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Faculteit Revalidatiewetenschappen
master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Walking fatigability: relation with peripheric underlying factors using different MVC and fatigue indexes

Sam Klijsen
Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie,

afstudeerrichting revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen

PROMOTOR :
Prof. dr. Peter FEYS

COPROMOTOR :
Mevrouw Fanny VAN GEEL

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Research context

Patients with Multiple sclerosis (MS) are confronted with a variety of symptoms interfering with functioning in daily live. One of the most frequently occurring deficits, even in early stages of MS, is fatigue. In literature, fatigue is described in many ways. Each explaining a different type of fatigue with a unique impact on functioning, activity and participation levels. To appropriately assess the impact of fatigue, a unified taxonomy was created. Performance motor fatigability (PMF) is described as an objective measurable physical/cognitive change during or after any form of activity. This conceptualization of fatigue allows us to investigate the impact on functioning and activity levels, which is an imported factor regarding quality of live.

PMF is a common problem in MS, especially in the lower limb, causing struggles with tasks on an activity level such as walking. A variety of underlying factors contribute to deficits in walking, such as balance, coordination, muscle strength and walking related PMF. According to literature pathological performance motor fatigability can be caused by various underlying factors. These underlying mechanisms can be divided into central and peripheral factors. Central factors are attributed to a deficit in the CNS such as central drive, conduction velocity and spinal motor excitability. Peripheral factors are attributed to the peripheral nervous system (PNS) such as muscle contractile function, oxidative capacity and metabolite production (Surakka, 2004), (Manouchehrinia, 2012), (Tremlett, 2009) [20,31,32]. Each of these factors can be a contributing factor and should be examined in a study of PMF. Every form of fatigue can be related to a decrease in both cognitive and physical functions, therefore different forms of fatigue may have an influence on performance motor fatigability. A connection between the other domains of fatigue and performance motor fatigability should be taken into consideration as well as the influence of the cognitive part of fatigue (Seamon, 2016) [33]. Internal and external factors such as cognitive and physical capacity, physical activity, Quality of live (QOL), can contribute to motor fatigability as well.

Further research is required to obtain an understanding in the underlying, related and influencing mechanisms on walking related performance motor. These underlying and influencing factors should be examined to bring them together in a clinical profile. With such a profile, interventions based on specific underlying factors could be a major game changer in the rehabilitation strategy for PwMS.

In order to create such a clinical profile based on walking related PMF, a study was conducted by order of Dra. Fanny Van Geel as her PhD in neurological rehabilitation in MS. The study was conducted at the REVAL center at the University of Hasselt with Prof. Dr. Peter Feys as ultimate responsible for the final results.

Three institutions participated in this study: REVAL center University of Hasselt, Revalidation and MS center Overpelt and Centre Hospitalier Universitaire de Liège (University Hospital center of Luik). The study consists of three testing days. Day one took place in the REVAL center, where descriptive data was collected and the 6MWT was conducted. Subsequently a static and dynamic fatiguing protocol was initiated, measuring maximal isometric and isokinetic torque by a Biodex system. The Interpolated twitch technique was used simultaneously in this protocol to test voluntary drive as a central drive component and lastly four motor tests, four cognition tests and two coordination tests were conducted in a random order which are further described in the appendix. Day two started with taking a blood sample, a glycogen test and a muscle biopsy. In the afternoon, subjects went under supervision to the University Hospital center of Luik, where they were examined with the triple stimulation technique. Day three was an optional day at the university of Maastricht where changes in biomechanics from the subjects walking pattern were assessed.

Sample size calculation states 40 PwMS and 20 ages- and gender matched healthy controls as four factors (10 per factor) will be analyzed as underlying causes (voluntary drive, coordination test, static and dynamic fatigue index) for DWI through a linear regression. Subjects will be tested until August.

Maximal Voluntary Contraction (MVC), static (SFI) and Dynamic fatigability index (DFI) of the knee flexors, extensors and ankle dorsiflexors were preliminary examined as possible underlying and correlated factors for walking related PMF in this part of the study. The first part of this Master thesis (part one) composed of a literature study in support of the second part of the Master thesis. This second part is conducted using preliminary data from the broader study conducted at the research center REVAL University of Hasselt in Diepenbeek. As indicated above, data extraction resulted from outcome measures of the BIODEX SYSTEM and 6MWT. These tests were conducted during day one of the major study conducted by Dra. Fanny Van Geel alongside other motor, cognitive and coordination tests, which are described in the appendix. This thesis contributes to the research project by Dra. Fanny Van Geel and is supervised by Prof. Dr. Peter Feys. Dra. Fanny Van Geel was responsible for the

recruitment of participants. Data acquisition and processing was part of this thesis work. Statistical analysis were discussed within the team and carried out by the student. This article was written entirely by the student with the assistance in the form of feedback moments by co-promotor Dra. Fanny Van Geel and promotor Prof. Dr. Feys.

Abstract

Background: Walking capacity and endurance is to some extent related to muscle strength. It is unknown if state fatigue measured on body faction or activity level is also a related factor. Understanding underlying factors of walking related fatigability will give us the knowledge to implement specific rehabilitation strategies in PwMS.

Objectives: Testing the relationship between walking fatigability and possible underlying factors such as muscle strength and muscle fatigability in knee extensors, knee flexors and ankle dorsiflexors at body function level.

Participants: 15 PwMS and 10 healthy controls were recruited. PwMS were further divided into two subgroups based on the DWI by a cut-off value of 10%: [(DWI 6 -DWI 1)/(DWI 1) × 100]. Subgroups were: 'Walking fatigability' (WF) n=7 and 'No walking fatigability' (NWF) n=8.

Measurements: An observational cross-sectional study design was applied. Walking fatigability was tested during a 6MWT. Fatigue was assessed by a prolonged (30s) isometric contraction (Static fatigue) or a series of 15 concentric contractions (dynamic fatigue). These fatiguing protocols were preceded and followed by a 5s isometric maximal voluntary contraction to assess maximal muscle strength. Assessment started with the knee extensors followed by knee flexors and ankle dorsiflexors using a Biodex system.

Results: Muscle strength related significantly to DWI in all three muscle groups. Only knee extensor strength related to total distance walked in PwMS. Strong correlation was found between the static fatigue index and DWI in PwMS. In the subdivided MS group WF, correlation was found between static fatigue index of the ankle dorsiflexors and DWI.

Conclusion: Knee extensor, knee flexor and ankle dorsiflexor weakness are important underlying factors for walking capacity and walking fatigability according to our data. Based on methods used in this study, motor fatigability on body function level contributes as an underlying factor to walking capability in knee flexors.

1. Introduction

Multiple sclerosis (MS) is a chronic demyelinating inflammatory disease of the central nervous system (CNS). Symptoms related to MS vary depending on which area of the CNS is affected [1]. A combination of deficits is often found in people with MS (PwMS) such as muscle weakness, ataxia, spasticity, sensory disfunction, visibility dysfunction, pain, fatigue, cognitive, psychosocial, behavioral and environmental problems [1-3].

In PwMS, fatigue is reported as one of the most common and first symptoms (40-80%) [5]. Fatigue has an impact on functioning, activity and participation levels in daily living such as walking. Therefore it is one of the more impactful and disabling symptoms in PwMS [4-7].

Different terms and definitions are used throughout literature in order to describe or conceptualize "fatigue". Such conceptualization was much needed in order to facilitate further research. A unified taxonomy was introduced by the research group at REVAL at the University of Hasselt, based on the available literature [5,10]. In this research, fatigue is divided into two main domains, trait fatigue and state fatigue. Trait fatigue is defined as the general feeling of fatigue that is always present within an individual. It is a characteristic and does not fluctuate over time. State fatigue on the other hand is a form of fatigue that changes according to tasks performed by, or circumstances and conditions to which an individual is exposed. State fatigue is also known as fatigability. Trait fatigue and fatigability can in their turn be subdivided into a cognitive and a motor domain. Each having a perceived and a performance component. Perceived fatigability is a subjective patient-reported change in physical and/or cognitive sensations of fatigue during and/or after an activity. Performance fatigability is an objectively measured change in physical and/or cognitive parameters during and after activity.

Performance motor fatigability (PMF) measured as muscle fatigability (static, dynamic fatigue indexes) and walking related motor fatigability (Distance Walked Index) will be the main focus in this research as it can be considered to be the most objective form of fatigue on body function and activity level according to the International Classification of Functioning, Disability and Health [4,7-9].

Previous studies show vast differences in protocol to measure motor fatigability in the lower limb [5]. Endurance time, decline in movement speed, decline in power and decline in movement accuracy are outcome parameters used during a fatiguing protocol to calculated motor fatigability on body function

level. The golden standard as outcome parameter however is to calculate motor fatigability as the decline in peak force[4].

Sustained maximal contractions and repetitive contractions are the isometric and concentric protocols used to provoke fatigue. According to literature, a sustained 30 seconds isometric contraction is the gold standard as a fatiguing protocol[5]. The observations of peak force can be plotted on a graph which allows to calculate the area between the axes and the curve in order to measure the static fatigue index. A decline of ± 30% in peak force under the curve is considerate the cut-off value for fatigability. One could argue that intermittent or submaximal contractions simulate motor fatigability during daily activity more closely, like walking[36]. In a recent study no significant differences between HC and MS were found during an intermittent protocol measuring hand grip fatigability in PwMS, contrary to the static protocol employed. Sustained maximal contraction in PwMS is supposed to be more reliable to measure fatigability[35].

Using repetitive concentric contractions as a fatiguing protocol is a different approach to assess motor fatigability on body function level. The biomechanical factors of muscle force generated during a concentric protocol might be more related to daily activities. Motor fatigability assessed on body function level using concentric contractions therefore might be more related to motor fatigability assessed on activity level. The dynamic fatigue index is calculated as a decline in average work between the beginning of the protocol and the end of the protocol, by comparing mean peak force. Variations made are the number of repetitions looked at, most studies used the first and last three to five repetitions[12-21,23].

Submaximal contractions were not used because they are influenced more by problems with selective motor control which requires a lot of concentration. This makes standardization of such a protocol difficult[37]. Secondly, PwMS often perform near their maximal strength during daily activities, which can lead to an underestimation of the influence of fatigability during daily activity such as walking[38]

Both of the aforementioned protocols measure muscle fatigability on a body function level of the International classification of Functioning, Disability and Health (ICF). In order to measure motor fatigability of the lower limb on activity level, one could apply a walking task, in which the 6MWT is most commonly used as it is the gold standard to measure walking endurance[10]. Walking is a dynamic

activity with concentric and eccentric motion of different muscles, which could correlate more with motor fatigability in daily activity[18,24]. The reliability and validity of these different protocols is still subject to more research before being considered as a golden standard. Impairment in walking is a major contributing factor to independence and self-sufficiency in PwMS [5,10,11]. More than one third of PwMS showed walking fatigability in a study by Leone et al.[10], with higher prevalence in the more disabling groups according to the EDSS-score.

