Implications of lower extremity muscle power and force for walking and fatigability in multiple sclerosis-An exploratory pilot-study

Peer-reviewed author version

RAMARI FERREIRA, Cintia; Hvid, Lars G.; Dalgas, Ulrik; Diniz, Ana R.; von Glehn, Felipe & de David, Ana C. (2022) Implications of lower extremity muscle power and force for walking and fatigability in multiple sclerosis-An exploratory pilot-study. In: Clinical biomechanics, 96 (Art N° 105668).

DOI: 10.1016/j.clinbiomech.2022.105668
Handle: http://hdl.handle.net/1942/37700

Title page

ORIGINAL ARTICLE

IMPLICATIONS OF LOWER EXTREMITY MUSCLE POWER AND FORCE FOR WALKING AND FATIGABILITY IN MULTIPLE SCLEROSIS – AN EXPLORATORY PILOT-STUDY

Running title: Implication of power for physical function in multiple sclerosis

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Publication Ethics

All participants provided informed written consent prior to involvement in the study, which was approved by the Research Ethics Committee - Faculty of Health Sciences (CEP/FS), University of Brasilia (CAAE: 05142918.7.0000.0030).

Word count of the Abstract: 247

Word count of the manuscript: 4050

Abstract

Background: Limitations in physical function are common in Multiple Sclerosis (MS), yet it is neither clear how muscle power implicates physical function and walking-fatigability. This pilot-study aims to investigate (1) deficits in muscle power/force alongside walking in persons with MS; (2) associations between muscle power/force and physical functions and (3) the impact of prolonged walking in muscle power/force. ***Methods:*** 30 relapse-remitting persons with MS and 28 healthy controls performed chair rise and plantar flexion on a force platform before and after 12-minutes of intermittent walking to measure lower extremity muscle power/force. GaitRite measured walking speed. The percentage change in distance walked was also calculated. Persons with MS were classified into subgroups according to walking-fatigability and mobility disability status (Patient Determined Disease Steps). ***Findings*:** Higher deficits in muscle power compared to force were observed in persons with MS *vs.* healthy controls particularly in persons with MS having higher disability. Muscle power and force were associated with walking capacity, mobility disability and subjective fatigue, but not with percentage change in distance walked. Persons with MS slowed down over the course of the 12-minutes intermittent walking, whereas decrements in walking speed and muscle power/force (derived from chair rise) were observed in persons with MS presenting walking-fatigability only. ***Interpretation:*** Muscle power and force are impaired in persons with MS and appear to be critical for physical function in MS. This exploratory pilot study further suggests that muscle power/force from chair rise could contributes to walking-fatigability which therefore offer future treatment targets.

***KEYWORDS*:** Multiple Sclerosis; Functional Capacity; Fatigue; Muscle Function; Walking; Disability.

1 Introduction

A pathological hallmark of multiple sclerosis (MS) is the accumulation of demyelinating lesions in the central nervous system (1). The bursts of focal inflammation, axonal loss and neurodegeneration are known as predominant causes of disability (2). Common limitations in physical functions in persons with MS (pwMS) include the decrement in walking speed and endurance (3-5), along with increment in the time to perform stair climbing and chair rise tasks (6-8). These are partly driven by an inability of the neuromuscular system to perform rapid limb movements due to insufficient volitional drive to a given muscle (9, 10), along with reduced rate of force development (RFD; force or torque production within a very short time window) (9). Indeed, marked deficits have been observed in the lower extremity muscle strength and RFD in pwMS vs. healthy controls (HC) (11). Moreover, systematic reviews have shown clear associations between lower extremity strength/RFD of different muscle groups and lower limb functional capacity such as walking and sit-to-stand (6, 7, 12). While the vast majority of the studies have examined lower extremity strength/RFD during isometric or dynamic muscle contractions at fixed slow-to-moderate velocities, few have examined muscle power (i.e., force multiplied by velocity) (13, 14). In MS, there is little information regarding muscle power, particularly when derived from functional weight-bearing tasks, and more importantly how muscle power implicates physical function in pwMS (15). Importantly, evidence derived from aging studies show that lower extremity muscle power is a stronger predictor of physical function than muscle strength, impacting mobility (16) and the ability to avoid falling during walking (17). Such a comparison between muscle power has nevertheless not been examined in pwMS.

Fatigue is another consequence of MS and is frequently reported by pwMS (18). It can be defined as perceived fatigue (subjective sensations of weariness) (19) and as motor fatigue or fatigability (absolute or relative change in performance over a period of time during or after a given task) (20). Importantly, fatigability is known to be associated with baseline lower extremity muscle strength (21). However, no studies have so far examined whether decrement in muscle power induced by prolonged walking contributes to walking-related fatigability.

The aims of this cross-sectional exploratory pilot-study were (1) to investigate and characterize deficits in lower extremity muscle power (and force) measured during chair rise and plantar flexion on a force platform alongside walking capacity in pwMS; (2) to investigate the associations between muscle power (and force) and walking capacity, mobility disability status, subjective fatigue and fatigability and

(3) to investigate the impact of 12-minutes of intermittent walking in lower extremity muscle power (and force). We hypothesized that pwMS would present substantial deficits in lower extremity muscle power/force (preferentially in power) and in walking capacity, particularly in pwMS having mobility disability and pwMS presenting walking-fatigability.

