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Faculteit Geneeskunde en Levenswetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Walking-related motor fatigability in patients with Multiple Sclerosis

Lien Dejaegere

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij kinderen

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Prof. dr. Peter FEYS

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De Bergen 15 2240 Zandhoven, juni 2018 L. D

Research Context

This study can be situated in the wider research context of neurological rehabilitation. Walking and fatigability are major symptoms which are often impaired severely in neurological and other chronic conditions. Fatigue is prevalent in stroke patients (20 – 40%), traumatic brain injuries, Parkinson's disease and is one of the most common and first symptoms in MS patients (40 – 80%) (Seamon et al. 2016, Kluger et al. 2013, Martino et al. 2016).

The focus in this paper will be on walking-related motor fatigability in MS patients. Nearly half of the patients with MS describe fatigability as their most disabling feature and almost 80% of them experiences walking difficulties e.g. decreased walking capacity.

The concept 'fatigability' describes how fatigued an individual gets in relation to defined activities (Barbosa et al. 2016). This approach measures the change in fatigue level as a function of the change in intensity, duration or frequency of activity (Barbosa et al., Glynn et al. 2015). A distinction is made between performance and perceived fatigability. Perceived fatigability reflects the self-reported change in tiredness, where the performance part refers to the objective change or decline during a performance: physic e.g. decreased walking speed or cognitive (Barbosa et al. 2016; Schnelle et al. 2012).

Since a qualitative good clinical examination is mostly based on objective outcome measures to increase the reliability and comparison of results, some ways to objectively assess walking-related motor fatigability have recently been investigated (Barbosa et al. 2016, Severijns et al. 2016, Murphy et al. 2017). However, there are still discrepancies in the current literature according to differences in study populations as well as wide variabilities in walking tasks the participants had to perform. Furthermore, the current methods to assess walking-related motor fatigability are based on different parameters e.g. walking speed, distance walked, heart rate, characteristics of gait analysis, or a combination. However, most studies do not provide a clear criterion to distinguish fatigability and non-fatigability individuals based on the objective assessment. Last, a golden standard measure or normative data based on the performance of healthy controls are currently unavailable.

This study will be the first to investigate test-retest reliability for the Distance Walked Index (DWI), an objective method to assess walking-related motor fatigability based on the study of Leone et al. (2016), which is part of our research unit. Leone investigated fatigability in MS patients during a 6MWT, provided a clear cut-off criterion to distinguish fatigability and non-fatigability individuals, and examined validity in relation to Phan-Ba et al. (2012).

The final research protocol was provided by promotor Prof. Dr. P. Feys and co-promotor Dra. F. Van Geel based on currently available literature. The role of the master student was to help refining this protocol by adding extras and trying to exclude pitfalls based on the proposed research protocol the student wrote last year. All master students were responsible for the recruitment of healthy controls and data-acquisition of both MS patients and healthy individuals.

Since every master student elaborated a different research question in relation to the acquired data, the master student performed data-analysis completely independent. Dra. F. Van Geel provided feedback after the data-analysis proposal and was always prepared to answer questions or provide help when difficulties arise. On consecutive moments, Dra. F. Van Geel and Prof. Dr. P. Feys provided feedback in relation to the academic writing process.

WALKING-RELATED MOTOR FATIGABILITY IN PATIENTS WITH MULTIPLE SCLEROSIS

Assessment, clinical profiling and manifestation: a cross-sectional study

1 Abstract

Background: Both fatigue and walking are the major challenging aspects of living with Multiple Sclerosis. Fatigue interferes within many aspects of daily living, on all levels of the ICF-model. Recently, literature provided a better conceptualization of fatigability and different methods to objectively measure walking-related motor fatigability (WRMF). However, psychometric properties, clear cut-off values and manifestation are lacking.

Objectives: To investigate the prevalence and test-retest reliability of several methods to objectively measure walking-related motor fatigability in healthy controls and PwMS based on e.g. speed and distance walked during the 6MWT. Furthermore the study investigated perceived fatigability based on VAS-scores. Last, the study aimed to delineate a clinical profile of PwMS showing this WRMF based on motor and cognitive function tests and questionnaires.

Participants: In total, 50 MS patients and 30 healthy controls participated in this cross-sectional study. The PwMS were recruited from the University of Hasselt, the National MS Center at Melsbroek and the Rehabilitation & MS Center at Overpelt.

Measurements: All subjects performed a six minute walk test on two test sessions which were spread over two consecutive moments with 3 – 5 days in between. At the end of the first session, the PwMS were given some MS-specific questionnaires to fill in at home. The second test session, MS patients also performed four additional motor and cognitive function tests.

Results: Walking-related motor fatigability had a prevalence of 48.9% in the MS sample, with a higher prevalence [41.7% (EDSS-score 4 – 5.5) and 20.8% (EDSS-score 6)] in the more disabled MS patients. Good reliability was shown for the total MS sample [ICC = 0.762, 95%CI (0.266 – 0.804)]. The ICC for healthy controls was 0.602 [95%CI (0.300 – 0.794)] showing moderate reliability. Other methods to calculate WRMF (Barbosa et al. 2016, McLoughlin et al. 2012, Murphy et al. 2017) showed good reliability.

Conclusion: This study showed good test-retest reliability for most of the methods investigated to measure walking-related motor fatigability. The formula this study examined had a good correlation with the MS-specific questionnaires. The biggest difference for VAS-score, heartrate and distance walked was between minute 6 – 1, which can indicate fatigability.

2 Introduction

Multiple Sclerosis (MS) is an autoimmune, neurodegenerative disorder of the central nervous system characterized by inflammation, selective demyelination and gliosis causing both acute and chronic symptoms. These result in a significant disability and impaired quality of life. Globally, 2.1 million people, mainly younger adults between 20 – 30 years, are affected by this disease (Physical Rehabilitation, O'Sullivan et al. 6th edition, Porth's Pathophysiology, 9th edition).