Previous research has tried to investigate motor fatigability during walking through objective measurements of walking speed[10], total distance walked[48], changes in gait parameters[49], changes in heart rate or a combination of the before mentioned parameters. Different formulas have been used to calculate a fatigue index using this parameters. Although these formulas are proven to be useful outcome measures to indicate walking fatigability, psychometric properties and cutoff values are still lacking. A more recent study examined a method to objectively measure motor fatigability during walking by means of a decline in distance walked (DWI) of more than 15% during a six-minute walking test (6MWT), which resulted in a good test-retest reliability and a intraclass correlation coefficient of .762 for PwMS[10]. The 15% threshold for walking related motor fatigability can be observed in most studies relating to subjects with neurological issues[52]. These studies show an average decline in walking distance of 14-17%. For the purpose of this study with a specific population of PwMS, a threshold of 10% was applied to evaluate walking related motor fatigability based on Van Geel et al[57].

Walking fatigue is generally measured as a decrease in performance that results from changes in not only peripheric factors but central and physiological factors as well. These factors in turn depend on environmental conditions and mental capacity. Walking fatigue is a result from interactive changes between central[20,31,32], peripheric and physiological factors[50]. The existing literature does however not address the underlying, influencing or related factors of walking related motor fatigability. Therefore a cross sectional observational study was conducted to examine the underlying causes of walking-related motor fatigability, along with other related and influencing factors to make up a clinical profile of PwMS exhibiting walking-related PMF. The purpose of the study is, to examine motor fatigability on a body function level with a static and dynamic protocol of the knee extensors, knee flexors and ankle dorsiflexors to find a correlation with walking fatigability.

2. Methods

2.1 Subjects

Subjects with MS were recruited from the Rehabilitation and MS center in Overpelt, National MS center in Melsbroek and the database of the Biomedical Research Institute (BIOMED), Hasselt University at REVAL. Healthy controls were contacted true social media, participating friends and other contacts.

The inclusion criteria were defined as: age between 18 and 70 years, confirmed diagnosis of MS according to the McDonald criteria, able to walk independently or with unilateral support for 6 minutes without rest. The exclusion criteria applied were: Exacerbation or relapse within the last 3 months before the study, not yet stabilized from previous relapse, medical condition interfering with walking ability such as cardiac or respiratory diseases, arthritis, fibromyalgia, stroke and Parkinson. The study was approved by the ethical committee of the University of Hasselt. All subjects gave there informed written consent to participate in this study.

In total, 15 PwMS and 10 age- and gender matched healthy controls (HC) were included in this study. Subjects were subdivided into groups based on our primary outcome Distance Walked Index (DWI) which was calculated with the distance walked minute per minute during a 6 Minute Walk Test (6MWT). DWI was calculated using the following formula: $((Distance\ walked\ in\ minute\ 6 - Distance\ walked\ in\ minute\ 1)/\ Distance\ walked\ in\ minute\ 1) \times 100$[10,51-53]. Seven PwMS were allocated to the walking-related performance fatigability group (walking fatigability , WF) and eight PwMS to the group without walking-related performance fatigability (non-walking fatigability, NWF) as they scored less than 10% decline on DWI.

2.2 Study design and procedure

This study has a cross sectional observational design. It started in February 2019 and concluded in May 2019. Upon arrival, the subjects signed their informed written consent and subsequently started with the 6 minute walking test. Walking related performance motor fatigability was tested, using the distance walked index (DWI).

Hereafter, subjects were randomly allocated to start with either part A or B. Part A was a series of tests to assess maximal voluntary force and static and dynamic fatigue of the quadriceps, hamstrings

and dorsiflexors of the ankle of the weakest leg. Part B consisted of randomly allocated motoric, cognitive and coordination tests. Subjects immediately started with the second part after completing part one. Subjects were given a small rest period between protocols. After the examinations, PwMS were handed self-reported questionnaires which could be answered at home and be returned by mail.

2.3 Measurements

Following demographic data was collected from the subjects: name, gender, date of birth, length, weight, nationality and place of residence. In addition, for PwMS the following MS-specific data was collected using self-reported questionnaires: MS type, duration of illness, date of last relapse (the last time the subject experienced severe symptoms of MS), name of treating neurologist or rehabilitation physician, EDSS-score (scale taken by neurologist or rehabilitation physician to evaluate the overall clinical state and progression of MS), FS score (to evaluate different function domains of MS), medication, additional treatments (e.g. physical therapy, rehabilitation), other influencing conditions (e.g. migraine, diabetes, osteoarthritis, ...), usage of a walking aid in daily life (e.g. walking stick, rollator). Only preliminary data was available for the following MS-specific variables in present study: EDSS-score, other influencing conditions and usage of a walking aid in daily life.

2.3.1 Distance walked index during 6MWT

The 6MWT test was conducted in a 30 meter corridor at REVAL, Hasselt University. Subjects were instructed to walk as fast as they could for six minutes straight. No encouragements were given during the test and the usage of unilateral, assistive advice was allowed if necessary.

Outcome parameters measured were distance walked minute by minute and total distance walked. Walking related performance motor fatigability (walking fatigability) was calculated, using the distance walked index (DWI). DWI can be defined as the percentage of decline from minute six to minute one[10]. DWI was measured using the following formula: $\frac{\text{Distance walked in minute 6} - \text{Distance walked in minute 1}}{\text{Distance walked in minute 1}} \times 100$. Based on a cut-off value of 10% PwMS were subdivided into groups with (>10% DWI) or without (<10% DWI) walking related fatigability (WF, NWF)[53,57].

2.3.2 T25FW

Timed 25Foot Walk (T25FW): was conducted twice consecutively in the same hallway as the 6MWT to assess maximal walking speed. Subjects were instructed to walk as fast as possible but within their

own safety limits. At least one of their feet needed to be in touch with the ground at any given time during each stride to avoid running.

2.3.3 Muscle strength and Static-, dynamic fatigue

2.3.3.1 Procedure

To increase organizational flow, a consequent chronical order was performed: first static, later dynamic fatigue was evaluated, beginning with knee extensors, followed by knee flexors and ankle dorsiflexors. For all contractions, subjects were asked to perform their maximal effort from the start of muscle activation (Maximal Voluntary Contraction; MVC).

Fatigue was assessed by a prolonged (30s) isometric contraction (Static fatigue) or a series of 15 concentric contractions (dynamic fatigue). These fatiguing protocols were preceded and followed by a 5s isometric contraction, intercepted by, rest periods of maximal 10 seconds. A small break was conducted in between testing the aforementioned muscles, allowing subjects to recover. During this moment, the Biodex system was adjusted by the examiner to the necessary requirements of the standardized starting position for the next test. All tests were examined by the same examiner, in the same order for every subject.

2.3.3.2 Subject positioning

Unilateral knee extension and flexion was tested in seated position using a Biodex System 3, Biodex Medical Systems, Shirley, NY, USA. All tests during part A were evaluated for the weakest leg. Participants were stabilized with chest, hip and leg straps. Arms folded across their chest and hands grasping straps. The seat back was tilted so that the hip joint angle was 90° flexion (0° is hip extended). The lower leg was stabilized at the leverarm from the Biodex. The knee angle for isometric knee extension and flexion was set at 75° (0° is knee fully extended) with the axis of rotation of the Biodex aligned with the axis of the knee.

To measure ankle dorsiflexors, subjects were positioned in a different starting position. The seat back was tilted down so that there was no back support. The lower leg was stabilized with Velcro straps and the foot was attached to the leverarm of the Biodex mechanism, with the rotational axis aligned with the ankle dorsi-/plantarflexion axis. The angle of the hip joint was 110° flexion and angle of the knee joint was 60° extension. A neutral position between plantarflexion and dorsiflexion was for isometric testing.

2.3.3.3 Muscle strength (F) (5s isometric MVC)

Muscle strength was measured by peak force during the 5s isometric MVC's. In total, four 5s isometric MVC's were conducted (preceding and following static and dynamic fatiguing protocol). The first 5s MVC (preceding static fatiguing protocol, [A]) is considered to be most valid to analyze muscle strength as the targeted muscles were not yet exposed to the fatiguing protocols. The other three MVC's [B,C,D] were included as additional data as they may contribute as underlying or related factors to walking fatigability and walking capacity, considering these outcome measures were affected by the fatiguing protocols. Figure 1. shows the sustained 30s (static) fatiguing protocol, preceded and followed by a 5s isometric contraction. Figure 2. shows the isokinetic (dynamic) fatiguing protocol, preceded and followed by a 5s isometric contraction.

2.3.3.4 Static fatigue

Static fatigue was measured using a maximal 30 seconds isometric contraction. The static fatigue index was calculated as the percentage difference between maximal peak torque within the first five seconds compared with the maximal peak torque in the last five seconds. Formula: $\left(\frac{MVC\ within\ first\ 5s - MVC\ within\ last\ 5s}{MVC\ within\ first\ 5s}\right) \times 100$.

In order to get as much information as possible about muscle performance on a functional level within each subject, a second method was used to calculate PMF, by calculating the relative decrease in maximal peak torque between the 5s MVC preceding and following the static fatiguing protocol. This is called the static decline in maximal force. Figure 1. Provides an overview of the preceding and following 5s MVC with in between the 30s isometric MVC.
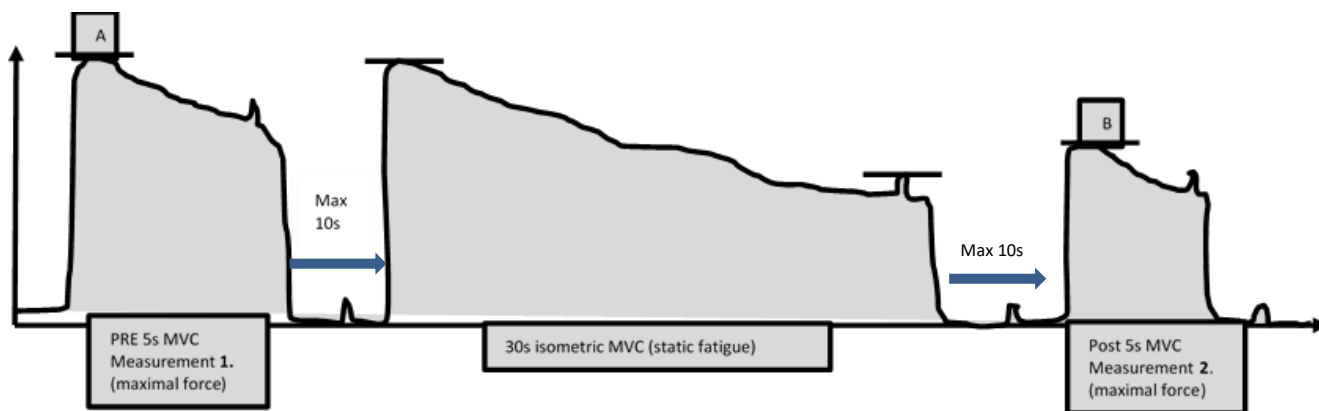

Figure 1. The performed consequent chronical order of tests measuring muscle strength and motor fatigability: 1) 5s isometric MVC [A], 2) 30s sustained maximal contraction (=static fatiguing protocol), 3) 5s isometric MVC [B].

