ; N of 1 (not improved): 9 Final loss: 15.58; $Chi^2(5)=17.74$; p=.003. Abbreviations: Const.B0: constant of logistic regression; MS type: type of Multiple Sclerosis; EDSS: Expanded Disability Status Scale.

Secondary outcome

Results following intervention for all outcome measures are shown in Table 2. A significant difference was found between groups in improvement in gait velocity and mobility.

The DT-Group improved significantly more on the TUG ($p<0.01$) than the R-group, with a reduced time to complete the test of 2.9 sec (19.1% improvement) versus an increased time taken by the R-group of 2.9 seconds (11% worsening). The DT-group also increased their speed significantly more than the R-group ($P=0.01$), with a 0.2 m/s increase (21.4%) in gait velocity from baseline versus no change in the R-group, 0.02 m/s (2.5%).

There were no other significant differences between groups in improvement at post. Both groups improved their static balance, the DTT-group by 4 points on the BBS (9.3%) and the R-group by 2.9 points (6.6%), as well as, dynamic balance with the DT- group improving by 2.4 points on the DGI (15.2%) and the R-group by 1.7 points (10.4%).

Regarding executive function measured with the FAB, there were no differences between groups at baseline nor following intervention. The DT group with a baseline of mean 14.8 points out of 18 possible increased 1.7 points (11%), while the R-Group with a baseline of 15.9 points increased 0.4 points (2.5%). There was a strong ceiling effect on the FAB. Only 10 out of the 26 persons in the DT group had an abnormal score on the FAB (<15) at baseline and 4 out of 12 in the R-group. Following intervention, the persons with abnormal scores in the DT-Group had augmented their scores on the average by 4.2 points and in the R-Group by 2.5 points.

Perception of health was moderately low at baseline in both groups at 39.3 and 42.0 respectively in the DTT-group and the R-group on the SF-12_Mental and there was no difference between groups following intervention. The same was true for SF-12-Physical, the groups scored 33.8 and 37.4 respectively at baseline and there was no significant difference between groups following treatment.

Discussion

The present study examined the response of moderately to severely affected PwMS to an intensive multimodal training on treadmill and compared it to a control group that received a strengthening program of similar intensity. More people in the treadmill group improved their gait resistance than in the strength training group and as a whole the group improved much more in gait resistance, speed and mobility. Factors to do with static and dynamic balance instead improved moderately in both groups while executive control and perception of health remained similar in both groups following training.

Gait resistance

Nineteen persons out of the 26 persons in the DT-group improved clinically (>15% from baseline) on the primary outcome, gait resistance, while only two of the 12 persons in the C-group improved clinically. The logistic regression analysis indicated that being in the DT-group was highly predictive of having a clinical improvement after intervention.

Post intervention the DT-group had improved on the 2 Minute walking test in a statistically and clinically significant way by increasing of 33,3% from baseline (30 meters), while there were no changes in the control group. The improvement reached was well above the 20-25% improvement reported by most studies reporting on persons with MS doing gait training on the treadmill and overground[30, 31] and well above the MCD of 9.6 meters established for the 2MWT by Feys et al.[32] A study carried out by Kalron and colleagues on persons with MS of similar disability severity that did training on the treadmill saw a mean change of 20 meters in gait resistance.[31] Some differences in the training protocol may explain the bigger efficacy of the treadmill training in the present study.

First of all, the intensity of our training is higher in terms of workload during a week compared to a previous study by Braendvik et al.in which subjects performed training 3 times per week for 8 weeks for a total of 24 sessions of treadmill or strength training.[33] In contrast, Mostert and Kesselring reported training of similar intensity to the present study (5*30 minutes per week) with benefits for aerobic fitness, fatigue, and an increase in level of physical activity and perception of health.[34] Our training

intensity was similar to the intensity used in the study by Mostert and Kesselring et al. confirming that higher disabled PwMS can benefit from a high training intensity resulting in improved mobility.

Moreover, with respect to the content of the sessions on treadmill, interval training and variability in speed and slope were conducted during the sessions. Although the type of treatments was not strictly tied to the activity during gait but rather to the cardiovascular parameters[34, 35] with bigger improvement in cardiovascular parameters in a group that did interval training compared to a group that did the same intensity of aerobic exercise but with continuous training.[36]

Gait velocity and TUG

Our results are supported by results from the literature indicating that task-specific training by treadmill walking is a favorable approach to improve mobility in persons with moderate to severe MS as compared with strength training.[37, 33]

The increase in gait resistance of the DT group was reflected in higher gait speed (+0.2 m/s) and an improvement in mobility with a reduction of 2.8 sec on the TUG. Similarly, Kalron observed an overall reduction of 2,3 secs on the 10-meter walking test and 2,4 sec on the TUG in the severe group.[37]

The present results thus strengthen proof from the existent literature adding to evidence based knowledge for the decision of optimal treatment approaches to improve mobility in PwMS.