2 Materials and methods

2.1 Participants

A convenience sample of thirty-four people with MS were recruited from private neurological clinics and via a MS community organization, via email and newsletter advertisements. Participants were eligible if they had a confirmed diagnosis of relapse-remitting MS (RRMS) according to the revised McDonald criteria (22). Participants were excluded if they had a confirmed exacerbation or relapse of MS in the month prior to testing; had significant cardiac or respiratory disease, which could pose a risk when performing the walking protocol; if they could not walk for two minutes without stopping. Twenty-eight healthy controls (HC) matched for age (acceptable range of ± 2 y), sex, height (acceptable range of ± 5 cm) and weight (acceptable range of ± 5 kg) were recruited from the university staff and from friends and family of the participants.

2.2 Clinical evaluations

Initially, participants were asked to determine their disability level according to walking function using the Brazilian Patient Determined Disease Step scale (PDDS-BR)(23). PDDS is a validated patient-reported measure of mobility disability. The PDDS has nine ordinal levels ranging from 0 (normal) to 8 (Bedridden), and presents strong correlations with the Expanded Disability Status Scale (EDSS) (coefficient of correlation ranging from 0.71 to 0.78).

The Modified Fatigue Impact Scale (MFIS) is a self-reported assessment of fatigue assessing physical, cognitive and psychosocial domains. The questionnaire contains 21-items concerning how fatigue have been impacting patient's lives in the past 4 weeks (24). Given to the best previously reported association between physical function and the MFIS physical subscore (25), it was a priori decided to use this for the association analysis.

2.3 Force platform measures

Measures of power (and force) during the chair rise and the plantar flexion tests were collected before and after the walking protocol. Ground reaction force was measured using an AMTI force platform (AMTI, Watertown, MA). Vicon Nexus software - v2.8 (Vicon, Oxford, UK) was used to acquire data on kinetics at a sample rate of 1000 Hz. Data processing was performed using personalized MATLAB scripts (R2015a, The Mathworks, Natick, Massachusetts, USA). Signals were filtered digitally with a 10-Hz low-pass Butterworth filter (4th order) with zero phase lag (26).

Participants were instructed to begin the chair rise from a sitting position on a standard wooden chair measuring 42 cm of height, with back support and no armrests, positioned adjacent to the force platform. With their feet at a comfortable self-selected width within the boundaries of the platform, the participants were instructed to cross their arms over the chest and to rise from the chair as fast but safely as possible, and to sit down at a slow speed, performing sequentially five sit-to-stand without rest (26).

The plantar flexion consisted of five bilateral plantar flexions (heel rises) on a force platform. Participants were instructed to rise to the tip of their toes with the feet at a comfortable position as fast as possible, keeping the knees straight, the arms crossed on the chest and trying to keep on their tiptoe for at least one second before go down (27).

2.4 Walking protocol

Participants were instructed to walk along a 10-meter corridor, turning 180 degrees, for 2-minutes. The complete protocol was composed of six 2-minute walks with a rest period of 30 seconds between bouts, adding up to a total of 12-minutes of walking. Participants were instructed to "walk as fast as possible, but safely". If necessary, the use of a walking aid was allowed. Before, during the rest periods and after the last 2-minute walk, the maximal walking speed (m/s) was assessed using a 4.88-meter GaitRite electronic walkway (CIR Systems Inc., Haverton, Pennsylvania, USA). Figure 1 presents the experimental protocol.

INSERT FIGURE 1

2.5 Data processing

Participant's body weight was assessed during quiet stance immediately before the trials. The ground reaction force (Fz) was normalized relatively to the body weight. The chair rise movement began with a relief phase and ended when Fz was equal to 1 - when the subject was standing (26, 28). We have not included the preparation phase in the analysis and we chose to analyse the chair rise from the first moment when the body weight was reached (Fz ~ 1, before the peak force) until the standing position (figure 2, A) (28). For the plantar flexion, the Fz was equal to 1 at the beginning of the movement, followed by an increase on Fz - reaching the peak force, and a rebound force event following the peak force. The end of the plantar flexion was defined when the Fz was around 1 after the rebound force event (figure 2, B).

INSERT FIGURE 2

Regarding to the Fz parameters, figure 2 presents the interval from the force-time curve chosen to extract force and calculate power. The peak force normalized per body weight (N/bw - Newton per

body weight) was used in the analysis. To calculate power, the velocity-time curve was obtained by dividing the resultant force-time curve by the participant's body weight to find the acceleration-time curve. The acceleration was then numerically integrated with respect to time using the trapezoid rule, and the instantaneous power was calculated as the product of the force and velocity (29). The normalized peak power (Watts per body weight - W/bw) was used in the analysis.

In order to investigate fatigability during walking, the Distance Walk Index (DWI%) (30) was calculated based on the total distance walked during the first and in the last 2-minute walks. Adopting a cut-off of 10% of slowing down, DWI [≤ -10] (31), pwMS were allocated into two groups: MS fatigability and MS non-fatigability. In addition, another subgroup classification was also adopted for pwMS according to their mobility disability status, based on the PDDS score. Those with PDDS equal to zero were included in the PDDS Low group, while the remaining participants with PDDS ≥ 1 were included in the PDDS High group.