2.3.3.5 Dynamic fatigue

Dynamic fatigue was measured using a maximal 15 repetitions isokinetic protocol. Subjects were instructed to perform 15 consecutive concentric contractions at a velocity of 30°/s. For knee extension, the contraction started from a joint angle of 90° flexion of the knee and ended at 20° extension of the knee. For knee flexion, the contraction started at 20° knee extension and ended at 90° knee flexion (0° is knee fully extended). As described in paragraph 5.3.2.2, subjects positioning changed to perform 15 consecutive concentric contractions. The contraction started from a joint angle of 20° plantarflexion and ended at 20° dorsiflexion. All concentric ankle dorsiflexion contractions were executed at a velocity of 20°/s. After every repetition, the joint was returned passively towards the starting position by the examiner. All repetitions were consecutively executed without any rest.

The dynamic fatigue index, which describes the decline in maximal produced torque during a isokinetic protocol, was calculated as the decline in mean torque of the first three isokinetic contractions compared to the last three isokinetic contractions[30]. Formula:

$$\left(\frac{Mean\ torque\ first\ 3\ contractions - Mean\ torque\ last\ 3\ contractions}{Mean\ torque\ first\ 3\ contractions} \right) \times 100.$$

For this protocol a second approach to dynamic fatigue was calculated as well. By calculating the relative decrease in maximal peak torque between the preceding and following 5s MVC. This is called the dynamic decline in maximal force. As there is 10s of rest between the fatigue protocol and the following 5s MVC, recovery is present and the effect of fatigue will be underestimated by this method.
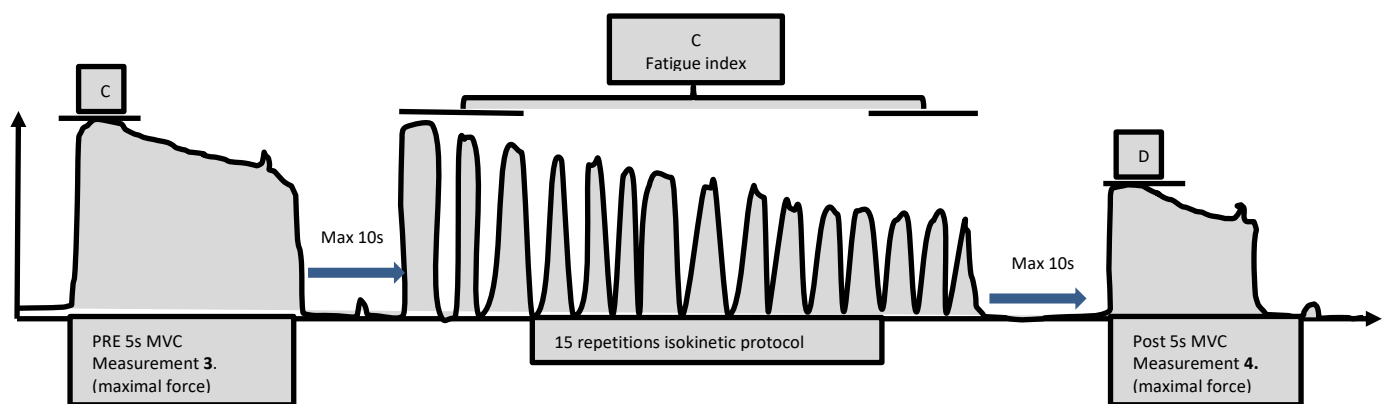

Figure 2. An overview of The performed consequent chronical order of tests measuring muscle strength and motor fatigability after subsequently after figure 1. : 1) 5s isometric MVC [C], 2) 15 maximal concentric contractions (dynamic fatigue protocol), 3) 5s isometric MVC [D].

2.4 Statistical analyses

For data analysis, subgroups were made based on population (healthy controls and patients with multiple sclerosis) and on the DWI, PwMS with or without walking fatigability (WF, NWF). For all data normal distribution was tested using the Shapiro-Wilk test. Homoscedasticity was analyzed based on the median with Levene's test. The assumptions for using parametric tests were not fulfilled as the sample size was to small, heteroscedasticity of residues occurred as well as no normal distribution of residues. Therefore data was further analyzed using non-parametric tests. Comparing data between multiple subgroups was done using the Kruskal Wallis test. To evaluate which subgroups were responsible for the significant interclass differences, post-hoc tests were performed using Mann Whitney U tests. Multiple comparison of variables increases the chance of type-I errors. Bonferroni was used for the correction of the significance level. Intergroup comparisons were made for three groups: ($\alpha = \frac{0.05}{3} = 0.016$). The contribution of each independent variable to the as dependent variables (DWI and total distance) was evaluated. To test the strength and direction of the linear relationship between two continuous variables Spearman Rank Order Correlation (rho) was used as assumptions for using the parametric Pearson correlation coefficient (r) test were not fulfilled. To interpret the strength of the relationship between values with the correlation coefficient, guidelines of Cohen (1988, pp. 79-81) were used. Small (r=0.10-0.29), medium (r=0.30-0.49) and large (r=0.50-1.00) correlation. The level of statistical significance to evaluate test results was set at p<0,05. Statistical analyses were made with IBM SPSS software version 25.

3. Results

3.1 Descriptive data

An EDSS-score was reported for 8 out of 15 subjects with MS. The other 7 PwMS did not write down the EDSS-score down on the self-reported questionnaires or had not yet returned their self-reported questionnaires. PwMS registered EDSS scores between 0 and 5, (mean=2.06). In subgroup with DWI > -10% (n=7), four EDSS-scores were available and ranged from 2 to 5 (mean=3). In the subgroup with DWI < -10%, four EDDS-scores were available as well with a range from 0 to 1.5 (mean=1). An overview of the subjects' characteristics are shown in table 1.

Table 1. *Demographic and clinical characteristics for the total MS and HC sample and subgroups based on DWI*

	Total MS sample	Subgroups based on DWI		Total HC sample
		≥ -10%	≤ -10%	
	(n=25)	(n=7)	(n=8)	(n=10)
Age (years)	48.57±13.92	54.16±3.49	48.52±13.92	48.44±19.09
Gender (F/M)	13/2 (86.6/13.3)	7/0 (100/0)	6/2 (75/25)	6/4 (60/40)
EDSS availability	8/15(53%)	4/7 (57.1%	4/8 (50%)	/
EDSS-score	2.06±1.47	3.12±1.25	.92±1.42	/

Abbreviations. MS= Multiple Sclerosis, DWI= Distance Walked Index, HC= Healthy Controls, n= number of subjects , F= Female, M= Male, EDSS= Expended Disability and Severity Scale, Missing data MS: Age n=1, EDSS-score n=7, Missing data (≥ -10%): Age n=1, EDSS-score n=3, Missing data (≤ -10%): EDSS-score n=4, Missing data HC: Age n=1.

3.2 Distance walked index (DWI)

Significant differences in the relative decline in distance walked between minute one to six were observed between healthy controls and PwMS. Within PwMS, 7 out of 15 subjects scored above the cut-of value of 10% decline in distance walked and were as such subdivided in the subgroup with walking fatiguability (WF). The other eight subjects were presented in PwMS without walking fatigability (NWF).

Table 2. *Overview of subscale scores on DWI (Median (Interquartile Range)) for total MS, HC sample and subdivided groups (WF,NWF) and P-value of between group differences (HC -MS, WF – NWF).*

	HC	MS	HC -MS	WF	NWF	WF - NWF
	Mdn (IQR)	Mdn (IQR)	P	Mdn (IQR)	Mdn (IQR)	p
DWI	-.4450 (5.05)	-7,0700 (14.58)	.002	-18,1800 (17.22)	-3,6050 (4.07)	.000

Abbreviations. HC= Healthy Controls, MS= Multiple sclerosis, HC – MS= between group difference, p= P value, WF= MS >-10%, NWF= MS <-10%, WF – NWF= between group differences, DWi= Distance walked index, Mdn= median, IQR= interquartile range.

3.3 Total distance walked and FTST

Total distance walked during the 6MWT was significantly lower in the overall MS sample compared to healthy controls. In the subdivided MS group [> -10%] DWI, a significantly lower total distance was covered during 6MWT compared to MS [< -10%] DWI. Table 3. provides an overview on median differences between the total MS and HC samples as well as the median difference between subdivided MS groups WF and NWF.

The significant differences in walking speed during the T25FW for the total MS sample and subdivided MS groups WF,NWF are shown in Table 3.

Table 3. *Overview of subscale scores on distance walked during 6MWT and T25FW (Median (Interquartile Range)) for total MS, HC sample and subdivided groups (WF,NWF) and P-value of between group differences (HC -MS, WF – NWF).*

	HC	MS	HC-MS	WF	NWF	WF-NWF
	Mdn (IQR)	*Mdn (IQR)*	p	*Mdn (IQR)*	*Mdn (IQR)*	p
Distance (M)	625.0 (77.25)	483.0 (186.00)	.008	412.0 (124.00)	551.5 (169.25)	.006
T25FW	3.445 (.78)	4.490 (1.46)	.000	5.29 (2.29)	3.970 (.69)	.029

Abbreviations. HC= Healthy Controls, MS= Multiple sclerosis, HC – MS= between group difference, p= P value, WF= MS >-10%, NWF= MS <-10%, WF – NWF= between group differences, Distance= total distance walked in meter during 6MWT, T25FW= Timed 25 foot walk.

3.4 Muscle strength (F) 5s MVC

3.4.1 Knee extensors

The total MS sample scored significantly lower in registered peak torque compared to healthy controls. In subdivided MS groups, subjects with walking fatigability registered significantly lower peak torque data compared to MS subjects who scored < -10% DWI. Results are shown in Table 4.