Balance

The sample was moderately affected in their balance with scores at baseline that were on the verge of the cut off for fall risk established by Cattaneo et al. for PwMS.[27] Both groups improved in static balance, by four points (9%) and approximately three points (7%) on the BBS respectively for the DT-group and the R-group Specifically, an improvement near or over the MCID of three points established by Gervasoni et al.[38] showed a small but clinically important overall effectiveness of both rehabilitation approaches. Results were similar for dynamic balance, there was an increase of 2,3 (15%) and 1,6 points (10%) on the DGI for the treadmill and

the resistance group respectively indicating that treadmill training was minimally effective in improving dynamic balance since SEM for the DGI has been established at 2 points of the scale and MDC at 4,2.[27] Although the treadmill training included parameters such as walking without hand support or turning head and walking with closed eyes during the treadmill training only about 12-15 minutes of the treadmill time was dedicated to these dual task activities, including both cognitive exercises and motor activities. It is possible that this was not enough time in balance training to have a bigger impact on balance deficits. Our hypothesis is line with a recent review by Gunn et al. that reported that a high volume of challenging balance exercise program may be needed in order to have greater benefit on balance and therefore potentially in reduction of falls.[39]

Executive function

Regarding executive function measured by the FAB, there were no significant changes after intervention. Our results are in contrast with Sangelaji et al. demonstrating that 24 sessions of combined aerobic and balance training resulted in a significant increase in cognition measured by Digit Symbol Modality Test (DSMT).[40] Moreover, a review by Kalron reported that persons with MS participating in active intervention or exercise groups improved more in cognitive measures than a not active controls, implying an impact of exercise on cognition.[41] Given our sample in which baseline values are near to the maximum score of the FAB scale, one explanation could be that FAB is not sensitive enough to depict changes after the rehabilitation period due to tool ceiling effect.

Perceived health

Regarding quality of life in terms of health perception, there were no significant changes neither in physical nor the mental domain in both our groups. Our results didn't support the results showed by Motl et al. reporting a significant effect for aerobic exercise, but not for non- aerobic exercise (e.g., yoga and resistance training) on improving quality of life.[42] One explanation could be that we treated both inpatient groups and they cannot experience real life at home during the period of recovery in the hospital, thus it is possible that they had difficulty to perceive improvements outside of their daily context.

General conclusions and limitations

In the current study the emphasis was on achieving speed and stressing the aerobic system during two thirds of the treadmill time. Our main result showed a significant improvement in the treadmill training group in all the parameters associated with gait resistance, speed and mobility compared to a control group that did strengthening exercises at a similar exercise intensity. Balance and cognitive dual tasking exercises were incorporated into the walking time for about one third of the treadmill time, however, for the rest of the time the subjects were allowed to hold onto the side rails in order to achieve faster walking speeds. It is possible that with more time spent in multimodal training the balance component of the training would have been even more effective. Given the importance of investigating methods to improve cardiovascular health and increase physical activity in persons with MS, further studies are needed.
We acknowledge some limitations of the study. Firstly, while the short-term effects of our exercise training study are encouraging, no follow up measures were performed. Secondly, no assessment measuring fatigue was done. Thirdly, aerobic multimodal training was compared to resistance training with many of the outcomes being more specific to the aerobic multimodal training. The possibility that resistance training was more effective in improving non-aerobic parameters (beyond balance, fatigue, QoL that should be common to all interventions) such as, muscle strength cannot be excluded.

Conclusion

A four to five-week aerobic multimodal training was much more effective in augmenting gait resistance and mobility in moderately to severely affected PwMS than resistance training while both groups had modest benefits from training on balance and quality of life. This underscores the possibility of improving mobility and cardiovascular health also in persons with MS with relatively high disability levels with a potential impact on their physical activity and daily life participation.

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Chapter 4

EFFECTS OF FUNCTIONAL ELECTRICAL STIMULATION ON REDUCING FALLS AND IMPROVING GAIT PARAMETERS IN MULTIPLE SCLEROSIS

Abstract
Background. Loss of neuromuscular control of the ankle joint is a common impairment in neurological conditions, leading to abnormal gait and a higher risk of falling. However, limited information is available on the effectiveness of Functional Electrical Stimulation (FES) on reducing falls, and no studies have investigated its usefulness in improving lower limbs kinematics related to foot clearance and energy recovery.
Setting. Clinical setting.
Study Design. Longitudinal study.
Participants. Fourteen people with multiple sclerosis (mean age ± standard deviation 50.93 ± 8.72 years).
Methods. The number of falls was assessed at baseline and after 8 weeks, and a clinical assessment was assessed at the baseline, 4-week and 8-week time points. A subsample of the 14 subjects comprised of 5 people with multiple sclerosis performed a gait analysis assessment at baseline and after 4-weeks. After receiving the equipment and the training schedule, subjects performed daily home walking training using FES for 8 weeks.
Main Outcome Measurements. The main outcomes were 1) the number of falls, 2) foot clearance, and 3) energy recovery.
Results. A reduction in the number of falls was observed from baseline to the 8-week assessment, p=.04. Foot clearance increased (+ 7.39 mm, p=.03) between the baseline without FES and at 4 weeks with FES (total effect). No statistically significant differences were found in energy recovery between baseline and 4 weeks.
Conclusions. The use of FES had an impact on gait, specifically reducing the number of falls and improving walking. A specific effect at the ankle joint was observed, increasing foot clearance during the swing phase of gait. This effect was not accompanied with a reduction in the energetic expenditure during walking in subjects with multiple sclerosis.