2.6 Statistical analysis

Statistical analyses were performed using linear mixed model in Stata version 14.2 (StataCorp LP, Texas, USA). Distribution of data was visually checked by box-plots, q-q-plots, histograms and dot-plots, showing that all the data were normally distributed, except for the plantar flexion force which was subsequently transformed prior to analysis: *(1/plantar flexion)^2*). All baseline data were analysed with Group (HC and MS All; HC, MS non-fatigability and MS fatigability; HC, PDDS Low and PDDS High) as a fixed effect and Participant ID as a random effect. Deficit scores were also calculated as the mean (95% confidence interval, CI 95%) percentage difference for pwMS in relation to the mean value from HC. To investigate the changes in the distance walked (m) and in the walking speed (m/s) over the 12-minutes of intermittent walking, analysis was performed with repeated measures for each group.

Simple linear regression analysis and multivariate regression analysis adjusting for age and sex were carried out to examine potential associations between muscle power and force with walking speed (walking speed at baseline, m/s), distance (total distance from the 12-minutes walking, m), DWI (%), PDDS (score) and MFIS physical (physical subscore) in the total sample of pwMS. Associations are presented as r^2-values (i.e., the square of the correlation coefficient), with $r^2 > 0.81$ ($r > 0.90$) interpreted as very strong, $r^2 = 0.49$-0.80 ($r = 0.70$-0.89) as strong, $r^2 = 0.25$-0.48 ($r = 0.50$-0.69) as moderate, $r^2 = 0.09$-0.24 ($r = 0.30$-0.49) as weak, and $r^2 < 0.08$ ($r < 0.29$) as negligible (32). Data are presented as mean (CI 95%) unless otherwise stated. The effects of the walking protocol on muscle power/force and walking

speed were analysed with Group (HC and MS All; HC, MS non-fatigability and MS fatigability; HC, PDDS Low and PDDS High) and Time (Pre and Post) as fixed effects and Participant ID as a random effect. Changes in force, power and walking speed were also calculated as the mean (CI 95%) percentage difference between pre and post (delta, Δ%) the 12-minutes of intermittent walking. Graphs were made using GraphPad Prism version 7.03 (GraphPad Software, California, USA). Level of statistical significance was set at $p < 0.05$.

3 Results

3.1 Baseline characteristics

Table 1 presents the characteristics of the participants along with clinical results. No differences were found regarding sex proportions, age, height, and weight between HC and pwMS. Subjective (perceived) fatigue measured using the MFIS were higher in pwMS compared to HC. The MS fatigability group presented a lower score for the MFIS total and a higher score for the MFIS physical, when compared to the MS non-fatigability group. MFIS total and all subscores were ~~all~~ higher for the PDDS High group compared to the PDDS Low and to the HC group. As a measure of physical function, the total distance (m) travelled during the 12-minutes of intermittent walking was shorter for pwMS vs. HC. Comparisons of subgroups revealed shorter distances walked in MS fatigability when compared to MS non-fatigability as well as in PDDS High compared to PDDS Low. In general, pwMS showed higher DWI (%) compared to HC suggesting the presence of walking-related fatigability. Moreover, DWI (%) was higher in MS fatigability group compared to the MS non-fatigability group. In addition, DWI (%) was not impacted by PDDS, and no differences could be found between PDDS Low and PDDS High groups.

INSERT TABLE 1

Figure 3 presents the course of the distance walked and the walking speed over the 12-minutes of intermittent walking for each group. Changes were predominantly observed in the MS fatigability group.

INSERT FIGURE 3

3.2 Deficit in lower extremity muscle power/force and walking capacity - comparisons of subgroups

As shown in figures 3 and 4, pwMS presented greater limitations in walking endurance and speed compared to HC. In addition, lower extremity muscle force and preferentially muscle power were substantially lower in pwMS compared to HC (corresponding to deficits of 5% in force and 15 to 20% in power). MS fatigability and MS non-fatigability groups presented deficits in total distance walked, in walking speed, and in plantar flexion muscle power when compared to the HC. Deficits in total distance

walked were found for MS fatigability group compared to the MS non-fatigability group. Deficits in plantar flexion muscle force and power as well as chair rise muscle power were only present in non-fatigability pwMS (figure 4b). PDDS High group showed deficits in walking capacity and in muscle power (and force) when compared to HC and PDDS Low groups (Figure 4c). Although the PDDS Low group showed deficits in walking capacity when compared to HC, measures of power (and force) were not different from HC.

INSERT FIGURE 4

3.3 Baseline associations between muscle power/force and walking capacity, mobility disability status and physical subjective fatigue in pwMS

Muscle power and force were significantly associated with walking speed (walking speed at baseline), distance (total distance from the 12-minutes walking) and mobility disability status (PDDS) (Table 2). No associations were found between muscle power/force and the reduced walking distance and speed over the 12-minutes of intermittent walking (i.e., DWI %). Associations between chair rise force and walking speed, total distance walked in the 12-minutes walking, disease steps (PDDS) as well as physical subjective fatigue (MFIS physical), were stronger compared to the associations found for plantar flexion force. In addition, age and sex did not impact the results as presented in table 3 for the multiple regression analysis.

INSERT TABLE 2

INSERT TABLE 3

3.4 Pre-post changes induced by the 12-minutes of intermittent walking - comparisons between subgroups

MS fatigability group presented trends towards delta changes (%) in power (and force) from chair rise compared to HC and to MS non-fatigability (see Table 3). No pre-post changes were found for the PDDS subgroups.

Regarding walking speed, pre-post change was only significant for the MS fatigability group, with reduced walking speed after the 12-minutes of intermittent walking. In addition, a trend for significance was found for delta (%) between MS fatigability group and non-fatigability group.