Fatigue, mostly defined as 'a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities', is one of the most common and first symptoms in MS (MS Council, 1998). This fatigue interferes within many aspects of daily living, both at activity and participation level regarding to the International Classification of Functioning (ICF) model. Therefore, fatigue is seen as one of the most impactful characteristics of MS, which nearly half of the PwMS describe as their most disabling feature (Ben-Zacharia et al. 2011, Bethoux et al. 2011, Kluger et al. 2013, Rudroff et al. 2016).

The concept 'fatigability' describes how fatigued an individual gets in relation to defined activities (Barbosa et al. 2016). This approach measures the change in fatigue level as a function of the change in intensity, duration or frequency of activity (Barbosa et al., Glynn et al. 2015). A distinction is made between performance and perceived fatigability. Perceived fatigability reflects the self-reported change in tiredness, where the performance part refers to the objective change or decline during a performance: physic e.g. decreased walking speed or cognitive (Barbosa et al. 2016; Schnelle et al. 2012).

Recent literature (Leone et al. 2016, Severijns et al. 2016) proposed a better conceptualization of fatigability. Within this concept a taxonomy is suggested to differentiate between two types of fatigability (motor or cognitive): (1) *Performance fatigability* which refers to 'the magnitude or rate of change in a performance criterion relative to a reference value over a given time of task performance or measure or mechanical output' (Leone et al. 2016). (2) *Perceived or perception fatigability* which is described as 'subjective sensations of weariness, increasing sense of effort, mismatch between effort expended and actual performance, or exhaustion' (Kluger et al. 2013, Severijns et al. 2016). Each type of fatigability can be either motor or cognitive. The current study will focus on walking-related motor fatigability (WRMF), with measurements of the performance and the perceived effort during walking.

Also walking is often rated as the most challenging aspect of living with Multiple Sclerosis (McLoughlin et al. 2016). Almost 80% of all patients experience walking difficulties such as a decreased walking capacity and physical activity level (Ben-Zacharia et al. 2011, Dlugonski et al. 2013). Already from the beginning of the disease, these features can be present.

Motor fatigue during walking is very common in patients with MS. Regarding to the article of Leone et al. (2016), more than one third of the PwMS showed walking-related motor fatigability, with a higher prevalence in the more disabling groups according to EDSS-score and type MS. Within this group of patients, walking-related motor fatigability may have an important contribution to independence, daily life and mobility ambulatory functions. Walking-related motor fatigability can be manifested by a higher energy cost or a lower capacity to walk longer distances (McLoughlin et al. 2016). Taking a walk with partner, friends or family, walking to the shop or even moving indoors could be difficult and therefore disturbing social, daily living activities (Leone et al. 2016).

Before, during or after walking tests e.g. the six minute walk test (6MWT), some researchers have tried to measure this walking-related motor fatigability through objective (performance) as well as subjective (perceived) methods. These methods can be based on a decline in walking speed, total distance walked or both of these or other parameters e.g. heart rate and characteristics of gait analysis. The Borg-scale or VAS-scale are examples of how this phenomenon can be measured subjectively (perceived fatigability).

An overview of some of these methods is shown in the table provided in the appendix page 30. This study will discuss the test-retest reliability of these methods, except for the formulas provided in the studies of Engelhard et al. (2016) and Qureshi et al. (2016). These authors based the measurement of walking-related motor fatigability on gait cycle parameters. To easily compare the different methods that investigate WRMF with the method the current study examined, it was chosen to only include formulas which were based on the 6MWT. Furthermore, this test is the golden standard to measure walking endurance (Leone et al. 2016).

Although these parameters and formulas seem to be useful to indicate walking-related motor fatigability objectively, psychometric properties and clear cut-off values are lacking. Furthermore, it is not well known how long this walking-related motor fatigability persists in patients with MS and how this fatigability manifests.

Therefore, the following research questions were investigated in this study: (1) *What is test-retest reliability of different fatigability formulas?* (2) *How prevalent is walking-related motor fatigability?* (3) *How and how long does walking-related motor fatigability manifest?*

In relation to these research questions, some hypotheses can be formulated. First, a clear distinction can be made in walking-related motor fatigability between healthy controls and patients with Multiple Sclerosis. Almost 80% of all the PwMS experience walking difficulties (Ben-Zacharia et al. 2011) and therefore will reach much sooner the moment of WRMF, in comparison to healthy individuals which may not even experience this during walking for six minutes. Next, walking-related motor fatigability will be more prevalent among MS patients which have a higher score on the Expanded Disability Status Scale (Leone et al. 2016).

Last, it is hypothesized that the biggest difference for the assessed parameters (VAS-score, heartrate and distance walked) will be between the first and the last minute of the 6MWT.

The aim of this cross-sectional study was, therefore, to examine prevalence and test-retest reliability of different methods which investigate walking-related motor fatigability. Furthermore, the present study aimed to investigate manifestations during the 6MWT and to delineate a clinical profile of MS-patients, especially those patients within the group of walking-related motor fatigability.

3 Methods

3.1 Study design

To investigate the research questions and hypotheses discussed in the introduction, a cross sectional observational study was set up. Participants attended for two days to one of the three research sites: REVAL Rehabilitation Research Center at Diepenbeek, Rehabilitation and MS Centrum at Overpelt or National MS Center at Melsbroek. The Medical Committee of the University of Hasselt approved the study protocol with code B9115201734276 at 29th November 2017.

3.2 Participants

The aim of the study was to subdivide the MS sample regarding their EDSS-score into three equivalent groups: group 1 [EDSS-score 1 – 3,5], group 2 [EDSS-score 4 – 5,5] and group 3 [EDSS-score 6], to cover the full spectrum of potential walking disabilities. Healthy controls were age and gender matched with the MS patients.

MS patients were mainly recruited from the University of Hasselt, Rehabilitation and MS Centrum at Overpelt and National MS Center at Melsbroek. Through family, participating PwMS and other contacts, another few patients with MS were recruited. Healthy controls were enrolled through different locations e.g. social media, family, friends and other contacts. The study was performed according to the Helsinki Declaration.

In- and exclusion criteria were defined for both study groups. Subjects were enrolled in the study if they were aged between 18 – 70 years, able to walk independently or with a walking stick (unilateral support) if necessary for six minutes without rest and have signed the informed consent documents. The persons with MS participating in the study should have a confirmed diagnosis of Multiple Sclerosis according to the McDonald criteria.