Introduction

Loss of neuromuscular control of the ankle joint is a common impairment in neurological conditions, such as multiple sclerosis[1], stroke[2] and traumatic brain injury.[3]

Damage to the motor cortex or corticospinal tract and variability in the area of lesion and the degree of pathology often result in a significant persistent distal weakness. Patients with this pattern are often unable to actively dorsiflex the foot during the swing phase of gait.[4] The deficit of motor control in the ankle joint, typically because of a combination of weakness of the agonist ankle dorsiflexors muscles and spasticity of the antagonist plantarflexor muscles,[5] results in slower and abnormal gait, and leads to gait compensation strategies consisting of hip hitching, circumduction and toe catch.[6] This inefficient gait pattern also contributes to slow walking, high energy expenditure, reduced foot clearance and muscles[7] that may result in a higher chance of stumbling and falling.[8]

Loss of neuromuscolar control of the ankle joint during the swing phase is traditionally treated by an ankle foot orthosis (AFO), but Functional Electrical Stimulation (FES) has been developed as an alternative treatment.[9] Previous studies using FES have demonstrated that the common peroneal nerve stimulates the tibialis anterior muscle to produce foot dorsiflexion during the swing phase of the gait cycle and reduces foot drop by facilitating increased voluntary muscle activity, and that this improves the quality and symmetry of gait.[5] In addition, others studies investigated the effect of FES showing improved walking speed and energy in subjects with multiple sclerosis.[10,11]

However, limited information is available on the effects of this device on reducing falls and on the kinematics changes in lower limbs. No studies have investigated an important kinematic parameter, such as foot clearance (defined as the minimum distance between the foot and the ground during the swing phase of the gait [12]), which has been found to be a common cause of falling in multiple sclerosis patients.[5,6,13] Moreover, to the best of our knowledge, no studies have investigated other parameters,

such as energy recovery (defined as the exchange between potential and kinetic energy in the movement of the centre of mass during walking). Energy recovery is associated with changes in gait speed observed with FES treatment.[14]

Therefore, the aims of this study are to assess 1) the effectiveness of FES on reducing falls, 2) the effectiveness of FES on improving foot clearance and lower limbs kinematics, and 3) the effectiveness of FES on promoting energy recovery.

Methods

Participants

A consecutive sample of 14 people with multiple sclerosis was recruited. The subjects were recruited from the outpatient/inpatient rehabilitation service of the Don Gnocchi Foundation.

Subjects were included in this study if they met the following inclusion criteria: diagnosis of or multiple sclerosis with at least 90 degrees of passive dorsi-flexion at the ankle and the ability to walk at least 10 m independently or with a cane, a Mini Mental State Examination [15] score greater than 24, aged between 18 to 80 years and willingness to participate in the study.

Subjects were excluded if they had a cardiac pacemaker, skin lesion at the site of the stimulation electrodes, Modified Ashworth Scale[16] score of the calf muscles that was more than 4, severe weight-bearing pain, any pre-existing conditions affecting walking function, diagnosis of depression or psychotic disorder, inability to elicit significant muscular contraction of tibialis anterior at baseline.

The study was conducted in accordance to the declaration of Helsinki and was approved by the ethics committee of Don Gnocchi Foundation. Subjects signed an informed consent form before the beginning of the study.

Primary outcomes:
According to the aims of this study, the primary outcome measures were number of falls, foot clearance and energy recovery factor.
The number of falls during the study were monitored prospectively for 8 weeks by the use of a diary. Participants were also interviewed to recall the number of falls in the 2 months before their study participation. The fall was defined as "an episode of unintentionally coming to rest on the ground or lower surface that was not the result of dizziness, fainting, sustaining a violent blow, loss of consciousness or other overwhelming external factors".[17]
Foot clearance, lower limbs kinematics and energy recovery factor were assessed using instrumented gait analysis on the subsample of 5 people with multiple sclerosis. Subjects were recorded while walking in the laboratory using comfortable shoes at their own comfortable speed without FES at baseline. The test was repeated 4 weeks later in the same condition with and without FES. SMART motion analysis system6 and LAMB protocol [18] were used to assess the three dimensional kinematics of the subject's lower limbs. Foot clearance, defined as the distance between the foot and the ground at minimum clearance during the swing phase, was measured [8]. To understand the contribution of each joint in determining foot clearance, hip elevation, hip flexion, knee flexion and ankle dorsiflexion were calculated at the minimum clearance value.[19] Step length and ankle dorsiflexion at initial contact were also recorded.
Energy recovery factor was computed as described by Cavagna[14], and it is defined as the percentage of mechanical energy recovered via exchange between kinetic and potential energy in the centre of mass movement.