INSERT TABLE 4

4 Discussion

The main findings of this exploratory pilot-study: (1) a more pronounced deficit in lower extremity muscle power vs. muscle force was observed in pwMS, particularly in pwMS having higher mobility disability (PDDS score ≥ 1); (2) lower extremity muscle power and force were (to a comparable extent) associated with walking capacity, PDDS score and MFIS physical (power r^2=0.11 - 0.39 / force r^2=0.11 - 0.43), but not with walking-related fatigability (i.e. DWI%); (3) pwMS significantly decreased walking speed over the 12-minutes of intermittent walking (preferentially in pwMS presenting walking-related fatigability = MS fatigability group); (4) the absence of any apparent walking-induced decrements in absolute values of lower extremity muscle power and force suggest that walking fatigability was not dependent of such factors in our sample.

4.1 Deficit in lower extremity muscle power/force and walking capacity - comparisons of subgroups

In general, pwMS presented approximately 20% of deficit in walking capacity in relation to HC, and our results thus corroborate with previous findings (5), both for short distance (15, 33) and long-distance walking (4).

For all pwMS, deficit in muscle power (15-20%) were shown to be more prominent than deficit in muscle force (5%). According to a review by Jørgensen et al. (11), a deficit of approximately 25% in pwMS compared to HC has been reported for lower extremity muscle strength (isokinetic dynamometer assessment) and for knee extensor muscle power (despite the absence of any deficit dorsiflexor muscle power) (13). Moreover, in a cross-sectional study by Stagsted et al. (15), a deficit in chair rise power as well as leg press power (assessed by use of position transducer) in pwMS compared to HC corresponded to 26% and 23%, respectively. The markedly lower deficit in force in the present study is probably partly due to the tasks performed, to the method applied to extract power/force (i.e. GRF), and to the enrolment of predominantly mildly impaired pwMS. Cruz et. al. (34) also found deficits in rapid muscle force (i.e. Rate of Force Development – RFD; derived from chair rise on a force platform) in pwMS vs. HC, known to be a pre-requisite of producing muscle power – as examined in the present study.

Analysis of subgroups revealed a substantial difference in the total distance walked during the 12-minutes of intermittent walking in MS fatigability compared to MS non-fatigability group, whereas baseline walking speed did not differ between groups. This emphasizes that assessment of walking-fatigability should be prioritized when assessing pwMS suffering from fatigue. Regarding the deficits in muscle power/force, our results showed no differences between MS fatigability and MS non-fatigability group. These results suggest that the decrements over time (i.e. DWI%) was not affected by the baseline

values of lower extremity muscle power/force in our sample (at least not in the way we have assessed it by performing the tasks with a fast yet safe speed). Subjective fatigue (i.e. MFIS) has been reported to be weakly associated with walking capacity (25) as well as muscle strength (35). Yet no studies have, to our knowledge, previously reported differences in walking speed and in lower extremity muscle power/force in resting conditions and after a 12-minutes of intermittent walking in pwMS (especially not in fatigability subgroups) and compared to HC have been proposed.

Concerning the subgroup's classification according to fatigability status and mobility disability status, disparate findings were observed. Whilst higher mobility disability status was accompanied by decrements in baseline outcomes, higher fatigability status was accompanied by higher decrement in walking speed. Since differences in muscle power/force between the PDDS Low and High groups were substantial during the chair rise task but not during the plantar flexion, this indicate that more complex dynamic tasks such as chair rise may require a more optimal motor control in order to synchronise different muscular groups (36) and might be more sensitive in terms of detecting motor deficiency across disability status in pwMS.

4.2 Baseline associations between muscle power/force and walking capacity, mobility disability status, and physical subjective fatigue in pwMS

Although associations between plantar flexion muscle power/force during and walking capacity, mobility disability status as well as subjective fatigue were observed (corresponding to weak associations), chair rise muscle power/force (i.e. a more complex motor task) presented better associations with walking capacity, mobility disability and subjective fatigue (corresponding to weak-to-moderate associations). Our findings corroborate with a review from our research group (12), where lower-limb muscle strength was associated with a number of lower-limb functional capacity tests (r^2-values ranging from 0.20 to 0.30). Despite the small sample size (n=30) presented in the current exploratory pilot-study, more pronounced deficits in muscle power vs. muscle force was found in pwMS, even so, muscle force presented higher associations with walking capacity.

4.3 Changes induced by the 12-minutes of intermittent walking - comparisons between subgroups

No apparent differences in absolute lower extremity muscle power/force were found between pre and post the 12-minutes of intermittent walking in pwMS and HC. In a study by McLoughlin et al. (37), a walking-induced (6-minutes walking) decrement in both knee extensor and dorsiflexor muscle strength assessed during isolated muscle contractions was reported in pwMS. However, the current exploratory

pilot study is the first to evaluate lower extremity muscle power/force using functional tasks before and after an intermittent walking in pwMS. The lack of decrements in muscle power/force that was hypothesised to occur, may be due to the time period (about 4 min) taken to perform the post evaluation. Future studies should consider to evaluate real-time lower extremity muscle power/force (i.e., during walking) and, to include a larger sample size of pwMS presenting walking-fatigability in order to identify potential mechanisms related to fatigability in MS.

Concerning the course of distance walked over the12-minutes, pwMS slowed down over time. However, when analysis of subgroups was carried out, differences over time could no longer be found for the MS non-fatigability group. Interestingly, decrement in distance walked was found in the PDDS Low group but not in the PDDS High group, suggesting a more conservative strategy from the more disable patients. Analysis of walking speed over time revealed significant decline only for the MS fatigability group. Previous studies investigating the impact of two- and six-minutes walking on spatiotemporal gait parameters in pwMS did not found decrement in walking speed (38, 39). In addition, it has been shown that six-minutes walking induced an increment in walking speed (at a comfortable pace) and there was no effect on fast walking speed in pwMS (40). Corroborating with the findings from the literature, no change in walking speed was found in our study when the analysis was carried out for the entire sample of pwMS.