Participants were excluded if they had any neurological, cardiac, respiratory, metabolic, orthopedic or other medical condition that could influence their performance on the different parameters assessed. MS patients were excluded if an exacerbation or relapse occurred within the last three months before the study starts and/or medication changed during the study.

3.3 Research protocol

3.3.1 Primary outcome measures

Previous literature stated that walking fatigability can be measured objectively by a decline in walking speed. Based on previous research of Leone et al. (2016), a distance walked index (DWI) was calculated as primary outcome measure. The DWI represents a percentage for the decline in distance walked from the sixth to the first minute. This is calculated through the decline in distance walked divided by the distance walked in the first minute.

Based on a cut-off score for DWI of ≤ –10%, MS-patients will be further subdivided into two groups: a group of patients that showed walking-related motor fatigability during the 6MWT and another group of MS-patients with an DWI above the cut-off (> –10%). The MS-patients in the walking fatigability group should at least in one of the two test sessions demonstrate a distance walked index that exceeds the cut-off score.

To become this primary outcome, subjects performed a six minute walk test (6MWT) according to the protocol of Butland et al. (1989) and Goldman et al. (2008). Subjects walked back and forth in a 30-meter corridor and were allowed to use their (unilateral) assistive device if necessary.

Instructions before the start of the walking test were given according to the protocol described above. The tester emphasized one specific and explicit instruction: 'Try to walk as fast as you can.' Furthermore, no encouragements were given during the walking test.

Each minute, the tester notified the subject minute n was past, and asked the subject to say heartrate and VAS-score (perceived walking fatigability). Mean walking speed, distance per minute and total distance walked in six minutes were the other outcome parameters registered during the 6MWT.

Heartrate expressed as beats per minute was measured with a Polar heart rate monitor and watch. Each minute, the subjects had to read their heartrate out loud, so that the tester could write down this value on the testing form. The walking speed and covered distance were calculated by counting the indicated meters in the 30-meter corridor, which were taped on the ground per meter.

Every minute, the subject was also asked the same question: 'How fatigued do you feel at this moment in the walking test?'. Participants had to indicate their perceived walking fatigability on a VAS-scale ranging from 0 to 10. This aspect relates to the subjective part of perceived walking fatigability.

3.3.2 Test-retest reliability

The six minute walk test was applied at two moments by the same blinded tester and time of the day, with 3 – 5 working days in between. This way, test-retest reliability was examined.

3.3.3 Secondary outcome measures

In order to obtain more information to design a clinical profile of the MS-patients that participated in the study, additional tests were performed at the day of the second test moment, before starting the 6MWT test session as described above. Figure 1 below represents the content and execution of both test sessions.

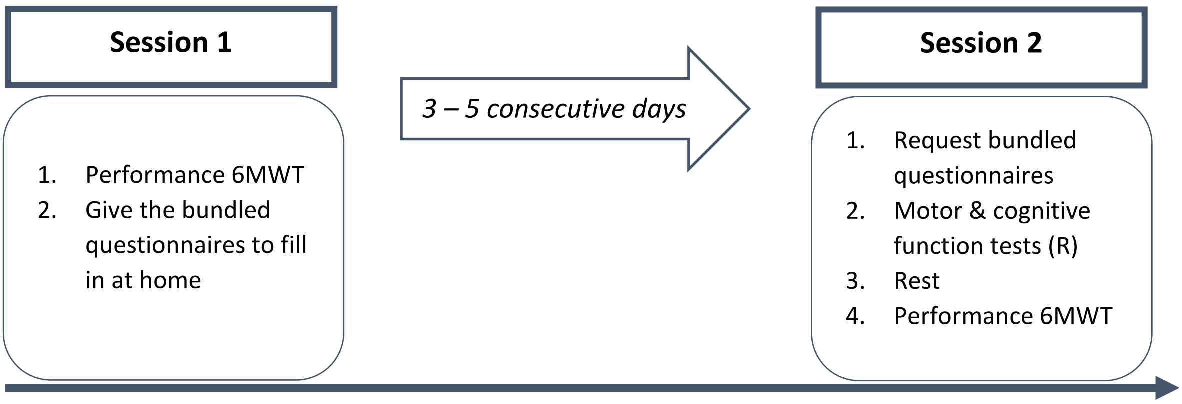


Figure 1. Overview of the content of each test session

These additional motor and cognitive function tests are part of the basic test battery for PwMS, including the Timed 25-Foot Walk (T25-FW) for motor function (1), the Nine-Hole Peg Test (NHPT) for motor function and manual dexterity (2), the Paced Auditory Serial Addition Test (PASAT) for cognitive fatigue and cognitive attentional function (3) and the Single Digit Modalities Test (SDMT) for cognitive processing speed (4). The MS-patients performed these tests in an randomized order.

Furthermore, patients were given a few self-reported questionnaires at the end of the first test session to fill in at home and bring back at the second test moment:

- Hospital Anxiety and Depression Scale (HADS) for depression, mood and motivation
- Modified Fatigue Impact Scale (MFIS) for the impact of perceived fatigue
- Fatigue Severity Scale (FSS) for the severity of perceived fatigue
- Fatigue Scale for Motor and Cognitive Functions (FSMC) for perceived fatigue and motor & cognitive functions
- Multiple Sclerosis Walking Scale 12 (MSWS-12) for walking difficulties
- The Sleep Condition Indicator (SCI) for sleep and insomnia
- Falls Efficacy Scale (FES-I)

3.4 Statistical analysis

Descriptive statistics were calculated in the total MS-sample (n = 50) and healthy control group (n = 30). By means of an Bland Altman plot, one MS-patient and two healthy controls were excluded as outliers, based the difference for DWI-values of both sessions (DWI_1 – DWI_2). Afterwards, statistical analyses were performed for a total of 49 MS patients and 28 HC.

An Intra-Class Correlation coefficient (ICC) was calculated for DWI-values of all included MS-patients, the subdivided groups of MS-patients with and without walking-related motor fatigability and the group of healthy controls. To calculate the ICC, a two-way mixed ANOVA model was set up with a confidence interval of 95% and absolute agreement.