Energy Recovery Factor = (Wne – Wext)/ Wne*100,

Wne is the maximum work one should do without energy shift, and Wext is the work actually performed. A 100% recovery means a perfect transfer

[6] BTS S.p.A.

between kinetic and potential energy, healthy subjects have an energy recovery of 65% while walking at 4 km/h.[14]

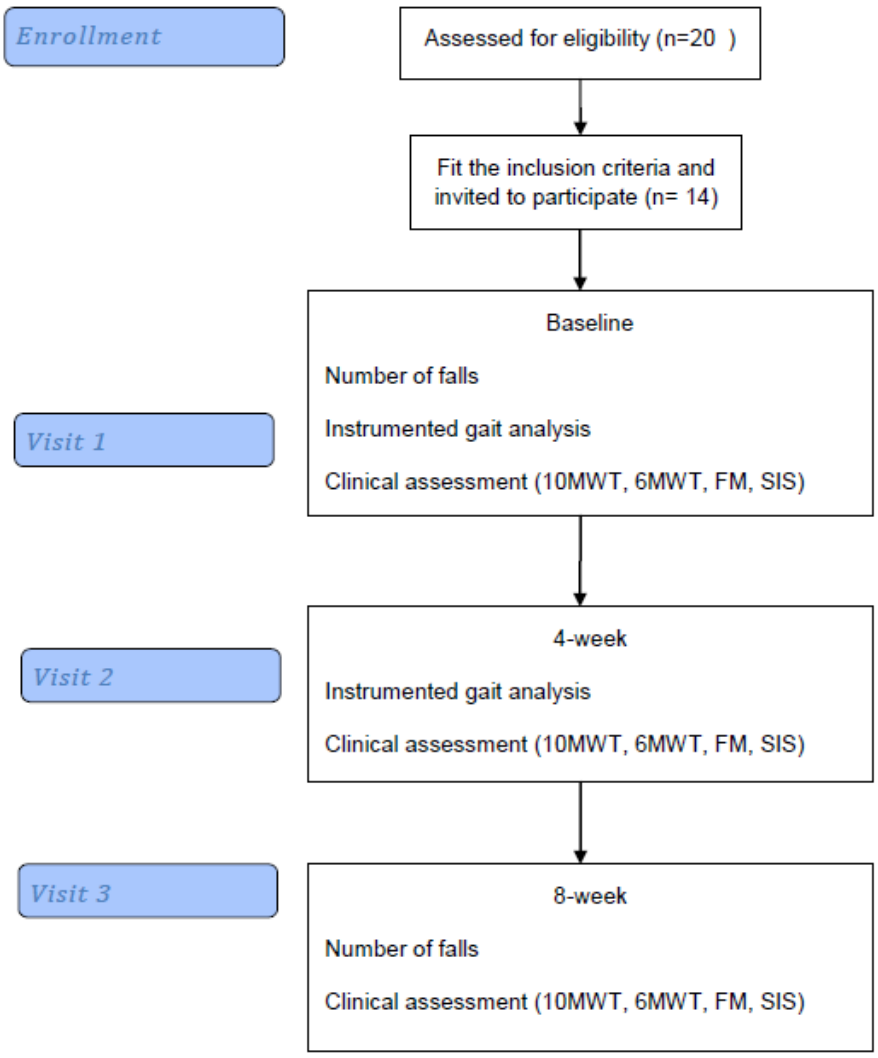
Clinical assessment

Gait measures were assessed in terms of walking speed by the ten-meter walking test (10-MWT) and walking endurance by the six-minute walk test (6-MWT). 10-MWT: The subjects were instructed to walk for 10 meters at their comfortable speed with and without FES. Gait speed reflects aspects of walking abilities and is commonly used to measure mobility in people with neurological dysfunction.[20,21] 6-MWT: The subjects were instructed to walk at their usual speed for 6 minutes. The distance they covered in 6 minutes was recorded. This is an endurance measure in people with stroke[22] and in people with multiple sclerosis.[23] For 10-MWT and 6-MWT, subjects walked twice with and without FES. For every subject, the trials were conducted in a randomized order with 10 minutes' rest between the two tests. Manual Muscle Test (MMT)[24] was used to assess the ankle dorsiflexors strength, with a score ranging from 0 to 5 where 0=no muscle recruitment; and 5=full muscle strength against external resistance.
Fugl-Meyer (lower limbs) (FM)[25] was used to assess motor function with a score ranging from 0 to 100 where 100 means best performance, sensory function, balance, joint range of motion, joint pain and each item is graded on a 3-point ordinal scale (0 = cannot perform; 1 = performs partially; 2 = performs fully) with a maximum score of 100.