Table 4. *Overview of subscale scores on peak force of the knee extensors (Median (Interquartile Range)) for total MS, HC sample and subdivided groups (WF,NWF) and P-value of between group differences (HC -MS, WF – NWF).*

5s MVC	HC	MS	HC - MS	WF	NWF	WF - NWF
	Mdn (IQR)	*Mdn (IQR)*	*p*	*Mdn (IQR)*	*Mdn (IQR)*	*p*
Knee extensors [A]	153.6 (41.3)	120.5 (25.0)	.01	79.9 (60.8)	132.0 (54.5)	.009
[B]	144.3 45.3)	91.9 (68.2)	.004	77.7 (23.0)	115.6 (53.7)	.006
[C]	153.2 (48.8)	117.2 (59.4)	.004	85.4 (26.8)	133.9 (43.3)	.014
[D]	145.1 (55.4)	99.5 (54.5)	.005	87.7 (22.3)	126.7 (55.3)	.001

Abbreviations. 5S MVC= 5 second isometric maximal voluntary contraction, [A]= First peak force measurement (before static fatiguing protocol), [B]= second peak force measurement (after static fatiguing protocol), [C]= third peak force measurement (before dynamic fatiguing protocol), [D]= fourth peak force measurement (after dynamic fatiguing protocol), Mdn= Median, IQR= Interquartile range, p= P value, HC= healthy controls, MS= subjects with Multiple sclerosis, NWF= MS < -10% DWI, WF= MS > -10% DWI

A strong correlation (Rs=.629, p>.05) was observed for muscle strength measured in peak torque MVC [A] with the distance walked index for PwMS. These results were perceived in all four measurements of peak torque [A-D].

Lower significant correlation (Rs=.521, p>.05) was found for knee extensor muscle strength [A] compared with total distance walked in PwMS. Subdivided MS groups (WF, NWF) did not present a significant correlation with DWI. However, in the walking fatigability subgroup of MS, strong correlation (Rs=-.786, p>.05) was observed for knee extensor muscle strength [A] and total distance walked as the Spearman's Rho coefficient was even higher than the correlation the total MS sample (Rs=.521<.786). Results for all four measurements of knee extensors are summarized in Table 5.

Table 5. *Spearman rho correlation comparing muscle strength (F) of the knee extensors with Distance walked index and total distance walked during 6MWT in total MS sample and subgroups WF, NWF.*

	5s MVC	DWI				Total distance			
		HC	MS	NWF	WF	HC	MS	NWF	WF
		N=10	N=15	N=8	N=7	N=10	N=15	N=8	N=7
Knee Extensors	[A]	.103	.629*	.310	.000	.358	.521*	.929**	-.786*
	[B]	.286	.689**	.024	.429	.297	.539*	.690	-.714
	[C]	.237	.661**	.310	.143	.176	.514*	.833*	-.893**
	[D]	.043	.682**	-.190	.107	.394	.504	.357	-.893**

Abbreviations. 5S MVC= 5 second isometric maximal voluntary contraction, [A]= First peak force measurement (before static fatiguing protocol), [B]= second peak force measurement (after static fatiguing protocol), [C]= third peak force measurement (before dynamic fatiguing protocol), [D]= fourth peak force measurement (after dynamic fatiguing protocol), DWI= distance walked index, total distance= total distance walked during 6MWT, HC= healthy controls, MS= subjects with Multiple sclerosis, NWF= MS < -10% DWI, WF= MS > -10% DWI

3.4.2 Knee flexors

Knee flexor muscle strength did not significantly differ for the total MS sample in comparison to healthy controls (Mdn=50.1 - Mdn=67.1, p=.084) in measurement [A]. By statistically analyzing PwMS specifically with walking fatigability (Md=32.7) and PwMS without walking fatigability (Md=66.4), similar results could be observed for subdivided MS groups as there was no significant difference in the first measurement of muscle strength [A]. In the three other measurements however [B,C,D], significantly lower knee flexor muscle strength was reported for the total MS sample compared to Healthy controls. Even larger difference in knee flexor muscle strength was found between subdivide MS groups WF and NWF. Results are shown in Table 6.

Table 6. *Overview of subscale scores on peak force of the knee flexors (Median (Interquartile Range)) for total MS, HC sample and subdivided groups (WF,NWF) and P-value of between group differences (HC -MS, WF – NWF).*

5s MVC		HC	MS	HC - MS	WF	NWF	WF - NWF
		Mdn (IQR)	Mdn (IQR)	p	Mdn (IQR)	Mdn (IQR)	p
Knee flexors	[A]	67.1 (13.0)	50.1 (45.4)	.084	32.7 (24.0)	66.4 (25.5)	.072
	[B]	69.3 (19.0)	49.0 (37.5)	.012	30.1 (12.0)	62.8 (21.0)	.016
	[C]	73.6 (27.2)	47.3 (36.0)	.025	33.8 (23.8)	61.0 (23.6)	.014
	[D]	65.3 (27.1)	47.3 (29.5)	.025	39.7 (21.1)	59.7 (27.8)	.029

Abbreviations. 5S MVC= 5 second isometric maximal voluntary contraction, [A]= First peak force measurement (before static fatiguing protocol), [B]= second peak force measurement (after static fatiguing protocol), [C]= third peak force measurement (before dynamic fatiguing protocol), [D]= fourth peak force measurement (after dynamic fatiguing protocol), Mdn= Median, IQR= Interquartile range, p= P value, HC= healthy controls, MS= subjects with Multiple sclerosis, NWF= MS < -10% DWI, WF= MS > -10% DWI

Knee flexor muscle strength did not significantly correlate (Rs=.482, p>.05) to the distance walked index in total MS sample in measurement [A]. In the other three measurements however [B,C,D], knee flexor muscle strength did significantly correlate (Rs= .593-.614, p>.05) to DWI. No significant correlation was however found for the subdivided MS groups WD and NWF separately with DWI. Furthermore, knee flexor muscle strength data did not reveal significant correlation with total distance walked in total MS sample compared to healthy controls. None of the two subdivided MS groups (WF and NWF) related significantly with DWI. Even though no correlation with DWI was found, the subdivided MS group WF did show a significant correlation (Rs= -.786, p>.05) with total distance walked. This result was only observed in the last 5s MVC measurement [D], all other results did not yield significant correlation with total distance walked during 6MWT. Spearman's Rho correlation coefficients are shown in Table 7.

Table 7. *Spearman rho correlation comparing muscle strength (F) of the knee flexors with Distance walked index and total distance walked during 6MWT in total MS sample and subgroups WF, NWF.*

	5s MVC	DWI				Total distance			
		HC	MS	NWF	WF	HC	MS	NWF	WF
		N=10	N=15	N=8	N=7	N=10	N=15	N=8	N=7
Knee flexors	[A]	.209	.482	.071	-.179	.283	.246	.333	-.750
	[B]	-.310	.593*	.405	-.679	.600	.454	.310	-.429
	[C]	-.218	.607*	.381	-.464	.733*	.400	.333	-.714
	[D]	-.192	.614*	.381	-.143	.600	.393	.333	-.786*

Abbreviations. 5S MVC= 5 second isometric maximal voluntary contraction, [A]= First peak force measurement (before static fatiguing protocol), [B]= second peak force measurement (after static fatiguing protocol), [C]= third peak force measurement (before dynamic fatiguing protocol), [D]= fourth peak force measurement (after dynamic fatiguing protocol), DWI= distance walked index, total distance= total distance walked during 6MWT, HC= healthy controls, MS= subjects with Multiple sclerosis, NWF= MS < -10% DWI, WF= MS > -10% DWI

3.4.3   Ankle dorsiflexors

Ankle dorsiflexors muscle strength data did not reveal significant differences between total MS sample and healthy controls. However, subdivided MS group WF did reach significantly lower peak torque results (Mdn=6.6) compared to subdivided MS group NWF (Mdn=16.2, p=.028) in measurement [A]. Results are shown in Table 8.

Table 8. *Overview of subscale scores on peak force of the knee extensors (Median (Interquartile Range)) for total MS, HC sample and subdivided groups (WF,NWF) and P-value of between group differences (HC -MS, WF – NWF).*

	5s MVC	HC	MS	HC - MS	WF	NWF	WF - NWF
		Mdn (IQR)	Mdn (IQR)	p	Mdn (IQR)	Mdn (IQR)	p
	[A]	13.7 (10.8)	10.6 (17.3)	.169	6.6 (2.83)	16.2 (14.5)	.028
Ankle dorsiflexors	[B]	15.5 (7.9)	14.8 (10.3)	.422	13.8 (8.6)	15.0 (9.4)	.368
	[C]	20.3 (9.3)	15.4 (7.8)	.277	14.8 (4.13)	15.9 (9.45)	.570
	[D]	15.1 (6.5)	14.8 (9.3)	.651	14.6 (1.05)	18.5 (11.9)	.570

Abbreviations. 5S MVC= 5 second isometric maximal voluntary contraction, [A]= First peak force measurement (before static fatiguing protocol), [B]= second peak force measurement (after static fatiguing protocol), [C]= third peak force measurement (before dynamic fatiguing protocol), [D]= fourth peak force measurement (after dynamic fatiguing protocol), Mdn= Median, IQR= Interquartile range, p= P Value, HC= healthy controls, MS= subjects with Multiple sclerosis, NWF= MS < -10% DWI, WF= MS > -10% DWI, Missing values MS: n=3, Missing values WF: n=3.

Ankle dorsiflexors muscle strength in total MS sample did relate significantly (Rs=.622) to DWI in measurement   [A]. No significant correlation was found for ankle dorsiflexors muscle strength and the total distance walked during the 6MWT . Ankle dorsiflexors muscle strength in subdivided MS groups WF and NWF did not relate significantly to total distance walked during 6MWT. Spearman's Rho correlation coefficient are summarized in Table 9.

Table 9. *Spearman rho correlation comparing muscle strength (F) of the knee flexors with Distance walked index and total distance walked during 6MWT in total MS sample and subgroups WF, NWF.*

		DWI				Total distance			
	5s MVC	HC	MS	NWF	WF	HC	MS	NWF	WF
		N=10	N=15	N=8	N=7	N=10	N=15	N=8	N=7
Ankle dorsiflexors	[A]	.644	.622*	.143	-.400	-.483	.462	-.095	.600
	[B]	.301	.469	.548	-.400	-.300	.182	.357	-.400
	[C]	.134	.505	.766*	-.400	-.250	.256	.263	.400
	[D]	.201	.543	.810*	.316	-.200	.277	.476	-.632

Abbreviations. 5S MVC= 5 second isometric maximal voluntary contraction, [A]= First peak force measurement (before static fatiguing protocol), [B]= second peak force measurement (after static fatiguing protocol), [C]= third peak force measurement (before dynamic fatiguing protocol), [D]= fourth peak force measurement (after dynamic fatiguing protocol), DWI= distance walked index, total distance= total distance walked during 6MWT, HC= healthy controls, MS= subjects with Multiple sclerosis, NWF= MS < -10% DWI, WF= MS > -10% DWI, Missing values MS: n=3, Missing values WF: n=3.

3.5 Motor fatigability: static and dynamic decline in maximal force (F)

Static decline in maximal force (F), calculated as the relative decline in peak force from 5s MVC [A] to 5s MVC [B], showed no significant differences between total MS sample and healthy controls in all three muscle groups tested (knee extensors, knee flexors and ankle dorsiflexors). Between subdivided MS groups WF and NWF no significant differences were found either.