Afterwards, the same reliability analysis was also calculated for the formulas provided in table 1 in the appendix which also aim to objectively measure walking-related motor fatigability (Barbosa et al. 2016, McLoughlin et al. 2012, Montes et al. 2010, 2016, Murphy et al. 2016).

To have a closer look to manifestations per minute during the 6MWT, a general linear model for repeated measures was performed, including some of the secondary outcome measures: VAS-score, heart rate and distance walked. Within this model, each minute presented a level (n = 6) and Bonferroni was set as a confidence interval adjustment.

At last, this study analyzed possible correlations between the distance walked index, the additional impairment and functional tests and several questionnaires the MS-patients had to perform and fill in. Since the MS sample consisted of > 30 participants, a parametric, two-tailed test of significance with Pearson correlation coefficient was executed to analyze this.

All data-analyses were performed using IBM SPSS Statistics version 25.

4 Results

4.1 Descriptive statistics

An overview of demographic and clinical characteristics for the total MS sample and for the sample of healthy controls is shown in table 2.

Table 2. Demographic & clinical descriptive characteristics (mean ± SD, %) of the MS sample and subgroups based on DWI

	Total MS sample	Subgroups based on DWI		Total HC sample
		[≥ – 10%]	[≤ – 10%]	
	(n = 49)	(n = 25)	(n = 24)	(n = 28)
Age (years)	47.5 ± 10.2	46.3 ± 10.3	48.7 ± 10.1	49.2 ± 11.7
Gender				
F/M, n (%)	35/13 (71.4/26.5)	16/8 (64.0/32.0)	19/5 (79.2/20.8)	21/7 (75.0/25.0)
MS phenotype, n (%)				
RR	41 (83.7)	23 (92.0)	18 (75.0)	
PP	2 (4.1)	0	2 (8.3)	
SP	3 (6.1)	0	3 (12.5)	
EDSS	3.3 ± 1.9	2.4 ± 1.9	4.2 ± 1.5	
EDSS-category, n (%)				
0 – 3.5	23 (46.9)	15 (60.0)	8 (33.3)	
4 – 5.5	15 (30.6)	5 (20.0)	10 (41.7)	
6	7 14.3)	2 (8.0)	5 (20.8)	

Abbreviations. MS: Multiple Sclerosis, HC: Healthy Controls, DWI: Distance Walked Index, F: Female, M: Male, MS: Multiple Sclerosis, RRMS: Relapse Remitting Multiple Sclerosis, PPMS: Primary Progressive Multiple Sclerosis, SPMS: Secondary progressive Multiple Sclerosis, EDSS: Expanded Disability Status Scale|| Missing data MS sample. Age n = 1, sex n = 1, EDSS n = 4, MS phenotype n = 3|| Missing data HC sample. Age n = 1

4.2 Prevalence of walking-related motor fatigability

Walking-related motor fatigability had a prevalence of 48.9% in the group MS-patients, with a higher prevalence [41.7% (EDSS-score 4 – 5.5) and 20.8% (EDSS-score 6)] in the more disabled MS patients according to their EDSS-score. An overview of this is provided in table 2. Healthy controls did not show any walking-related motor fatigability.

The table below gives an overview for the prevalence of walking-related motor fatigability in relation to all possible EDSS-scores ranging from 0 – 6.

Table 3. Overview of the prevalence of walking-related motor fatigability per EDSS-score in the total MS sample

	Total sample	Subgroups based on DWI	
		[≥ – 10%]	[≤ – 10%]
	(n = 49)	(n = 25)	(n = 24)
EDSS-category, n (%)			
0	4 (8.2)	4 (16)	0
1	3 (6.1)	3 (12)	0
1.5	2 (4.1)	1 (4)	1 (4)
2	6 (12.2)	5 (20)	1 (4)
2.5	5 (10.2)	4 (16)	1 (4)
3	2 (4.1)	1 (4)	1 (4)
3.5	1 (2.0)	0	1 (4)
4	6 (12.2)	3 (12)	3 (12)
4.5	3 (6.1)	1 (4)	2 (8)
5	4 (8.2)	1 (4)	3 (12)
5.5	2 (4.1)	0	2 (8)
6	7 (14.3)	2 (8)	5 (20)

Abbreviations. DWI: Distance Walked Index, EDSS-category: Expanded Disability Status Scale|| Missing data: 4

4.3 Psychometric properties for distance walked index (DWI)

An intra-class correlation coefficient analysis was used to analyze the reliability of the distance walked index 6 – 1 which represents the walking-related motor fatigability in this study. Table 4 gives an overview of the ICC for all different groups: healthy controls, MS-patients and the subdivision in this last group (walking fatigability and non-walking fatigability).

Table 4. Intra-Class Correlation Coefficient analysis for DWI of healthy controls and MS-patients

Groups	ICC	95% Confidence interval	
		Lower bound	*Upper bound*
Healthy controls	0.602	0.300	0.794
Persons with MS	0.762	0.614	0.859
MSWF	0.598	0.266	0.804
MSNWF	0.543	0.195	0.769

Abbreviations. ICC: Intra-Class Correlation Coefficient, MSWF: Multiple Sclerosis Walking-related motor Fatigability, MSNWF: Multiple Sclerosis Non-Walking-related motor Fatigability

The ICC for DWI is highest in the total group MS-patients, showing a good reliability. When the MS group is subdivided according to the cut-off score for DWI, poor to moderate reliability was shown for the non-walking and walking fatigability group respectively. Also in the group of healthy controls, moderate reliability was analyzed (Foundations of Clinical Research Applications to Practice, Pearson New International Edition, 2014).

Not only distance walked index (DWI) seems to be a good parameter to determine walking-related motor fatigability, but also heart rate and walking speed are used to calculate a fatigability score by some authors. Therefore, an ICC for these formulas was also analyzed. Table 5 provides an overview of this analysis.