4.4 Clinical implications

The present exploratory pilot study highlights the importance of including objective methods to identify pwMS presenting walking-fatigability. From our MS sample, 30% slowed down during the 12-minutes of intermittent walking. In this context, it is important to perform analysis of subgroups with larger sample size including pwMS presenting and not presenting walking-fatigability. PwMS presenting walking-fatigability may alter biomechanical gait parameters (i.e., spatiotemporal, kinematics and kinetics) and muscle functions during prolonged walking, and, the real-time assessment of these parameters could elucidate potential factors related to fatigue in MS. In addition, muscle power/force are modifiable factors that can be trained and improved with physical exercise, more precisely with resistance training. Improvements in muscle functions such as power, should be considered in clinical practice during rehabilitation and exercise interventions in order to improve physical functions in pwMS.

4.5 Limitations of the study

The current study is the first to investigate the effects of 6 x 2 minutes (12-minutes in total) of intermittent walking on walking speed and on muscle power/force and the associations with walking-related fatigability in pwMS. A number of limitations nevertheless deserve mentioning: (1) characterized as an exploratory pilot-study (and thus not powered a priori to examine the selected outcomes), the results must be interpreted as such, hence without drawing strong conclusions regarding the impact of prolonged walking on the decrement of muscle power/force in pwMS; (2) the sample size may have been too small, especially across the subgroups (e.g. MS fatigability and MS non-fatigability); (3) pwMS enrolled in this study had mostly mild MS; (4) the time taken to perform the muscle power/force evaluation after the 12-minutes walking may have allowed partial recovery of muscle function and thus hampering the detection of the effects of the prolonged walking; (5) the chair rise task was performed at a fast and safe speed, but perhaps not maximal, which affected the absolute values of power and, possibly, diminishing the associations of muscle power with physical functions; (6) the cross-sectional design do not allow inference related to causality from impairments in the lower extremity muscle power/force and walking-fatigability; (7) as pwMS in general usually present impairments in balance control and coordination, these motor capacities were not evaluated in our study and their potential interference with the performance of motor tasks should also be taken into consideration.

5 Conclusions

The present exploratory pilot-study revealed greater deficits (pwMS *vs*. HC) in muscle power compared to force, particularly in pwMS having higher mobility disability (PDDS ≥ 1). Muscle power and force were associated with walking capacity, mobility disability status and subjective fatigue, but not with slowing down over time (i.e., DWI %). PwMS slowed down over the course of the 12-minutes intermittent walking, whereas decrements in walking speed and muscle power/force delta (derived from chair rise) were observed in pwMS presenting walking-fatigability only.

Muscle power as well as force are impaired in pwMS and appear to be critical for physical function in MS. This exploratory pilot study further suggest that muscle power/force could contribute to walking-fatigability which therefore offer future treatment targets.

Acknowledgements

This work was partially funded by the Coordination for the Improvement of Higher Education (CAPES, Brazil – Finance Code 001).

We thank the neurologists Carlos Bernardo Tauil and Eber Castro Correa for the assistance with inviting the patients from their private clinics to participate in this study, and the Apemigos (Association of People with Multiple Sclerosis from the Federal District) for encouraging the participants to contribute with the multiple sclerosis research projects. At last, we thank all the participants.

Author contribution:

- Conception or design of the work: CR, LGH, ACD, FG
- Data collection: CR, ARG, FG
- Data-analysis: CR, UD, LGH
- Interpretation of data: All
- Drafting the work: CR, LGH
- Revising the work: All
- Final approval of the version to be published: All
- Agreement to be accountable for all aspects of the work: All

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Tables

Table 1. Characteristics and clinical results of the participants.