Experimental procedures

The study protocol is shown in Figure 1.

Figure 1:Flow chart of the study



Visit 1: Baseline
The participants were assessed for the following outcomes: Number of falls, instrumented gait analysis and clinical assessment. Furthermore, subjects received the equipment, the training schedule and were shown how to use the device. A daily diary was used to record the training time and any adverse events.

Visit 2: 4-week
After 4 weeks, subjects returned to the hospital and repeated the instrumented gait analysis and clinical measures.

Visit 3: 8-week
Finally, at 8 weeks, subjects brought back their falls diary and repeated all clinical measures.

Walking Training Protocol

Subjects were asked to walk daily using Functional Electrical Stimulation daily for a total of 8 weeks. Training time was increased according to the following schedule: the first week, the subjects wore the device for 15 minutes to 1 hour according to individual tolerance, in the second week, for 30 minutes to 4 hours and in the third week, subjects were asked to wear the device for as long as possible. From the third week until the eighth week, participants maintained the training schedule achieved in week three. The device used in the study was the Ness L300 Functional Electrical Stimulator. This device delivers electrical pulses to the common peroneal nerve throughout the swing phase of gait leading to ankle dorsiflexion. An expert clinician set the device intensity and pulse frequency to obtain an optimal dorsiflexion response[26]

Statistical analysis

Results were presented as the mean ± standard deviation for normally distributed variables and median ± interquartile range for non-normally distributed variables. The Wilcoxon signed rank test was used to analyze a statistically significant difference in the number of falls between baseline and 8-weeks. For the foot clearance, lower limbs kinematics and energy recovery factor, the comparisons between performances with FES and without FES were conducted on data from the treated leg. Data were tested for normality and were analyzed with repeated measures ANOVA. Statistically significant differences between groups were assessed with the Newman–Keuls post hoc test. The total effect (baseline without FES vs 4-week with FES), walking training effect (baseline without FES vs 4-week without FES) and 4-week without FES vs 4-week without FES were calculated.
For clinical assessment, non-parametric Friedman ANOVA and Friedman ANOVA post-hoc tests were used. Similar to instrumented gait analysis, we calculated the total effect, walking training effect and orthotic effect. We used a per protocol analysis and an intention-to-treat analysis on clinical measures. Since no differences were observed between the per protocol and intention-to-treat analysis, we reported results pertaining to the intention-to-treat analysis. In the case of missing data, a last observation carried forward procedure has been used. The level of statistical significance test was set at $P<.05$.

Results

Fourteen subjects were included in the study. Patient characteristics are shown in Table 1. A subgroup of 5 people performed instrumented gait analysis, and the characteristics of this subsample are also presented in Table 1.

Table 1: Demographic and clinical features of the total sample and subsample. Mean and standard deviation (SD) or number (%) are reported.

	People with multiple sclerosis (n=14)	Subsample (n=5)
Female N(%)	7 (50%)	3 (30%)
Age Years	50.93 (8.72)	56.87 (14.01)
Time since Onset Years	17.51 (9.41)	12.83 (12.60)
Affected side (right) N (%)	12 (86%)	3 (60%)
Assistive device N (%)	6 (43%)	3 (60%)

Effectiveness of FES on the primary outcomes

7 falls were recorded at baseline and 1 fall were recorded after eight weeks of walking training showing a statistically significant reduction in the number of falls compared to the baseline, $p = .04$. Number of fallers (at least one fall) and frequent fallers (more than one fall) were reported in Figure 2.

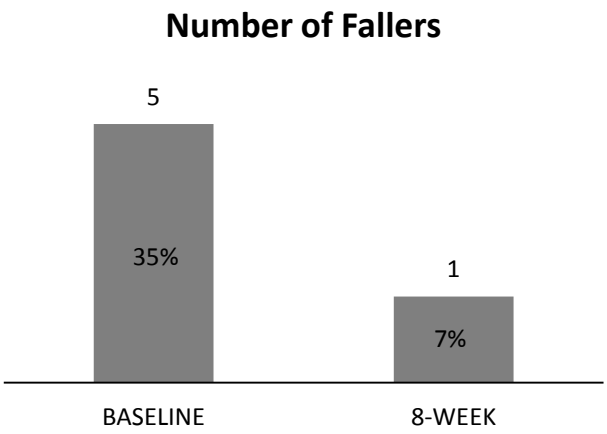


Figure 2: Hystograms showing number of Fallers at baseline and 8-week

There was an overall statistically significant improvement in foot clearance between baseline and 4-weeks. Post hoc analysis showed a significant total effect (+7.39 mm, p =.03). On the other hand, no statistically significant differences were observed for the walking training effect and the orthotic effect. An overall statistically significant change was observed in ankle dorsiflexion at the initial contact (p=.05). No changes were observed in ankle dorsiflexion at clearance (Table 2).
Finally, no changes were observed in the energy recovery factor between baseline and the 4-week assessment (Table 2).