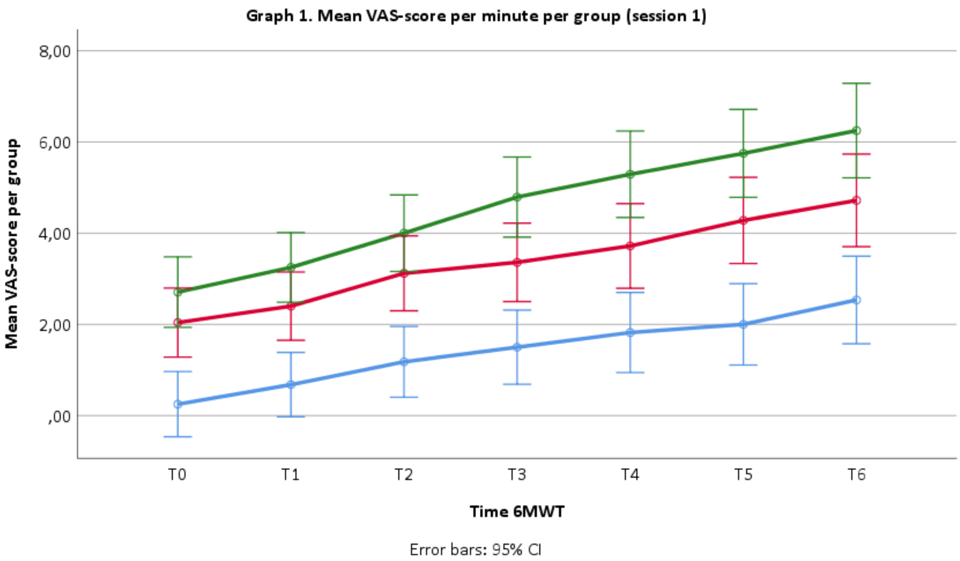
Table 5. Intra-Class Correlation Coefficient analysis for other methods to investigate walking-related motor fatigability

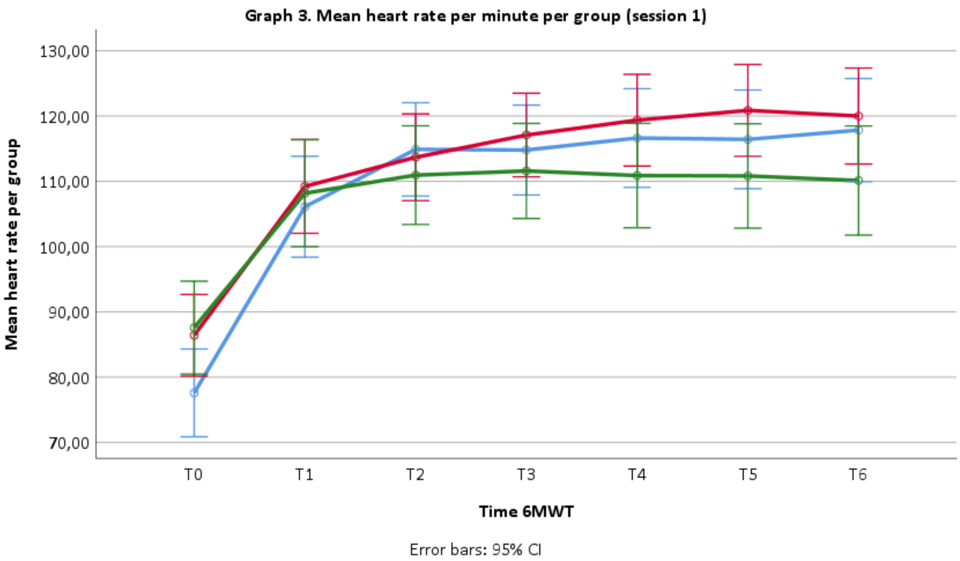
Article	Formula	ICC	
		HC	**MS**
Barbosa et al. 2016	$\frac{Walking\ speed\ in\ the\ 6th\ minute / Walking\ speed\ in\ the\ 1st\ minute}{Total\ distance\ walked}$	0.758	0.799
McLoughlin et al. 2012	$\frac{Average\ 6MWTHR - Average\ restingHR}{Walk\ speed}$	0.801	0.652
Montes et al. 2010	$\frac{DW\ 1st\ minute}{DW\ 6th\ minute}$	0.343	0.133
Montes et al. 2016	$\frac{Walking\ speed\ 1st\ minute}{Walking\ speed\ 6th\ minute}$	0.343	0.133
Murphy et al. 2017	$\frac{Mean\ speed\ over\ 6\ minutes / Mean\ speed\ over\ 2\ minutes}{Total\ distance\ walked}\ x\ 1000$	0.449	0.763

Abbreviations. ICC: Intra-Class Correlation Coefficient, HC: Healthy Controls, MS: Multiple Sclerosis

4.4 Manifestations per minute

The manifestations per minute for VAS-score, heartrate and distance walked are illustrated in the graphs below. Each line represents a group: healthy controls (blue line), MS patients showing walking-related motor fatigability (green line) and the PwMS without walking-related motor fatigability (red line). Since the manifestations during the second test session were very similar, these graphs are provided in the appendix at page 31.


Graph 1. Mean VAS-score per minute per group (session 1)
Mean VAS-score per group
8,00
6,00
4,00
2,00
,00
T0
T1
T2
T3
T4
T5
T6
Time 6MWT
Error bars: 95% CI


Graph 3. Mean heart rate per minute per group (session 1)
Mean heart rate per group
130,00
120,00
110,00
100,00
90,00
80,00
70,00
T0
T1
T2
T3
T4
T5
T6
Time 6MWT
Error bars: 95% CI