	HC	MS All	MS non-fatigability	MS fatigability	PDDS Low	PDDS High
n (females)	28 (22)	30 (24)	21 (18)	9 (6)	13 (11)	17 (13)
Age (y)	40.3 (35.9 : 44.6)	41.9 (37.7 : 46.1)	40.6 (36 : 45.2)	45 (34.6 : 55.4)	39.8 (32.8 : 46.9)	43.5 (37.9 : 49.1)
Height (m)	1.66 (1.62 : 1.70)	1.65 (1.61 : 1.69)	1.63 (1.59 : 1.67)	1.70 (1.61 : 1.78) ***b***	1.64 (1.59 : 1.69)	1.66 (1.60 : 1.71)
Weight (kg)	67.6 (62.05 : 73.31)	68.37 (62.5 : 74.2)	63.9 (58.4 : 69.5)	78.6 (64.4 : 92.9) **a,b**	66.8 (57.2 : 76.4)	69.5 (61.3 : 77.6)
PDDS (0 - 8)	---	1.23 (0.6 : 1.81)	1 (0.42 : 1.57)	1.77 (0.20 : 3.35)	0	2.1 (1.42 : 2.93) **c**
Walking aid (n)		5	2	3	0	5
Time since diagnosis (yrs)	---	7.7 (5.3 : 10.1)	6.5 (4.2 : 8.8)	10.6 (4.05 :17.2) ***b***	6.8 (3.0 : 10.6)	8.4 (4.8 : 11.9)
MFIS total (0 - 84)	24.6 (19.3 : 29.8)	39.1 (31.7 : 46.5) **a**	39.7 (30 : 49.4) **a**	37.7 (24.8 : 50.7) **a,b**	29.4 (18.1 : 40.8)	46.6 (37.5 : 55.6) **a,c**
MFIS cognitive (0 - 40)	12.3 (9.3 : 15.2)	17.3 (13.6 : 20.9) **a**	18 (13.1 : 22.9) **a**	15.5 (9.6 : 21.4)	13.3 (7.2 : 19.4)	20.2 (15.7 : 24.8) **a,c**
MFIS physical (0 - 36)	10.5 (7.9 : 13.1)	18.2 (14.9 : 21.4) **a**	17.9 (13.9 : 22) **a**	18.8 (12.1 : 25.6) **a,b**	13.5 (8.9 : 18.0)	21.8 (17.7 : 25.9) **a,c**
MFIS psychosocial (0 - 8)	2.0 (1.3 : 2.7)	3.6 (2.7 : 4.5) **a**	3.7 (2.5 : 4.9) **a**	3.3 (1.5 : 5.1)	2.5 (1.2 : 3.8)	4.4 (3.2 : 5.7) **a,c**
Distance total, 12 min (m)	1156 (1102 : 1210)	898.3 (808.4 : 988.3) **a**	955.9 (867.1 : 1045) **a**	764.1 (538.3 : 989.9) **a,b**	1051 (985.5 : 1117) ***a***	781.4 (652.6 : 910.1) **a,c**
DWI (%)	-1 (-3 : 1)	-7 (-10 : -3) **a**	-1 (-3 : 1)	-19 (-25 : -13) **a,b**	-6 (-11 : -2) ***a***	-7 (-13 : -1) **a**

Results are presented as mean and 95% confidence interval (CI). PDDS, patient determined disease steps. MFIS, modified fatigue impact scale. Walking aid to perform the walking protocol. DWI, distance walked index. Statistical significance ($p \leq 0.05$) and trends ($0.05 < p < 0.10$, shown in italic) are denoted by **a**: different from healthy controls (HC), **b**: different from Non-Fatigable persons with MS, and **c**: different from PDDS Low.

Table 2. Associations between muscle power/force and walking capacity, fatigability, perception of fatigue and mobility disability status in persons with MS.

	Plantar Flexion				Chair Rise			
	Power (W/bw)		Force (N/bw)		Power (W/bw)		Force (N/bw)	
	r^2	p-Value	r^2	p-Value	r^2	p-Value	r^2	p-Value
Walking speed (m/s)	0.18	0.019 [d]	0.25	0.005 [d]	0.15	0.038 [d]	0.33	0.001 [d]
Distance total (m) - 12 min	0.20	0.013 [d]	0.19	0.014 [d]	0.27	0.003 [d]	0.43	0.000 [d]
DWI (%)	0.05	0.197	0.00	0.865	0.00	0.866	0.01	0.557
MFIS phys., score	0.13	0.048 [d]	0.14	0.035 [d]	0.39	0.000 [d]	0.35	0.001 [d]
PDDS, score	0.21	0.010 [d]	0.11	0.068 *[d]*	0.18	0.022 [d]	0.25	0.005 [d]

DWI, distance walked index. PDDS, patient determined disease step. MFIS, modified fatigue impact scale. N/bw, Newton/body weight. W/bw, Watts/body weight. Statistical significance ($p \leq 0.05$) and trends ($0.05 < p < 0.10$, shown in italic) are denoted by d.

Table 3. Multivariate regression analysis adjusting for age and sex between muscle power/force and walking capacity, fatigability, perception of fatigue and mobility disability status in persons with MS.

		Plantar Flexion						Chair Rise					
		Power	Age	Sex	Force	Age	Sex	Power	Age	Sex	Force	Age	Sex
WS, m/s	β	0.38	-0.14	-0.15	0.47	-0.17	-0.15	0.42	-0.06	-0.32	0.60	-0.01	-0.31
	p-value	*0.05[d]*	0.42	0.40	**0.01[d]**	0.32	0.38	**0.02[d]**	0.71	0.08	**0.00[d]**	0.92	*0.05[d]*
	Model	*R^2 =0.13*			*R^2 =0.21*			*R^2 =0.16*			*R^2=0.36*		
Dist.-12m, m	β	0.43	-0.34	-0.03	0.42	-0.33	-0.15	0.53	-0.22	-0.28	0.67	-0.17	-0.28
	p-value	**0.01[d]**	**0.04[d]**	0.85	**0.01[d]**	*0.05[d]*	0.35	**0.004[d]**	0.17	0.09	**0.00[d]**	0.22	*0.05[d]*
	Model	*R^2 =0.23*			*R^2=0.23*			*R^2=0.31*			*R^2 =0.47*		
DWI, %	β	0.18	-0.14	-0.21	0.02	-0.15	-0.26	0.01	-0.16	-0.34	0.16	-0.12	-0.37
	p-value	0.35	0.44	0.27	0.90	0.42	0.16	0.94	0.40	0.08	0.41	0.52	*0.05[d]*
	Model	*R^2=-0.01*			*R^2=-0.02*			*R^2=0.02*			*R^2=0.05*		
MFIS phys., score	β	-0.39	0.03	-0.11	-0.38	0.02	-0.00	-0.70	-0.12	0.16	-0.67	-0.13	0.13
	p-value	**0.04[d]**	0.86	0.54	**0.04[d]**	0.90	0.97	**0.000[d]**	0.42	0.29	**0.000[d]**	0.42	0.42
	Model	*R^2 =0.04*			*R^2 =-0.05*			*R^2 =0.36*			*R^2=0.31*		
PDDS, score	β	-0.40	0.13	0.21	-0.33	0.12	0.33	-0.55	0.01	0.47	-0.62	-0.01	0.46
	p-value	**0.03[d]**	0.44	0.23	0.06	0.47	0.06	**0.003[d]**	0.92	**0.008[d]**	**0.001[d]**	0.91	**0.005[d]**
	Model	*R^2 =0.18*			*R^2=0.13*			*R^2 =0.31*			*R^2 =0.39*		