Table 2:Instrumented gait analysis: foot clearance, lower limbs kinematic and energy recovery factor. Means (Standard Deviations) are reported.

	BASELINE Without FES	4-WEEK Without FES	4-WEEK With FES	Overall p-level	Post-hoc total effect (Baseline without FES vs 4-week with FES)
Clearance (mm)	15.41 (6.38)	22.8 (12.53)	17.82 (7.19)	p=.04	7.39 (7.8) p=.03
Ankle dorsiflexion at the initial contact (degrees)*	-37.66 (9.46)	-35.29 (6.32)	-41.17 (8.64)	p=.05	2.38 (6.02) p=.05
Energy Recovery factor (%)	40 (0.5)	43 (1)	42 (1)	p=.59	-2

Overall p-value: ANOVA's p values across means. * higher values indicate increase of ankle dorsiflexion

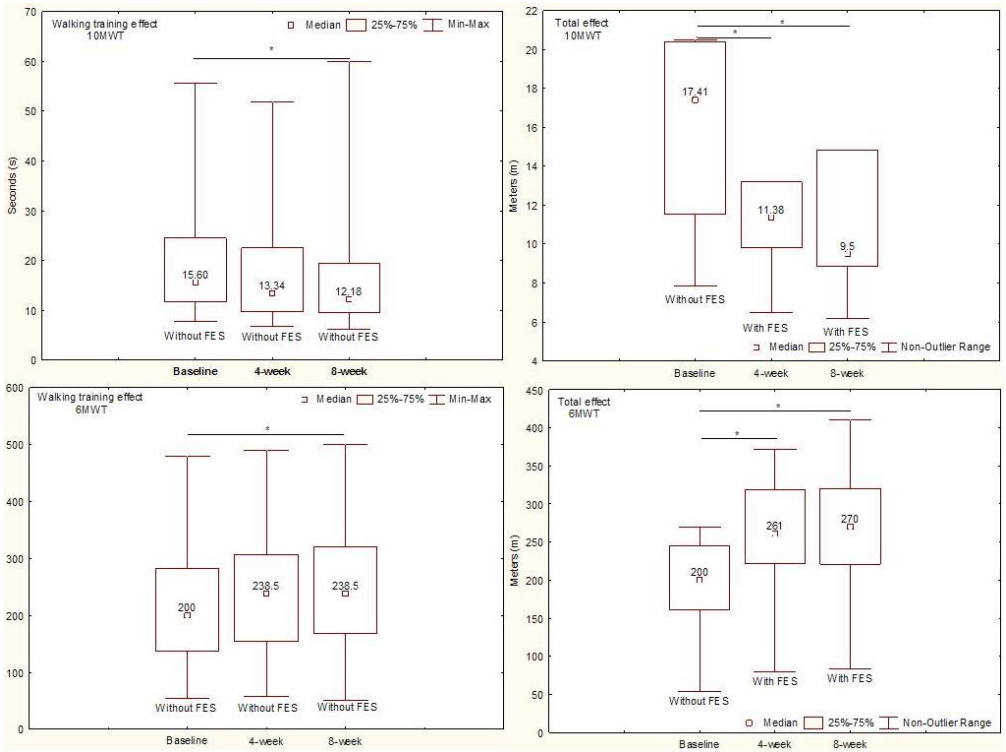
Effectiveness of FES on clinical assessment

There was a significant overall effect of FES on 10-MWT ($p<.05$, Figure 3). Post hoc comparisons showed differences in the total effect between baseline (without FES) and the 4-week assessment (with FES) and between baseline and the 8-week assessment (with FES). Subjects completed the test 1.63s (4-week) and 5.12s (8-week) faster than at baseline corresponding to a change in gait velocity from 0.48 m/sec (baseline) to 0.63 m/sec (4-week) and 0.64 m/sec (8-week), respectively. Post hoc comparisons also showed a walking training effect between baseline (without FES) and the 8-week assessment (without FES).
There was a significant overall effect of FES on 6-MWT ($p<.05$, Figure 3). Post hoc comparisons showed differences in the total effect between

baseline and the 4-week assessment and between baseline and the 8-week assessment where subjects walked 59 meters (4-week) and 66 meters (8-week) more than at baseline. Post hoc analysis also showed a walking training effect between baseline and 8-week assessment. At 8-weeks, subjects walked 41 meters more than at baseline.

Finally, medians and interquartile ranges of the Manual Muscle Test, Fugl-Meyer and Stroke Impact Scale at baseline, at 4 weeks and at 8 weeks were reported in Table 3, showing a statistically significant improvement between assessments.