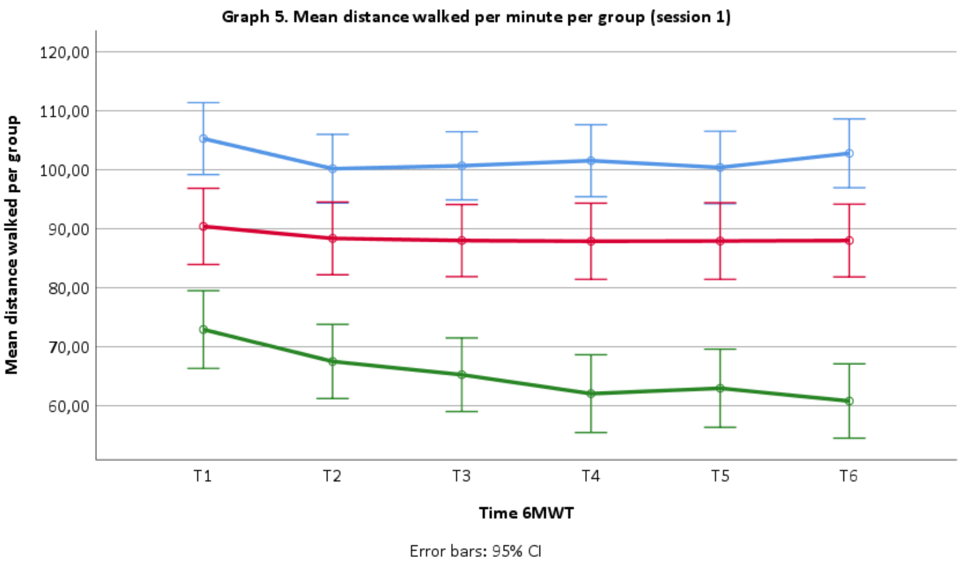

Graph 5. Mean distance walked per minute per group (session 1)
Mean distance walked per group
120,00
110,00
100,00
90,00
80,00
70,00
60,00
T1
T2
T3
T4
T5
T6
Time 6MWT
Error bars: 95% CI

Table 6 shows where the biggest difference during the 6MWT can be situated. An asterisk indicates that the difference between those minutes was significant.

Table 6. Repeated measures analyses corrected with Bonferroni for differences per minute

	HC	MSWF	MSNWF
Mean VAS	6 – 1*	6 – 1*	6 – 1*
Mean HR session 1	6 – 1*	3 – 1	5 – 1*
Mean HR session 2	6 – 1*	2 – 1	6 – 1*
Mean DW session 1	2 – 1	6 – 1*	6 – 1
Mean DW session 2	4 – 1*	6 – 1*	4 – 1*

Abbreviations: HC = Healthy Controls, MSWF = Multiple Sclerosis Walking Fatigability, MSNWF Multiple Sclerosis Non-Walking Fatigability, VAS = Visual Analogue Scale score, HR = Heart Rate, DW = Distance Walked|| Missing data heartrate. MS patients session 1: n = 8, session 2: n = 6; HC session 1: n = 9, session 2: n = 6

4.5 Clinical profile based on DWI correlations

The MS-patients performed four additional tests: T25FW, NHPT, SDMT and PASAT. For all these tests, this study analyzed if there is a correlation between the DWI and the results of the motor and cognitive function tests. Furthermore, a correlation between the DWI and the questionnaires the MS-patients had to answer was analyzed. An overview is shown in table 7.

Table 7. Bivariate correlations for distance walked index and additional tests & questionnaires in the group MS-patients

	DWI session 1	DWI session 2
Timed 25 Foot Walk Test	- 0.020	0.012
Paced Auditory Serial Addition Test	0.026	0.183
Nine Hole Peg Test		
dominant hand	- 0.383**	- 0.281
non-dominant hand	- 0.366**	- 0.281
Symbol Digit Modalities Test	0.177	0.327*
Motor Fatigue Impact Scale	- 0.255	- 0.260
Fatigue Severity Scale	- 0.209	- 0.314*
Fatigue Scale for Motor &Cognitive Functions	- 0.142	- 0.207
Multiple Sclerosis Walking Scale 12	- 0.491**	- 0.449**
Hospital Anxiety & Depression Scale	- 0.328*	- 0.229
Sleep Condition Inventory	0.425**	0.349*
Falls Efficacy Scale	- 0.556**	- 0.447**

Abbreviation. DWI: Distance Walked Index

** Pearson correlation is significant at the 0.05 level (2-tailed) ** at the 0.01 level*

At last, a relation between the group MS-patients which showed walking-related motor fatigability and a score on several questionnaires that exceeded the cut-off score was studied. Mean total and subscale score as well as the number of patients exceeding the cut-off criterion for some questionnaires are provided in tale 8 and 9.

Table 8. Overview of total and subscale scores (mean; ± SD) for total MS sample and subdivided groups

	Total MS sample	Subgroups based on DWI	
		[≥ – 10%]	[≤ – 10%]
	(n = 49)	(n = 25)	(n = 24)
MFIS			
Physical	17. 48 ± 8.13	15.13 ± 8.02	19.83 ± 7.70
Cognitive	17.69 ± 9.33	15.96 ± 8.69	19.42 ± 9.81
Psychosocial	3.29 ± 2.05	2.79 ± 1.91	3.79 ± 2.11
Total	38.31 ± 18.00	33.58 ± 16.94	43.04 ± 18.14
FSS	42.71 ± 12.51	39.79 ± 12.92	45.63 ± 11.62
FSMC			
Motor	33.17 ± 9.34	30.41 ± 11.03	36.04 ± 6.18
Cognitive	30.40 ± 10.02	28.63 ± 9.95	32.26 ± 9.97
Total	63.30 ± 18.70	59.04 ± 20.49	67.95 ± 15.70
MSWS-12	34.92 ± 14.48	28.67 ± 14.31	41.17 ± 11.94
HADS			
Depression	5.66 ± 4.83	4.29 ± 4.49	7.09 ± 4.86
Anxiety	6.21 ± 4.45	5.38 ± 3.86	7.09 ± 4.94
Total	11.87 ± 8.50	9.67 ± 7.62	14.17 ± 8.92
SCI	20.39 ± 8.26	22.58 ± 8.48	18.00 ± 7.48
FES-I	28.81 ± 11.85	23.00 ± 8.31	34. 63 ± 12.14

Abbreviations. MFIS: Motor Fatigue Impact Scale, FSS: Fatigue Severity Scale, FSMC: Fatigue Scale for Motor and Cognitive functions, MSWS: Multiple Sclerosis Walking Scale, HADS: Hospital Anxiety and Depression Scale, SCI: Sleep Condition Inventory, FES: Falls Efficacy Scale

Table 9. Prevalence of exceeding cut-off scores for total MS sample and subdivided groups