WS, walking speed. DWI, distance walked index. PDDS, patient determined disease step. MFIS, modified fatigue impact scale. N/bw, Newton/body weight. W/bw, Watts/body weight. Statistical significance ($p \leq 0.05$) and trends ($0.05 < p < 0.10$, shown in italic) are denoted by d.

Table 4. Lower extremity force/power and walking speed pre and post the walking-fatigability protocol.

		HC	MS All	MS non-fatigability	MS fatigability	PDDS Low	PDDS High
Plantar Flexion							
Force (N/bw)	pre	1.40 (1.35 : 1.45)	1.33 (1.28 : 1.39) **a**	1.33 (1.27 : 1.39) **a**	1.34 (1.19 : 1.50)	1.38 (1.27 : 1.48)	1.30 (1.24 : 1.36) **a**
	post	1.39 (1.34 : 1.45)	1.35 (1.29 : 1.42)	1.34 (1.28 : 1.41)	1.37 (1.18 : 1.56)	1.42 (1.28 : 1.55)	1.31 (1.24 : 1.37)
	Δ %	*0 (-3 : 2)*	*1 (-1 : 3)*	*0 (-2 : 4)*	*2 (-3 : 7)*	*2 (-1 : 5)*	*0 (-3 : 4)*
Power (W/bw)	pre	5.06 (4.48 : 5.65)	3.94 (3.40 : 4.47) **a**	4.02 (3.33 : 4.72) **a**	3.73 (2.82 : 4.65) **a**	4.43 (3.53 : 5.34)	3.55 (2.90 : 4.21) **a, *c***
	post	5.31 (4.63 : 5.99)	4.15 (3.63 : 4.67)	4.19 (3.55 : 4.83)	4.03 (2.91 : 5.16)	4.66 (4.09 : 5.22)	3.79 (3.01 : 4.58)
	Δ %	*5 (-3 : 13)*	*15 (-4 : 33)*	*15 (-11 : 41)*	*14 (-2 : 31)*	*22 (-20 : 65)*	*9 (-8 : 27)*
Chair Rise							
Force (N/bw)	pre	1.33 (1.29 : 1.37)	1.27 (1.22 : 1.32) **a**	1.27 (1.21 : 1.33) ***a***	1.26 (1.13 : 1.39)	1.33 (1.26 : 1.40)	1.22 (1.15 : 1.28) **a, c**
	post	1.36 (1.32 : 1.40)	1.28 (1.22 : 1.33)	1.29 (1.23 : 1.35)	1.24 (1.09 : 1.40)	1.34 (1.27 : 1.41)	1.23 (1.16 : 1.31)
	Δ %	*2 (0 : 4)*	*1 (-0 : 2)*	*2 (1 : 3)*	*-2 (-5 : 2)* ***a, b***	*1 (-2 : 3)*	*1 (-0 : 3)*
Power (W/bw)	pre	5.47 (4.52 : 6.43)	4.58 (3.75 : 5.41)	4.44 (3.46 : 5.41)	4.94 (2.92 : 6.96)	5.64 (4.44 : 6.85)	3.71 (2.65 : 4.77) **a, c**
	post	5.60 (4.80 : 6.41)	4.89 (3.92 :5.86)	4.89 (3.78 : 5.99)	4.35 (1.69 : 7.0)	5.96 (4.40 : 7.53)	3.84 (2.68 : 5.01)
	Δ %	*11 (-4 : 26)*	*14 (-12 : 41)*	*27 (-5 : 60)*	*-15 (-49 : 19)* ***b***	*6 (-9 : 22)*	*21 (-28 : 70)*
Gait Parameter							
Walking speed (m/s)	pre	1.90 (1.81 : 2.00)	1.52 (1.37 : 1.68) **a**	1.55 (1.37 : 1.73) **a**	1.45 (1.05 : 1.86) **a**	1.71 (1.56 : 1.86) ***a***	1.39 (1.15 : 1.63) **a, c**
	post	1.83 (1.71 : 1.94)	1.42 (1.25 : 1.60)	1.52 (1.30 : 1.74)	1.20 (0.88 : 1.52) **d**	1.58 (1.36 : 1.80)	1.30 (1.03 : 1.57)
	Δ %	*-4 (-8 : 1)*	*-4 (-17 : 10)*	*2 (-16 : 21)*	*-20 (-27 : -12)* ***b***	*-6 (-20 : 8)*	*-2 (-24 : 20)*

Results are presented as mean and 95% confidence interval (CI). Statistical significance ($p \leq 0.05$) and trends ($0.05 < p < 0.10$, shown in italic) are denoted by **a**: different from healthy controls (HC), **b**: different from MS Non-Fatigable, **c**: different from PDDS Low, and **d**: different from Pre (within same group).