Dynamic decline in maximal force (F), calculated as the relative decline in peak force from 5s MVC [C] to 5s MVC [D], showed similar results as the Static decline in maximal force. No significant differences were obtained between total MS sample and healthy controls or between subdivided MS groups WF and NWF for knee extensor and knee flexor muscle groups. In ankle dorsiflexors a significant decline in maximal force was observed in healthy controls (Mdn=22.6) compared to total MS sample(Md=-0.5, p<.001). Data is summarized in Table 10.

Table 10. *Overview of subscale scores on static decline in maximal force (Median (Interquartile Range)) for total MS, HC sample and subdivided groups (WF,NWF) and P-value of between group differences (HC -MS, WF – NWF).*

Motor fatigability		HC	MS	HC-MC	WF	NWF	WF -NWF
		Mdn (IQR)	Mdn (IQR)	p	Mdn (IQR)	Mdn (IQR)	p
Static decline in maximal force	Knee ext	10.3 (16.4)	18.5 (21.3)	.261	15.2 (48.7)	21.6 (20.7)	.152
	Knee flex	2.9 (15.7)	-2.0 (10.4)	.907	-7.5 (28.6)	3.2 (10.2)	.281
	Ankle dor	-13.1 (47.6)	-21.4 (126.3)	.422	-91.7 (222.8)	4.5 (116.3)	.214
Dynamic decline in maximal force	Knee ext	7.4 (14.5)	0,0 (30.0)	.935	4.2 (20.6)	-5.7 (33.0)	.463
	Knee flex	2.9 (15.7)	-2.0 (10.4)	.907	-7.5 (28.6)	3.2 (10.2)	.281
	Ankle dor	22.6 (16.5)	-0.5 (15.0)	.000	1.4 (42.7)	-0.5 (16.1)	.933

Abbreviations. Static decline in maximal force= (MVC [A] – MVC [B]) / MVC [A], Dynamic decline in maximal force= (MVC [C] – MVC [D]) / MVC [C], Mdn= Median, IQR= Interquartile range, p= P value, HC= healthy controls, MS= subjects with Multiple sclerosis, NWF= MS < -10% DWI, WF= MS > -10% DWI, knee ext= knee extensors, knee flex= knee flexors, ankle dor= ankle dorsiflexors, Missing values MS= ankle dor n=3, Missing values WF: ankle dor n=3.

Static decline in maximal force did not relate significantly to DWI or total distance walked during 6MWT in any of the three tested muscle groups.

Dynamic decline in maximal force in the overall MS sample did not relate significantly to DWI or total distance walked. The knee extensors in subdivided MS group NWF, revealed a large significant spearman's Rho coefficient with DWI (Rs=.762) and total distance walked (Rs=.714). Spearman's Rho coefficients are shown in Table 11. on the following page.

Table 11. *Spearman rho correlation comparing static and dynamic decline in maximal force (F) of the knee flexors, knee flexors and ankle dorsiflexors with Distance walked index and total distance walked during 6MWT in total MS sample and subgroups WF, NWF.*

Motor fatigability		DWI				Total distance			
		HC N=10	MS N=15	NWF N=8	WF N=7	HC N=10	MS N=15	NWF N=8	WF N=7
Static decline in maximal force	Knee ext	-0,486	0,404	0,286	-0,286	0,285	0,164	0,095	-0,679
	Knee flex	,711*	0,343	-0,214	0,571	-0,517	0,186	0,095	-0,357
	Ankle dor	0,393	0,301	-0,214	0,200	-0,033	0,406	-0,119	0,800
Dynamic decline in maximal force	Knee ext	0,444	0,043	,762*	-0,107	-0,139	0,082	,714*	0,000
	Knee flex	,711*	0,343	-0,214	0,571	-0,517	0,186	0,095	-0,357
	Ankle dor	-0,351	-0,154	-0,167	-0,400	0,200	-0,049	-0,071	0,400

Abbreviations. Static decline in maximal force= (MVC [A] – MVC [B]) / MVC [A], Dynamic decline in maximal force= (MVC [C] – MVC [D]) / MVC [C], DWI= distance walked index, Total distance= total distance walked during 6MWT, HC= healthy controls, MS= subjects with Multiple sclerosis, NWF= MS < -10% DWI, WF= MS > -10% DWI, knee ext= knee extensors, knee flex= knee flexors, ankle dor= ankle dorsiflexors, Missing values MS= ankle dor n=3, Missing values WF: ankle dor n=3.

3.6 Motor fatigability: static and dynamic fatigue index

Static fatigue index, as the relative decline in peak torque (F) measured within the first 5s and last 5s of the 30s sustained, isometric, fatiguing protocol did not reveal significant differences between the MS sample and healthy control for the three muscle groups tested. Subdivided MS group WF results showed a significant higher static fatigue index compared to subdivided MS group NWF for knee flexors and ankle dorsiflexors.

Dynamic fatigue index, as the relative decline in mean force from the last 3 repetitions to the first 3 repetitions within the 15 (concentric) repetitions fatiguing protocol, did not show significant differences between total MS sample and healthy controls or between subdivided MS groups WF and NWF.

Table 12. *Overview of subscale scores on static decline in maximal force (Median (Interquartile Range)) for total MS, HC sample and subdivided groups (WF,NWF) and P-value of between group differences (HC -MS, WF – NWF).*

Motor fatigability		HC Mdn (IQR)	MS Mdn (IQR)	HC-MC p	WF Mdn (IQR)	NWF Mdn (IQR)	WF -NWF p
Static fatigue index	Knee ext	17.0 (14.9)	22.1 (15.8)	.367	22.1 (11.3)	19.9 (20.5)	.613
	Knee flex	20.1 (7.3)	25.2 (13.9)	.064	31.7 (6.4)	23.4 (10.0)	.014
	Ankle dor	30.2 (12.4)	31.9 (31.5)	.508	58.6 (32.6)	30.1 (7.4)	.004
Dynamic fatigue index	Knee ext	3.1 (27.5)	-1.3 (24.6)	.177	3.0 (25.0)	-8.2 (23.4)	.336
	Knee flex	18.5 (19.0)	7.4 (20.6)	.138	6.7 (19.8)	8.8 (13.9)	.536
	Ankle dor	35.5 (28.2)	32.6 (7.3)	.862	39.2 (13.3)	29.2 (16.7)	.073

Abbreviations. Static fatigue index= decline in peak force last 5s to first 5s of 30s sustained MVC, Dynamic fatigue index= decline in mean force last 3 concentric contractions to first 3 concentric contractions, Mdn= Median, IQR= Interquartile range, p= P value, HC= healthy controls, MS= subjects with Multiple sclerosis, NWF= MS < -10% DWI, WF= MS > -10% DWI, knee ext= knee extensors, knee flex= knee flexors, ankle dor= ankle dorsiflexors, Missing values MS= ankle dor n=3, Missing values WF: ankle dor n=3.

Static fatigue index of the knee flexors related significantly (Rs=-.564) to DWI in total MS sample. The ankle dorsiflexors static fatigue index related strongly in the subdivided MS group NWF. The static fatigue index did not relate significantly to total distance walked (6MWT) in total MS sample or in the subdivided MS groups for any of the three muscle groups tested.

Dynamic fatigue index showed no significant correlation coefficient with DWI or total distance walked (6MWT) in total MS sample for any of the three muscle groups tested. However, by analyzing subdivided MS groups WF and NWF separately, data showed the dynamic fatigue index of the ankle dorsiflexors to be strongly related to DWI and the dynamic fatigue index of the knee extensors to be strongly related to total distance walked in subdivided MS group WF. Spearman's Rho data for both the static and dynamic fatigue index are summarized in Table 13.

Table 13. *Spearman rho correlation comparing static and dynamic decline in maximal force (F) of the knee flexors, knee flexors and ankle dorsiflexors with Distance walked index and total distance walked during 6MWT in total MS sample and subgroups WF, NWF.*

Motor fatigability		DWI				Total distance			
		HC N=10	MS N=15	NWF N=8	WF N=7	HC N=10	MS N=15	NWF N=8	WF N=7
Static fatigue index	Knee ext	0,347	-0,250	-0,357	-0,107	0,309	-0,175	0,167	-0,643
	Knee flex	-0,410	-,564*	-0,119	-0,107	-0,117	-0,186	0,429	0,500
	Ankle dor	-0,427	-0,378	,952**	0,400	-0,250	-0,189	0,571	0,400
Dynamic fatigue index	Knee ext	0,140	-0,239	-0,262	0,357	0,406	-0,346	0,571	-,821*
	Knee flex	0,276	0,125	0,310	-0,500	0,383	0,218	0,500	0,179
	Ankle dor	-,669*	-0,512	0,072	-1,000**	0,500	-0,512	-0,156	-0,400

Abbreviations. Static decline in maximal force= (MVC [A] – MVC [B]) / MVC [A], Dynamic decline in maximal force= (MVC [C] – MVC [D]) / MVC [C], DWI= distance walked index, Total distance= total distance walked during 6MWT, HC= healthy controls, MS= subjects with Multiple sclerosis, NWF= MS < -10% DWI, WF= MS > -10% DWI, knee ext= knee extensors, knee flex= knee flexors, ankle dor= ankle dorsiflexors, Missing values MS= ankle dor n=3, Missing values WF: ankle dor n=3.=significant level <0.05, **= significant level <0.01.*

4. Discussion

Few studies have previously investigated correlation between motor fatigability on a body function level and walking related motor fatigability on an activity level. Within this study walking related motor fatigability was measured by calculating the Distance Walked Index during a 6MWT[10,51-53]. This recently new method to assess fatigability during walking is yet been tested on underlying correlations with periphericfactors such as muscle strength and motor fatigability of the lower limb in PwMS. The aim of this study was: a) to determine the correlation of muscle strength, measured as peak torque during a 5s isometric MVC before and after fatiguing protocols, with DWI and total distance walked (6MWT) and b) to determine if motor fatigability, tested by applying isometric and concentric fatiguing protocols, related with DWI or total distance walked.

Walking related motor fatigability had a prevalence of 46.6% in the total MS sample, as 7 out of 15 PwMS scored [> -10%] on DWI and were allocated as such in the subgroup WF. Furthermore, the subdivided MS group WF (based on DWI > -10%) achieved a median score of 412m on the total distance walked during 6MWT, which was well below the 551m median score of subdivided MS group NWF. During this trial the T25FW was conducted as an additional test to analyse walking speed as a parameter for walking ability along with DWI and total distance walked. The subdivided MS group WF showed a median score of 5.29 seconds compared to 3.97 seconds in subdivided MS group NWF. The overall MS sample displayed a median score of 4.29 seconds. One subject with MS used an assistive device (walking stick) for safety.

Preliminary data on EDSS-scores was available for 53.3% of the total MS sample, with a mean score of 2.06. All but one subjects scored below the cut of value of 4 on the EDSS-scale, which is defined as the cutoff value for mild disability. In the subdivided MS groups WF and NWF, preliminary data on EDSS-scores was available for 57% and 50% of participants respectively. The subdivided MS group NWF scored a mean EDSS-score of 1.0 and the subgroup WF scored a mean EDSS-score of 3.0.