	Total MS sample	Subgroups based on DWI	
		[≥ – 10%]	[≤ – 10%]
	(n = 49)	(n = 25)	(n = 24)
MFIS (%)			
Total score > 38	25 (51)	9 (36)	16 (66)
FSS (%)			
Total score ≥ 4	37 (75)	17 (68)	20 (83)
FSMC (%)			
Motor score ≥ 22	36 (73)	17 (68)	19 (79)
Cognitive score ≥ 22	41 (84)	19 (76)	22 (91)
Total score ≥ 43	38 (77)	19 (76)	19 (79)
HADS (%)			
Total score 8 – 10	5 (10)	3 (4)	2 (16)
Total score ≥ 11	22 (45)	8 (32)	14 (41)

5 Discussion

The focus in this study was on examining the prevalence and test-retest reliability of several methods to objectively measure walking-related motor fatigability in healthy controls and PwMS based on e.g. distance walked during the 6MWT. Furthermore the study investigated perceived fatigability during six minutes of walking based on VAS-scores. Last, manifestations per minute were analyzed and correlations for the DWI with four additional tests and seven MS-specific questionnaires were calculated to delineate a clinical profile.

Walking-related motor fatigability had a prevalence of 48.9% in the group MS-patients, with a higher prevalence [41.7% (EDSS-score 4 – 5.5) and 20.8% (EDSS-score 6)] in the more disabled MS patients according to their EDSS-score. Furthermore, these patients show higher VAS-scores during the walking tests and exceed in most cases the cut-off scores on several questionnaires such as the Modified Fatigue Impact Scale, Fatigue Severity Scale and Hospital Depression and Anxiety scale.

Good reliability was shown for the total MS sample. The test-retest reliability for the two subdivisions in the MS sample was poor to moderate. The ICC for healthy controls showed moderate reliability.

These findings are consistent with the study of Leone et al. (2016), although they used a cut-off score of ≤ – 15% for DWI. The current study defined a more strict cut-off score of ≤ – 10% based on the collected data of healthy individuals and Figure 3. in the study of Leone et al. (2016) which represent the percentage DWI for each consecutive minute compared with the first minute of the 6MWT for the different groups.

Since there are only a few studies that studied walking-related motor fatigability in PwMS using a 6MWT, comparisons are not easily made. The studies of Leone et al. 2016, McLoughlin et al. (2012, 2015), the study of Engelhard et al. (2016) and the study of Qureshi et al. (2016) are the only studies available on this specific topic in the MS-population. MgLoughlin et al. based the formula for walking-related motor fatigability on different parameters e.g. heartrate, distance walked and walking speed, which are parameters the current study also measured during the test sessions. A comparison with the other studies isn’t possible, since they used more technical analyses to measure WRMF based on gait analysis characteristics.

Since the test sessions took place in different rehabilitation centra, it's possible that there were slightly different test conditions for the 6MWT e.g. the corridor at Overpelt was broad and clear, where at Melsbroek there was a smaller corridor with some transfer material that shouldn't be moved. Patients also could have been disturbed during the test session because other staff members walked in and out the corridors where the subjects performed the 6MWT. Next, the subjects had to read their heart rate each minute, but for some patients the combination with keeping on walking was difficult, and they slowed down their walking pace. Since there were three different test locations and only one coffer of test material, some data like heart rate per minute couldn't always be obtained. Furthermore, the heart rate monitor wasn't always working sufficiently.

The current study was the first to investigate test-retest reliability for the distance walked index in a healthy control and MS-patients sample, showing moderate to good reliability. The sample size of the two subdivided groups of PwMS was rather small with low scatter, which explains the lower ICC values statistically. Further research however should repeat the test session several times in bigger sample sizes to see if the DWI is a sustainable and reliable parameter to determine WRMF.

Further research could also investigate the DWI as experimental outcome measure during a longer follow-up period, for instance to see the effect of a rehabilitation intervention on changes or a positive progression in walking-related motor fatigability.

Although the ICC-values of the formulas provided by the studies of Montes et al. (2010, 2016) only showed poor reliability, the other methods to calculate walking-related motor fatigability (Barbosa et al. 2016, McLoughlin et al. 2012, Murphy et al. 2017) showed good reliability. Future research should certainly take these into account e.g. to examine psychometric properties, cut-off values.

MS patients reported that their walking speed during the 6MWT did not reflect their 'normal' walking capability. They assumed that their maximum speed was much better in a standardized corridor compared to ADL-walking in their daily life environment (with uneven footpaths, the state of the road, ...).

Future research should examine whether the DWI remains a good formula to estimate the influence of the different environmental condition on walking-related motor fatigability.

Furthermore, differences in walking-related motor fatigability can be influenced by the activity level of participants and their walking performance in daily life. Participants which have a more active lifestyle and/or walk more during the day, won't experience soon the feeling of being fatigued. On the other hand, participants with a more sedentary lifestyle or patients with MS which are restricted in walking activities, will show more quickly walking-related performance fatigability during the 6MWT. Therefore, it would be valuable to take into account the physical activity level in relation to walking-related motor fatigability.

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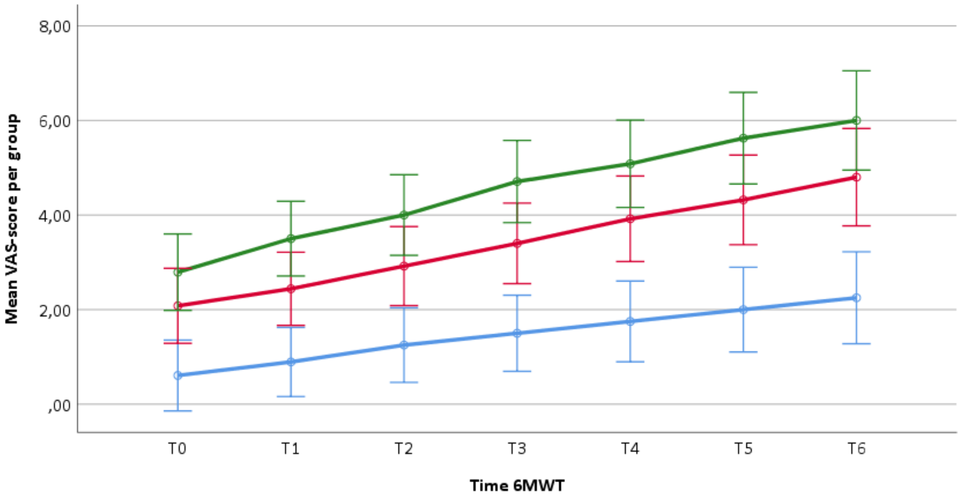
Appendices