Figure 3: Total effect and walking training effect of 10MWT and 6MWT at baseline, 4-week, 8-week



10MWT: Ten meters walking test; 6MWT: Six minutes walking test; With FES: device switched on; Without FES: device switched off; 4-week: assessment after 4 weeks; 8-week: assessment after 8 weeks

Table 3: Medians and Interquartile range of clinical outcomes at baseline, at 4-week and at 8-week.

	BASELINE Median (IRQ)	4-WEEK Median (IRQ)	8-WEEK Median (IRQ)	Overall p-value
MMT	1 (1)	2 (2)	2 (1)	.02
FM	76.00 (19)	83.00 (18.00)	82.00 (15.00)	< .001

MMT: Manual Muscle Test; FM: Fugl-Meyer; SIS Mob: Stroke Impact Scale Mobility; overall p-value: Friedman ANOVA's p values across medians.

Means and standard deviations of the kinematic parameters were reported in the supplementary table (Table S1). Hip and knee motion at clearance, step length, gait speed and cadence did not show changes between baseline and 4-weeks with and without FES.

Table S1: Kinematic analysis of hip, knee motion, step width, step length, gait speed, cadence. Means (Standard Deviations) are reported.

	Baseline Without FES	4-week Without FES	4-week With FES	Overall p-level	Total effect (Baseline without FES vs 4-week with FES)
Knee flexion at clearance (degrees)	22.78 (10.18)	27.57 (11)	27.12 (10.92)	p=.07	4.79 (4.54)
Hip flexion at clearance (degrees)	24.08 (2.65)	24 (7.14)	25.43 (5.78)	p=.78	-0.08 (6.55)
Hip elevation at clearance (degrees)	-2.69 (2.95)	-1.79 (0.93)	-2.72 (1.78)	p=.71	0.90 (3.48)
Step length (%body height)	52.34 (3.26)	50.75 (4.63)	51.14 (3.95)	p=.07	1.58 (2.74)
Gait speed (%body height/sec)	29.87 (7.92)	31.13 (11.31)	29.44 (10.09)	p=.65	1.26 (4.42)
Cadence (steps/min)	36.83 (3.9)	37.18 (6.43)	36.84 (4.49)	p=.39	0.35 (2.62)

Overall p-value: ANOVA's p values across means.

Discussion

The results of this study demonstrate that in group of patients with multiple sclerosis, a walking training protocol with FES for 8 weeks benefited individuals with neurological disorders who had unstable ankle joints, thereby reducing the number of falls and improving walking kinematic parameters without any improvement in energy recovery.

The first result of this study is that the use of FES reduced the number of falls even if subjects were asked to walk for longer than before and to increase their daily activities. This is an important issue, which show high prevalence of falls leading to fractures and diminished quality of life.[27,28] To understand whether this reduction in number of falls was related to changes in the gait pattern, we examined the effects of FES on foot clearance and in lower limbs kinetic variables.[29,30] We found an improvement in clearance after 4 weeks training, providing evidence to support the link between foot clearance and trips and slips due to lack of control of the ankle muscles[31] leading to an abnormal position of the foot and its premature contact with the ground.[32]

The second result of this study is that the improvement in foot clearance was due to increased ankle dorsiflexion with a small contribution at knee and hip level. This finding suggests that the FES had a specific effect at the ankle and that the increase of clearance was not due to compensatory movements at proximal joints. Increased dorsiflexion was also evident at initial contact, improving the ability to place the foot in the right position with respect to the ground avoiding premature forefoot contact and promoting foot eversion during mid swing. Our results are in agreement with the study of Van der Linden et al. in which subjects gained 2.6° at the ankle joint during gait with FES.[33]

The third result is that the use of FES did not improve energy recovery, resulting in a less efficient exchange between kinetic and potential energy. This finding could be partially due to the small differences in energy recovery between our sample and healthy subjects walking slowly[34] suggesting that the basic energy recovery mechanism was already partially

exploited. It is also possible that even with FES, subjects did not properly place the foot in the right position to use the heel as a pivot at foot strike, conserving the momentum generated at push-off to propel the centre of mass forward and up favoring the exchange between kinetic and potential energy at heel strike.[35] In addition, it has been suggested that FES of the dorsiflexors alone does not address other critical gait deficits, such as reduced push-off forces and ankle plantar flexor moment during terminal stance. Recent work has shown that delivering FES to ankle dorsi and plantarflexors increases the production of external mechanical energy improving energy recovery of stroke patients.[36]

Finally, reduction in falls and improvement in ankle dorsiflexion were associated with changes in endurance and gait speed, reduction of impairments and increased independence in activity of daily living.