Comparing data from DWI, total distance walked and T25FW with data from previous studies on walking ability in MS, suggests that the total sample of MS from present study score well below the threshold of moderate disability (i.e. EDSS-score <4), even in the subdivided MS group with WF. Although limitations in walking ability emerge already in the early (mild disability) stages of MS, walking related impairments are more present in PwMS with moderate disability (EDSS >4-6.5). Leone

et al. even stated that higher EDSS-scores related to increased decline in walking speed of prolonged tests[10]. Interpretation of present study results should be made cautiously as the relatively low scores on EDSS-scale, total distance walked (6MWT) and T25FW in our study can lead to an underestimation of the relation between peripheric factors (muscle strength, motor fatigability) and walking ability[14,24,58].

The first objective was to analyse the clinical relevance of muscle strength in relation with DWI, measured in three different muscle groups for the total MS sample. Knee extensor, knee flexor and ankle dorsiflexor muscle strength showed a strong correlation with the DWI. When investigating whether the relationship between each muscle group and the DWI differed, systematically greater correlation with DWI was found for knee extensor strength compared to knee flexor and ankle dorsiflexor strength.

The correlation coefficients within the four (5s isometric MVC) measurements of knee extensor and knee flexor muscle strength showed stronger correlation with DWI after both the static and dynamic fatiguing protocol (measurement [B] and [D]) compared to the correlation coefficient before both of the fatiguing protocols. Maximal muscle strength, influenced by the preceding isometric or concentric fatiguing protocols related more to walking fatigability.

Secondly, the relationship between muscle strength and total distance walked during 6MWT was assessed. Only knee extensor strength showed a significant correlation with the total distance walked. In the subdivided MS group WF, correlation between knee extensor strength and total distance walked was even higher compared to the subgroup NWF and total MS sample.

Muscle strength of the quadriceps might be more valuable as a predicting factor for walking related motor fatigue compared to walking capacity or walking ability, as the spearman's Rho correlation coefficient between knee extensor strength and DWI was observed to be significantly stronger than the correlation coefficient between knee extensor strength and total distance walked.

Previous studies on walking ability in MS reported similar findings as the mild disability group scored a significant correlation of knee extensor strength with the 2MWT. However, comparing the link between knee flexor strength and knee extensor strength with walking capacity showed systematically greater correlation in the knee flexors. The highest and most significant correlations in that study were

observed in the moderate disability group while in the mild disability group correlations were generally low and not significant. Considering these results, knee flexor strength might increasingly relate stronger with DWI when evolving to the later stages of MS, as knee flexion strength decreases below a certain threshold where it effects gait biomechanics and therefore walking capacity. Secondly, the total MS sample performed considerably well during knee flexion measurements. This might have induced a floor effect, which resulted in a reduced relationship between knee flexor strength and walking capacity[14,24].

The second objective of this study was to analyse the clinical relevance of motor fatigability in relations to walking related motor fatigability and walking capacity. The first method used to calculate motor fatigability on body function level was the Static decline in maximal force[42,43]. No correlation was found between this fatigue index and DWI or total distance walked. A study by Skurvydas et al. used a similar calculation method (in combination with measurements of central fatigue) which resulted in decreases in muscle torque up to 65%. Whereas the total MS sample in the study at hand revealed a mean decline of no more than 10%. This might be explained due to the use of a 2-min fatiguing protocol instead of a 30s protocol[22]. More profound correlation might have been occurred using a longer isometric fatiguing protocol, but for the purpose of this study isometric and isokinetic fatiguing protocol were matched in time to compare one another.

The second method employed to calculate motor fatigability on a body function level was the Dynamic decline in maximal force. No significant relationship was identified with DWI or total distance walked in any of the three tested muscle groups. Both Static and Dynamic decline in maximal force calculations were based on the 5s isometric MVC as they preceded and followed [B,D] the static and dynamic fatiguing protocols respectively. As there is a 10s rest period between the fatigue protocol and the following 5s MVC, subjects were able to recover, potentially resulting in underestimation of the fatigue effect.

The third method used to calculate motor fatigability on body function level was the static fatigue index. The fatigue index of knee flexors in the total MS sample showed strong correlation with DWI. No correlations was however found with the total distance walked. Comparing data for this static fatigue index is difficult as no study has used this calculation method when testing lower limb muscle fatigability. Wolkorte et al. (2015, 2016) used a variation of this protocol by comparing mean torque

within the first and last 6 seconds in a 2 minute protocol, but no results were reported related to walking. As to our data, motor fatigability shows a stronger correlation with walking related motor fatigability compared to walking capacity.

The fourth method used to calculate motor fatigability on body function level was the Dynamic fatigue index. Although previous studies showed a strong relationship between knee extensor motor fatigability and walking capacity, our data did not reveal a relation for those parameters in the total MS sample. However, data from the subdivided MS group did reveal a strong link between muscle fatigue in the knee extensors with the total distance walked. This result is in line with a study by Broekmans et al. as descriptive date (EDSS-score, T25FW, total distance walked) was more comparable to our subdivided MS group WF as compared to our overall MS sample. The sample used in this study of PwMS in Broekmans et al. had a large moderate disability group, whereas mainly mild disability was represented in our study[14].

Lastly, strong correlation was observed for the dynamic fatigue index of the ankle dorsiflexors in the subdivided MS group WF. A study from 2013 revealed that ankle dorsiflexor weakness occurred significantly more in PwMS compared to healthy controls. Furthermore this impairment correlated strongly with standing balance in PwMS. The relationship between increased muscle weakness and decreased muscle control has an impact on postural balance and gait. Motor fatigability in the ankle dorsiflexor therefore can be a contributing factor to walking related motor fatigability according to our data[59].

An interesting observation during the isokinetic fatiguing protocol indicated that healthy controls had a much more stable pattern in the maximal torque produced troughout all concentric contractions. The total MS sample especially the subdivided MS group with WF, showed great variability between the maximal peak torque produced for each contraction. Further research recommendations might include using a protocol with a larger duration of 30 to 50 repetitions[15,16,44,45], as a result a more predictable outcome might be obtained and the dynamic fatigue index could be calculated as the relative decrease in mean torque between a more profound variation of first to last repetitions. A second recommendation is using a pretrial before the actual test, including a sufficient rest period to familiarize with the isokinetic protocol.

During this study we encountered some methodical limitations: whenever subjects perform in more than one condition there is a risk of carryover effects. The sequence of tests was fixed and not randomized. Secondly, no warm-up was included before testing because the implementation of the interpolated twitch technique during the knee extensor protocol. A warm-up can provide higher conduction velocity, which translates in faster muscle fiber activation and an increase in power output[47]. PwMS n=3, reported that the 6MWT under standardized conditions felt easier than daily walking activities outside. Therefore higher walking speed could be reached and their 'normal' walking ability could possibly be underestimated. Recently a new way of calculating the static fatigue index (as 100%*[1-Auc/HAuc]) was investigated. Surakka et al. concluded that this method showed a good test-retest reliability and validity to measure muscle fatigability. In our study we tried to use this protocol, but due to the inability to extract the data needed, alternative calculations of the static fatigue index had to be used. Further research should nonetheless strive to include postural balance and hip flexion/extension strength as possible underlying variables to walking related motor fatigability to increase content validity of the study. Further research should be conducted with a larger sample size of PwMS, where participants with moderate disability (EDSS scores: >4.5 EDSS < 6.5) are represented more.

5. Conclusion

Muscle strength of all three measured muscle groups during this study, related to motor fatigability on an activity level during walking. Our data suggested the strongest correlation with knee extensor. However, comparing this data with previous studies suggest that the link between muscle group strength and walking capability depends on the level of disability, where moderate disability groups will show increasingly stronger correlation of knee flexor weakness with walking capability. Ankle dorsiflexor weakness is an important outcome parameter for walking capability as well, as it is a contributing factor to walking fatigability.

Motor fatigability measured on body function level with the methods used in our study suggest that the static fatigue index of the knee flexors is a valuable underlying factor for walking fatigability in PwMS. Results from the dynamic fatigue index only showed a relationship with walking capability in the subdivided MS group with walking fatigability, which might suggest that this Dynamic fatigue index could be more useful in the later stages of disability in MS.

Reference List

1. Makris, A., Piperopoulos, A., Karmaniolou, I. & Anesth, J. (2014). Multiple sclerosis: basic knowledge and new insights in perioperative management. 28: 267. https://doi.org/10.1007/s00540-013-1697-2.
2. Khan, L., Turner-Stokes, L., Ng, T., & Kilpatrick, B. (2007). Amatya. Multidisciplinary rehabilitation for adults with multiple sclerosis. Cochrane Database Syst Rev (2) (2007), p. CD006036.
3. Khan, F., & Amatya, B. Rehabilitation in Multiple Sclerosis: A Systematic Review of Systematic Reviews. Archives of Physical Medicine and Rehabilitation volume 98, Issue 2, February 2017, Pages 353-367. https://doi.org/10.1016/j.apmr.2016.04.016.
4. Kluger, B., Krupp, L., & Enoka, R. Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. Neurology. 2013;80(4):409-16.
5. Severijns, D., Zijdewind, I., Dalgas, U., Lamers, I., Lismont, C., & Feys, P. The Assessment of Motor Fatigability in Persons With Multiple Sclerosis: A Systematic Review. Neurorehabil Neural Repair. 2017;31(5):413-31.
6. Seamon, B., & Harris-Love, M. Clinical Assessment of Fatigability in Multiple Sclerosis: A Shift from Perception to Performance. Front Neurol. 2016;7:194.
7. Loy, B., Taylor, R., Fling, B., & Horak, F. Relationship between perceived fatigue and performance fatigability in people with multiple sclerosis: A systematic review and meta-analysis. J Psychosom Res. 2017;100:1-7.
8. Enoka, R., & Duchateau, J. Translating Fatigue to Human Performance. Med Sci Sports Exerc. 2016;48(11):2228-38.
9. Langeskov-Christensen, M., Bisson, E., Finlayson, M., & Dalgas, U. Potential pathophysiological pathways that can explain the positive effects of exercise on fatigue in multiple sclerosis: A scoping review. J Neurol Sci. 2017;373:307-20.
10. Leone, C., Severijns, D., Doležalová, V., Baert, I., Dalgas, U., & Romberg, A. et al. Prevalence of Walking-Related Motor Fatigue in Persons With Multiple Sclerosis: Decline in Walking Distance Induced by the 6-Minute Walk Test. Neurorehabil Neural Repair. 2016;30(4):373-83.
11. Phan-Ba, R., Calay, P., Grodent, P., Delrue, G., Lommers, E., & Delvaux, V. et al. Motor fatigue measurement by distance-induced slowdown of walking speed in multiple sclerosis. PLoS One.
12. Kalron, A., & Achiron, A. Dvir, Z. (2012). Motor impairments at presentation of clinically isolated syndrome suggestive of multiple sclerosis: Characterization of different disease subtypes. NeuroRehabilitation, 31(2), 147-155. doi:10.3233/NRE-2012-0784.
13. Kalron, A., Dvir, Z., Gurevich, M., & Achiron, A. (2013). Do motor impairments detected on onset of multiple sclerosis suggest an early second attack? A prospective study. NeuroRehabilitation, 33(3), 423-430. doi:10.3233/NRE-130973.
14. Broekmans, T., Gijbels, D., Eijnde, B. O., Alders, G., Lamers, I., Roelants, M., & Feys, P. (2013). The relationship between upper leg muscle strength and walking capacity in persons with multiple sclerosis. Multiple Sclerosis, 19(1), 112-119. doi:10.1177/1352458512444497
15. Manca, A., Cabboi, M. P., Dragone, D., Ginatempo, F., Ortu, E., De Natale, E. R., & Deriu, F. (2017). Resistance Training for Muscle Weakness in Multiple Sclerosis: Direct Versus Contralateral Approach in Individuals With Ankle Dorsiflexors' Disparity in Strength. Archives of Physical Medicine and Rehabilitation, 98(7), 1348-1356 e1341. doi:10.1016/j.apmr.2017.02.019.
16. Manca, A., Dvir, Z., Dragone, D., Mureddu, G., Bua, G., & Deriu, F. (2017). Time course of strength adaptations following high-intensity resistance training in individuals with multiple sclerosis. European Journal of Applied Physiology, 117(4), 731-743. doi:10.1007/s00421-017-3534-z.
17. Schwid, S. R., Thornton, C. A., Pandya, S., Manzur, K. L., Sanjak, M., Petrie, M. D., . . . Goodman, A. D. (1999). Quantitative assessment of motor fatigue and strength in MS. Neurology, 53(4), 743-750.