Table 1. Overview of methods to objectively investigate walking-related motor fatigability

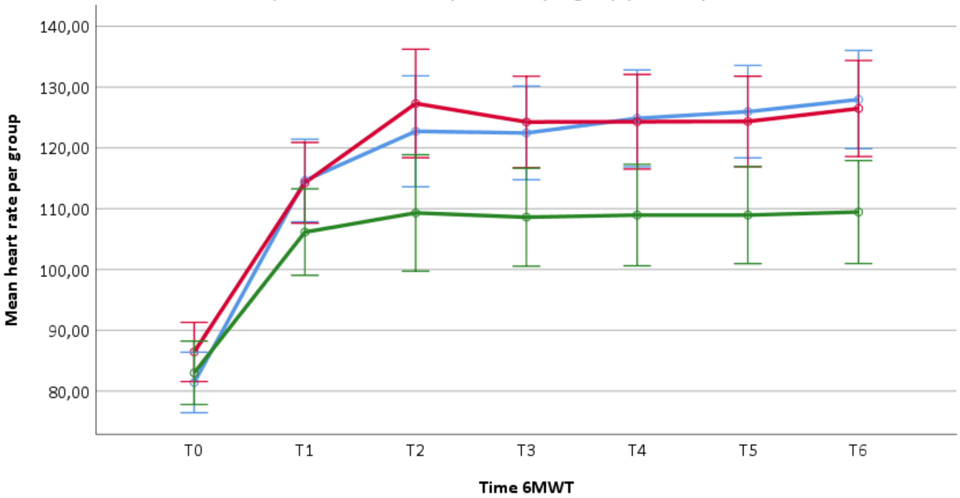
Article	Formula	Population
Barbosa et al. 2016	$\frac{WSminute6/WSminute1}{Total\ DW}$	Older women (n = 44)
Engelhard et al. 2016	Distance Time Warping ▪ Template cycles = gait cycles from the 1^{st} & 2^{nd} minutes of the 6MWT ▪ Test cycles = cycles from subsequent minutes ▪ Warping length = difference in length between input cycles & DTW-aligned counterparts ▪ Distance Score = DTW distances from each minute ▪ Warp Score = warping lengths from each minute	Ms patients (n = 86) Healthy controls (n = 29)
Leone et al. 2016	$\mathbf{\frac{DW\ at\ minute\ n - DW\ at\ minute\ 1}{DW\ at\ minute\ 1}\ x\ 100}$	**MS patients (n = 208)**
McLoughlin et al. 2012	$\frac{Mean6MWTHR - MeanRestHR}{Walking\ speed}$	MS patients (n = 40)
Montes et al. 2010	$\frac{DW\ minute\ 1}{DW\ minute\ 6}$	SMA patients (n = 18)
Montes et al. 2016	$\frac{WS\ minute\ 1}{WS\ minute\ 6}$	SMA patients (n = 9)
Murphy et al. 2017	$\frac{Mean\ WS\ minute\ 6/Mean\ WS\ minute\ 2}{Total\ DW}\ x\ 1000$	Older adults OA (n = 163)
Qureshi et al. 2016	Gait cycle length variance and speed for each minute	MS patients (n = 28)

Graph 2. Mean VAS-score per minute per group (session 2)



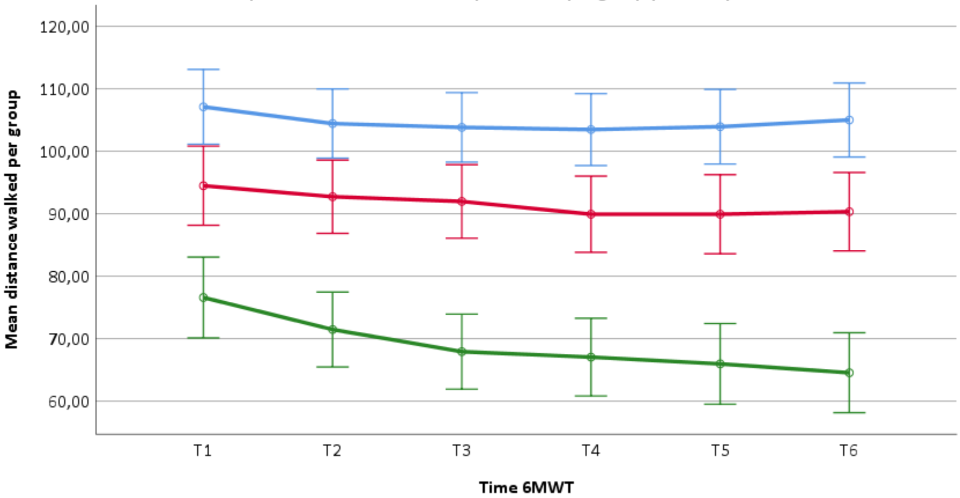
Error bars: 95% CI

Graph 4. Mean heart rate per minute per group (session 2)



Error bars: 95% CI

Graph 6. Mean distance walked per minute per group (session 2)



Error bars: 95% CI

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6/10/17	oefenen pre-testing	Promotor: Copromotor: [signature] Student(e): [signature] ~~Student(e):~~
13/2/18	stand van zaken + voorbereiden, afspraken testing	Promotor: Copromotor: [signature] Student(e): [signature] ~~Student(e):~~
6/3/18	overlopen stand van zaken, to do's, taakverdeling, deadline	Promotor: Copromotor: [signature] Student(e): [signature] ~~Student(e):~~
9/5/18	bespreken & feedback voorstel data-analyse	Promotor: Copromotor: [signature] Student(e): [signature] ~~Student(e):~~
16/5/18	bespreken herwerkte data-analyse	Promotor: Copromotor: [signature] Student(e): [signature] ~~Student(e):~~
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