Previous studies reported improvements in walking endurance for periods ranging from 6 to 30 weeks.[8] Our data suggest that a period of 8 weeks is optimal to achieve a clinically meaningful effect on walking endurance. After the training, subjects walked almost 40 m farther than at baseline on 6-MWT. According to Baert et al., an improvement greater than 21.6 m can be considered clinically relevant for people with multiple sclerosis.[37] Improvement in walking endurance was also accompanied by greater walking speed at 10-MWT than the baseline without reaching the threshold (>1.04 m/s) to pass from unlimited household walker to most-limited community walker.[38] After training, subjects improved walking endurance even without the device. These results are consistent with the findings reported by Dunning et al. [8] and Robbins et al.,[39] suggesting the walking protocol increased subjects' resources independently from the use of the device. Interestingly, we did not observe statistically significant changes when comparing subjects' performance with and without FES at baseline (orthotic effect). On the other hand, significant improvements were observed at 4 and 8 weeks. This suggests that a treatment protocol should always be performed before the prescription of the device.

After training motor impairments decreased, the muscle strength of the tibialis anterior was increased, as revealed by the Manual Muscle Test, and

ankle attitude and movements of the lower limbs improved, as suggested by changes in the Fugl-Meyer scale. These results are consistent with the findings reported in a review in people with stroke by Glinsky et al., indicating that electrical stimulation can be effective for increasing voluntary muscle strength.[40]

There are several limitations to this study that need to be addressed. Firstly, the study sample is small and without a control group. Studies on a larger sample with an instrumented and clinical assessment are warranted to apply these results to a larger population. Secondly, an instrumented assessment should be added at 8 weeks to understand whether the same results were maintained during the entire protocol. Thirdly, a longer follow-up period could be useful to evaluate long-lasting effects of FES and adherence.

Conclusions

The use of FES had an impact on gait, reducing the number of falls and improving walking. A specific effect at the ankle joint was observed, increasing foot clearance during the swing phase of gait. This effect was not accompanied by a reduction in the energetic expenditure during walking in subjects with multiple sclerosis.

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Conclusions

Conclusions

This doctoral work provides insights on a more comprehensive evaluation of fatigue and motor functional impairments and mobility disorders. It provides results based on a specific controlled physiological and clinical rehabilitation assessment and what effect the rehabilitation has on daily activities.
Furthermore, the present work provides information helping clinicians to better tailor rehabilitation strategies aimed to reduce fatigue and improve motor function.

Our findings can be outlined in the following central messages:

We set up a cross-sectional study and we integrated basal and functional measures of cardiac autonomic tone to evaluate the presence of subclinical autonomic dysfunction in PwMS and evaluate how this may have an impact on cardiovascular responses to everyday life activities, as light exercise and postural challenges. We found that parasympathetic basal tone and post-exercise reactivation appear to be impaired in PwMS, but heart rate modulation during postural challenge and exercise seems to be preserved. Furthermore, subclinical autonomic dysfunction doesn't seem to affect perceived fatigue.

Given the safety of exercise and the lack of cardiac autonomic dysfunction during exercise, we designed a crossover study which combines aerobic training and task oriented exercises aimed to reduce fatigue and improve upper limb impairments and function. We found that this combined training is effective in reducing fatigue but not intense enough to improve impairments in manual dexterity suggesting to clinicians the provision of tailored and more intensive interventions is needed to reduce manual impairments.

Since aerobic and task oriented training is suitable to improve upper and lower limb performances. We set up a further randomized controlled trial to evaluate the safety, feasibility and preliminary effects of a high-intensity rehabilitative multimodal (aerobic and task oriented) training

protocol carried out on treadmill on mobility, balance, executive function and health-related quality of life in a sample of persons with moderate to severe MS mobility compared to a control group that received a strengthening program of similar intensity. Our results showed people in the treadmill group improved their gait resistance more than the strength training group and as a whole the group improved much more in gait resistance, speed and mobility. Factors to do with static and dynamic balance instead improved moderately in both groups while executive control and perception of health remained similar in both groups following training.

Finally, we designed a longitudinal study aimed at verifying if the use of a device providing functional electrical stimulation was effective to improve walking endurance, reducing falls and improving lower limbs kinematics related to foot clearance and energy recovery assessed with instrumented gait analysis. A walking training protocol was set up and subjects were asked to walk wearing the device as long as possible. We found an improvement in gait resistance, reduction in number of falls and a specific increase of foot clearance during the swing phase of the gait. This effect was not accompanied with a reduction in the energetic expenditure during walking.

Future studies

From the present work findings, future studies could deeply investigate the impact of neurorehabilitation in MS and the role of specificity and intensity of rehabilitation in this population.
In particular, from the physiological point of view since aerobic exercise has been shown to ameliorate the aerobic conditioning in PwMS, it will be interesting to study whether an aerobic training may also reverse the cardio-vagal autonomic damage.
Further investigations are needed on the role of aerobic training as a “priming” technique to enhance the effects of rehabilitation evaluating motor behaviour, white matter microstructural and cortical plasticity changes.