18. Dalgas, U., Kjølhede, T., Gijbels, D., Romberg, A., Santoyo, C., & de Noordhout BM, et al. Aerobic intensity and pacing pattern during the six-minute walk test in patients with multiple sclerosis. J Rehabil Med. 2014;46(1):59-66.

19. Wens, I., Dalgas, U., Vandenabeele, F., Grevendonk, L., Verboven, K., & Hansen D, et al. High Intensity Exercise in Multiple Sclerosis: Effects on Muscle Contractile Characteristics and Exercise Capacity, a Randomised Controlled Trial. PLoS One. 2015;10(9):e0133697.

20. Surakka, J., Romberg, A., Ruutiainen, J., Aunola, S., Virtanen, A., & Karppi SL, et al. Effects of aerobic and strength exercise on motor fatigue in men and women with multiple sclerosis: a randomized controlled trial. Clin Rehabil. 2004;18(7):737-46.

21. Surakka, J., Romberg, A., Ruutiainen, J., Virtanen, A., Aunola, S., & Maentaka K. Assessment of muscle strength and motor fatigue with a knee dynamometer in subjects with multiple sclerosis: a new fatigue index. Clin Rehabil 2004; 18: 652-659.

22. Skurvydas, A., et al., The effect of multiple sclerosis and gender on central and peripheral fatigue during 2-min MVC. Clin Neurophysiol, 2011.

23. Wens, I., Dalgas, U., Vandenabeel, F., Grevendonk, L., Verboven, K., Hansen, D., & Eijnde B. (2015). High Intensity Exercise in Multiple Sclerosis: Effects on Muscle Contractile Characteristics and Exercise Capacity, a Randomised Controlled Trial. Sep 29;10(9):e0133697. doi: 10.1371/journal.pone.0133697.

24. Thoumie, P., Lamotte, D., Cantalloube, S., Faucher, M., & Amarenco, G. (2005). Motor determinants of gait in 100 ambulatory patients with multiple sclerosis. Multiple Sclerosis 11: 485–491. doi: 10.1191/1352458505ms1176oa.

25. Zijdewind, I., Prak, RF., & Wolkorte R. Fatigue and Fatigability in Persons With Multiple Sclerosis. Exerc Sport Sci Rev. 2016;44(4):123-8.

26. Swinnen, SP. Intermanual coordination: from behavioural principles to neural-network interactions. Nat Rev Neurosci. 2002;3(5):348-59.

27. Shield, A., & Zhou, S. Assessing voluntary muscle activation with the twitch interpolation technique. Sports Med. 2004;34(4):253-67.

28. Swinnen, SP. Intermanual coordination: from behavioural principles to neural-network interactions. Nat Rev Neurosci. 2002;3(5):348-59.

29. Serrien, D. J., & Swinnen, S. P. (1998). Load compensation during homologous and non-homologous coordination. Experimental Brain Research, 121(3), 223–229. doi:10.1007/s002210050455

30. Thorstensson, A., & Karlsson, J., (1976) Fatiguability and fibre composition of human skeletal muscle. Acta Physiol Scand 98:318–322.

31. Manouchehrinia, A., & Constantinescu, CS. Cost-effectiveness of disease-modifying therapies in multiple sclerosis. Curr Neurol Neurosci Rep. 2012;12:592–600.

32. Tremlett, H., Zhao, Y., & Devonshire, V. Natural history comparisons of primary and secondary progressive multiple sclerosis reveals differences and similarities. J Neurol. 2009;256:374–81.

33. Seamon, BA., & Harris-Love, MO. Clinical Assessment of Fatigability in Multiple Sclerosis: A Shift from Perception to Performance. Front Neurol. 2016;7:194.

34. Thoumie, P., Lamotte, D., & Cantalloube S, et al. Motor determinants of gait in 100 ambulatory patients with multiple sclerosis. Mult Scler 2005; 11: 485–491.

35. Severijns, D., Lamers, I., Kerkhofs, L., & Feys, P. Hand grip fatigability in persons with multiple sclerosis according to hand dominance and disease progression. J Rehabil Med. 2015;47:154-160.

36. Lloyd, AR., Gandevia, SC., & Hales, JP. Muscle performance, voluntary activation, twitch properties and perceived effort in normal subjects and patients with the chronic fatigue syndrome. Brain. 1991;114(pt 1A):85-98.

37. Sheean, GL., Murray, NM., Rothwell, JC., Miller, DH., & Thompson, AJ. An electrophysiological study of the mechanism of fatigue in multiple sclerosis. Brain. 1997;120 299-315.

38. Zijdewind, I., Zwarts, MJ., & Kernell D. Influence of a voluntary fatigue test on the contralateral homologous muscle in humans? Neurosci Lett. 1998;253:41-44.

39. Wolkorte, R., Heersema, DJ., & Zijdewind, I. Reduced dual-task performance in MS patients is further decreased by muscle fatigue. Neurorehabil Neural Repair. 2015;29:424-435.

40. Wolkorte, R., Heersema, DJ., & Zijdewind, I. Reduced voluntary activation during brief and sustained contractions of a hand muscle in secondary-progressive multiple sclerosis patients. Neurorehabil Neural Repair. 2016;30:307-316.

41. Steens, A., de Vries, A., & Hemmen J, et al. Fatigue perceived by multiple sclerosis patients is associated with muscle fatigue. Neurorehabil Neural Repair. 2012;26:48-57.

42. Streckis, V., Skurvydas, A., & Mamkus, G. Effect of the time of day on central and peripheral fatigue during 2-min maximal voluntary contractions in persons with multiple sclerosis: gender differences. J Electromyogr Kinesiol. 2014;24: 601-606.

43. Dobkin, BH. Fatigue versus activity-dependent fatigability in patients with central or peripheral motor impairments. Neurorehabil Neural Repair. 2008;22:105-110.

44. Gehlsen, G.M., Grigsby, S.A., & Winant, D.M. Effects of an aquatic fitness program on the muscular strength and endurance of patients with multiple sclerosis. Phys Ther, 1984. 64(5): p. 653-7.

45. Hameau, S., et al., Relationship between neuromuscular and perceived fatigue and locomotor performance in patients with multiple sclerosis. Eur J Phys Rehabil Med, 2017. 53(6): p. 833-840.

46. Liu, JZ,., Zhang, L,., Yao, B., Sahgal, V., & Yue, GH. Fatigue induced by intermittent maximal voluntary contractions is associated with significant losses in muscle output but limited reductions in functional MRI-measured brain activation level. Brain Res. 2005;1040:44-54.

47. Stewart, D., Macaluso, A., & De Vito, G. The effect of an active warm-up on surface EMG and muscle performance in healthy humans. Eur J Appl Physiol. 2003 Aug;89(6):509-13.

48. Burschka, J.m., Keune, P.M., Menge, U., Hofstadt-van Oy, U., Oschmann, P., & Hoos, O. An exploration of impaired walking dynamics and fatigue in multiple sclerosis. BMC Neurol. 2012;12:161.

49. Sehle, A., Mundermann, A., & Starrost, K., et al. Objective assessment of motor fatigue in multiple sclerosis using kinematic gait analysis: a pilot study. J Neuroeng Rehabil. 2011;8:59.

50. Rudroff T, Kindred JH, Ketelhut NB. Fatigue in multiple sclerosis: misconceptions and future research directions. Front Neurol. 2016;7:122.

51. Aldughmi, M., Huisinga, J., Lynch, S.G., & Siengsukon, C.F. (2016). The relationship between fatigability and sleep quality in people with multiple sclerosis. Mult Scler J Exp Transl Clin.

52. Proessl, F., Ketelhut, N.B., & Rudroff, T. (2018). No association of leg strength asymmetry with walking ability, fatigability, and fatigue in multiple sclerosis. Int J Rehabil Res. 2018.

53. Ramari, C., Moraes, A.G., Tauil, C.B., von Glehn, F., Motl, R., & de David, A.C. (2018). Knee flexor strength and balance control impairment may explain declines during prolonged walking in women with mild multiple sclerosis. Mult Scler Relat Disord. 2018.

54. Barbosa, J.F., Bruno, S.S., Cruz, N.S., de Oliveira, J.S., Ruaro, J.A., & Guerra, R.O. Perceived fatigability and metabolic and energetic responses to 6-minute walk test in older women. Physiotherapy. 2016 Sep;102(3):294-9.

55. Murphy, S.L., Kratz, A.L., & Schepens Niemiec, S.L. Assessing Fatigability in the Lab and in Daily Life in Older Adults With Osteoarthritis Using Perceived, Performance, and Ecological Measures. J Gerontol A Biol Sci Med Sci. 2017 Jan;72(1):115-120.

56. Golden, L.C., & Voskuhl, R. The importance of studying sex differences in disease: The example of multiple sclerosis. J Neurosci Res. 2017 Jan 2;95(1-2):633-643.

57. Van Geel, F., Bielen, H., & Feys, P. (2018). Walking-related performance fatigability in people with Multiple Sclerosis: Clinical manifestation and test-retest reliability of the assessment method.

58. Langeskov-Christensena, d., Feys, P., Baert, b. I., Riemenschneidera, M., Stenager, E., & Dalgasa, U., (2017). Performed and perceived walking ability in relation to the Expanded Disability Status Scale in persons with multiple sclerosis. Journal of the neurological sciences 381, 131-136

59. Citaker, S., Guclu-Gunduz, A., Yazici, G., Bayraktar, D., Nazliel, B., & Irkec, C. Relationship between lower extremity isometric muscle strength and standing balance in patients with multiple sclerosis. NeuroRehabilitation. 2013;33(2):293-8.

Appendix

Part B: In this part all the tests conducted in day one that will be used in other studies are explained

Protocol B exists of a variety of tests in order to develop a clinical profile of possible underlying factors of fatigability. Three main types of tests could be distinguished. Motoric tests which were used to measure physical capacity. Cognitive tests to measure cognitive capacity and coordination tests to measure central motor control. These tests were randomly allocated to the subjects and were conducted by the same examiners. Patients were given the advice to avoid strenuous activity prior to testing.

Motor tests

In order to assess the strength of the lower limb, a Five Times Sit To Stand (FTSTS) was conducted using a free-standing chair with a height of 45cm. Subjects arms were folded across their chest and were instructed to stand up completely and sit back down for five repetitions as fast as possible whilst avoiding contact with the back of the chair in between each repetition. The FTSTS ended when the subjects spine touched the back of the chair after repetition five.

Furthermore a Nine Hole Peg Test (NHPT) was performed two times on the dominant side and non-dominant side of the upper limb to test hand function and motor skills. Starting with the dominant side, subjects were instructed to take the pegs one by one and put them in the holes. Then remove the pegs one by one and put the back in the container as fast as possible. If a peg fell out of the subjects hands, they were obliged to pick it up and put it back in the original container before completing the test.

Timed 25Foot Walk (T25FW): was conducted twice consecutively in the same hallway as the 6MWT to assess maximal walking speed. Subjects were instructed to walk as fast as possible but within their own safety limits. At least one of their feet needed to be in touch with the ground at any given time during each stride to avoid running.

Jamar handgrip was used to test the static fatigue index during an isometric maximal voluntary contraction (MVC) of the injured side for PwMS or non-dominant side for healthy controls. Subjects were seated in a free standing chair without armrests. The elbow joint of the evaluated arm was positioned in 90 degrees flexion and a neutral position between pronation and supination of the forearm. Three consecutively MVC were asked and mean MVC was calculated. Afterwards a thirty second MVC was asked to assess the decline of their maximal strength output.

Cognitive tests

Digit Span was used to test the working memory, which is a cognitive system in the brain responsible for temporarily holding information to process. A sequence of numbers is read out loud by the app 'Cognitive games' on an iPad. Subjects were instructed to repeat the numbers in reverse order. This started with three consecutive numbers and progressed to eight. If the subject answered correctly twice, transition was made to the next level until there was an incorrect answer. Stroop test was conducted to measure attention, inhibition and error monitoring. The test consisted of three timed trails. Trail one consisted of reading words as fast as possible. The secondary trail consisted of colored boxes (participants needed to indicate the color of each box. The third trail is called the interference trail and consisted of words printed in incongruent colors. Subjects were asked to indicate color of each word. Interference occurs when the simultaneous task processing

from previous trails interrupts with current task processing in trial three. These trials were timed and the Interference Score was calculated based on the following formula: $Time\ trail\ 3 - \frac{Time\ trail\ 1 + Time\ trail\ 2}{2}$
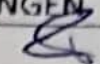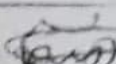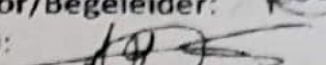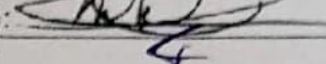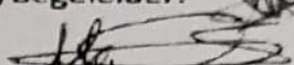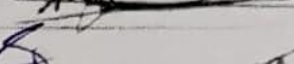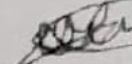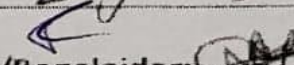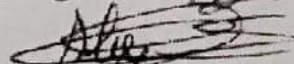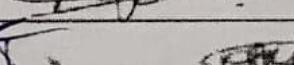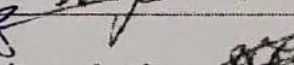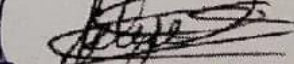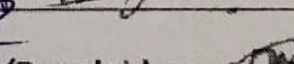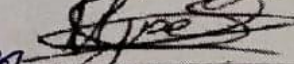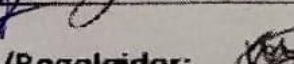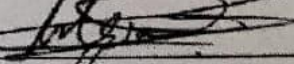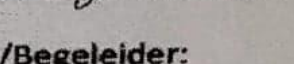
The Single Digit Modality Test (SDMT) provides information about the brains' information processing speed and efficiency. Subjects were instructed to orally report the matching number with the figures in the right order, as fast as possible without making any mistakes for 90 seconds.

Paced Auditory Serial Addition Test (PASAT) was used to test participants sustained attention, processing speed and working memory. Subjects were given an audio clip where they were told a number from one to nine every 3 seconds. The first two digits had to be added up. There after, every new digit had to be added up with the last digit they heard before. Prior to the effective test, a practice trail was conducted of eleven numbers. Afterwards the test trail started consisting of sixty-one numbers. Performance cognitive fatigability was measured for both the SDMT and PASAT using following formula: $\left(Correct\ last\ \frac{1}{3} - Correct\ first\ \frac{1}{3}\right) x\ 100$

Coordination tests

When the central nervous system is not working accordingly it may cause problems during gait, especially with coordination [26]. This in turn can be an underlying factor for walking fatigue. In order to indirectly test central drive, two coordination tests were randomly conducted. Subjects were seated with their legs in 90 degrees hip and knee flexion. Lower legs were attached to levers so that the axis of rotation of the levers was aligned with the center of rotation from the knee (28,29). From this position, flexion and extension of the knee in antiphase movement was performed in the form of a 6 minute coordination test (6MCT) or a frequency coordination test (FCT). The 6MCT consisted of antiphase movement with an amplitude at will during 6 minutes. VAS was conducted at the beginning of the test and after each subsequent minute during the 6MWT. For the FCT, subjects were given a auditory frequency with a metronome through a headphone. During the first minute, the metronome played a sound at a speed of 0,75HZ. The third minute at a speed of 1 HZ and the fifth minute at speed of 1,25 HZ. After the first, third and fifth minute there was a one minute break. The results from this part of the study fall outside of the scope of this thesis, nonetheless they are further analyzed and reviewed in another master thesis for 2020.

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UHASSELT

INVENTARISATIEFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
15 okt	overleg inhoud MT deel 2	Promotor: Copromotor/Begeleider: Student(e): Student(e):
10 dec	bespreking literatuurstudie en protocol	Promotor: Copromotor/Begeleider: Student(e): Student(e):
4 feb	bespreking nieuw protocol want langer de interventie maar het onderzoek (deels)	Promotor: Copromotor/Begeleider: Student(e): Student(e):
15 April	bespreking en verbetering introductie	Promotor: Copromotor/Begeleider: Student(e): Student(e):
29 April	bespreking uitgeschreven methode	Promotor: Copromotor/Begeleider: Student(e): Student(e):
10 Mei	bespreking data extractie - bidex SPI problemen met Peter Feys	Promotor: Copromotor/Begeleider: Student(e): Student(e):
26 Mei	verbetering Ruwe data en resultaten door Fanny Van Geel	Promotor: Copromotor/Begeleider: Student(e): Student(e):
Testing Maart - Juni	Tijdens testing, overleg met Fanny Van Geel	Promotor: Copromotor/Begeleider: Student(e): Student(e):
27 Mei	Samenkomst bespreking verdediging 1e zit	Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):

In te vullen door de promotor(en) en eventuele copromotor aan het einde van MP2:

Naam Student(e): Sam Klijsen .... Datum: 27 mei 2019

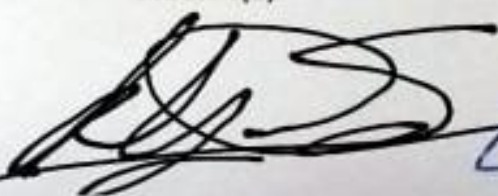Titel Masterproef: ....

1) Geef aan in hoeverre de student(e) onderstaande competenties zelfstandig uitvoerde:
   - NVT: De student(e) leverde hierin geen bijdrage, aangezien hij/zij in een reeds lopende studie meewerkte.
   - 1: De student(e) was niet zelfstandig en sterk afhankelijk van medestudent(e) of promotor en teamleden bij de uitwerking en uitvoering.
   - 2: De student(e) had veel hulp en ondersteuning nodig bij de uitwerking en uitvoering.
   - 3: De student(e) was redelijk zelfstandig bij de uitwerking en uitvoering
   - 4: De student(e) had weinig tot geringe hulp nodig bij de uitwerking en uitvoering.
   - 5: De student(e) werkte zeer zelfstandig en had slechts zeer sporadisch hulp en bijsturing nodig van de promotor of zijn team bij de uitwerking en uitvoering.
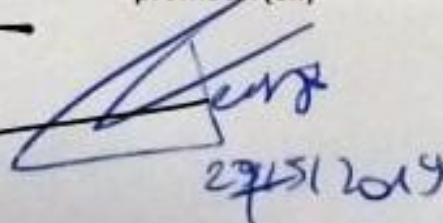
Competenties	NVT	1	2	3	4	5
Opstelling onderzoeksvraag	●	O	O	O	O	O
Methodologische uitwerking	●	O	O	O	O	O
Data acquisitie	O	O	O	O	O	●
Data management	O	O	O	O	O	●
Dataverwerking/Statistiek	O	O	O	O	O	●
Rapportage	O	O	O	O	O	●

2) <u>Niet-bindend advies:</u> Student(e) krijgt toelating/geen toelating (schrappen wat niet past) om bovenvermelde Wetenschappelijke stage/masterproef deel 2 te verdedigen in bovenvermelde periode. Deze eventuele toelating houdt geen garantie in dat de student geslaagd is voor dit opleidingsonderdeel.

3) Deze wetenschappelijke stage/masterproef deel 2 mag wel/niet (schrappen wat niet past) openbaar verdedigd worden.

4) Deze wetenschappelijke stage/masterproef deel 2 mag wel/niet (schrappen wat niet past) opgenomen worden in de bibliotheek en docserver van de UHasselt.

Datum en handtekening Student(e)

Datum en handtekening promotor(en)

Datum en handtekening Co-promotor(en)

27/5/2019