Figures and Captions

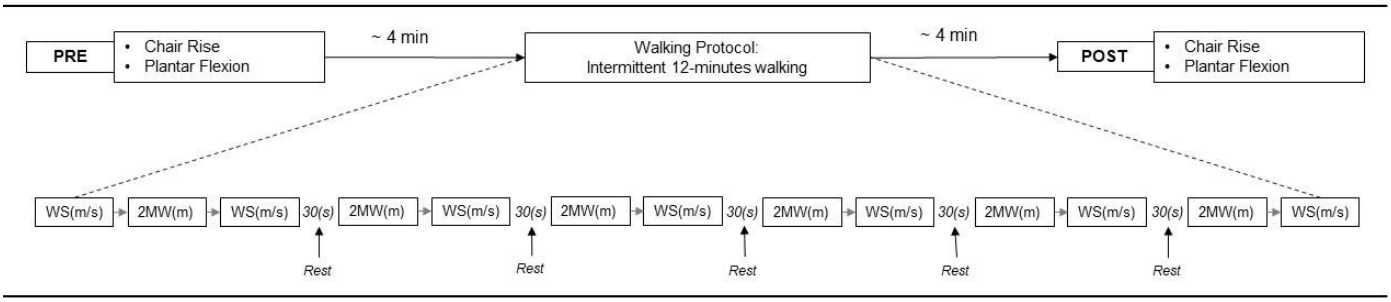

Figure 1. Experimental protocol. WS, maximal walking speed (meters/second). 2MW, 2-minute walk (distance in meters). Rest (30 seconds).

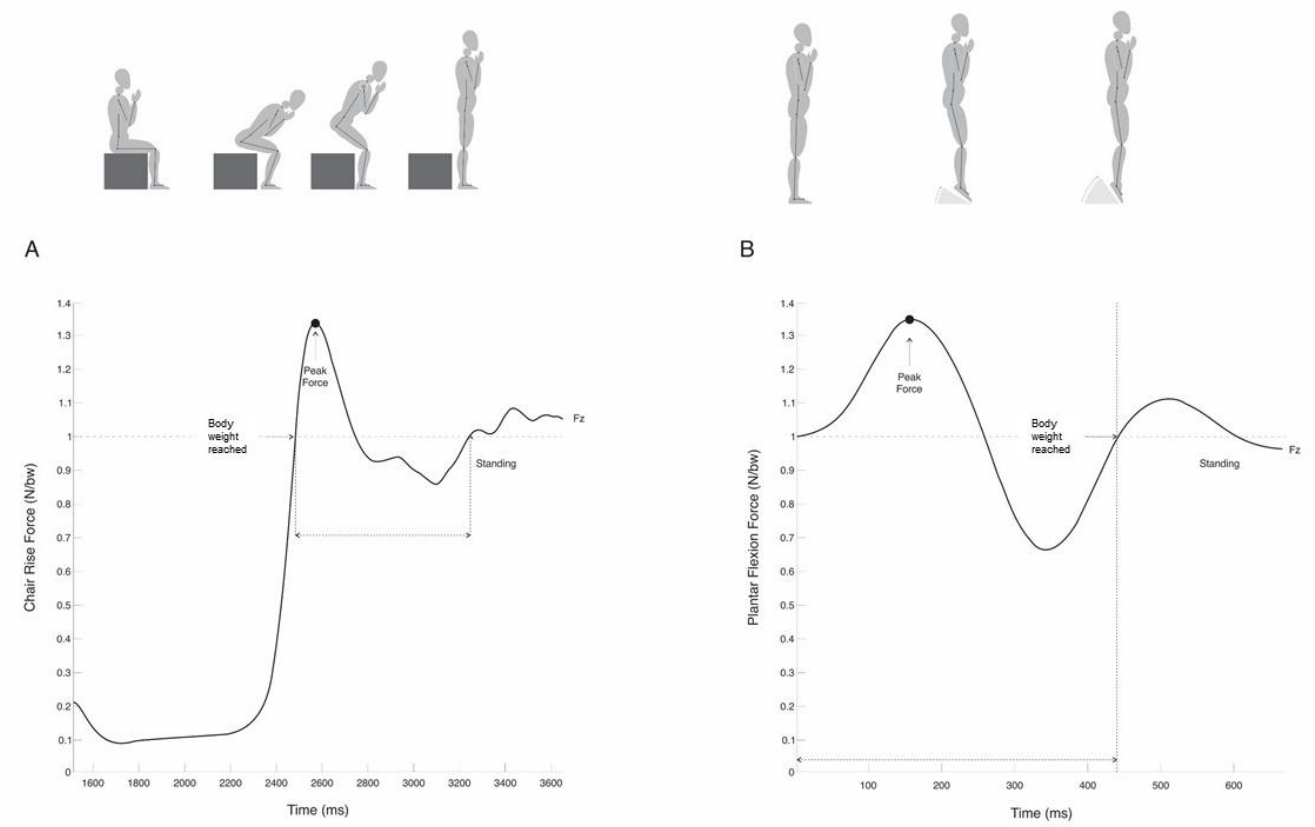

Figure 2. Individual data from a MS participant with mild disability (PDDS = 0) during the chair rise (A) and the plantar flexion (B) performance. The grey dotted line indicates the normalized body weight (=1). Non-dotted arrows indicate the events when the body weight and the peak force were reached. The black dotted two-sides arrows and the black dotted lines indicate the force-time curve interval used to extract force and power parameters.

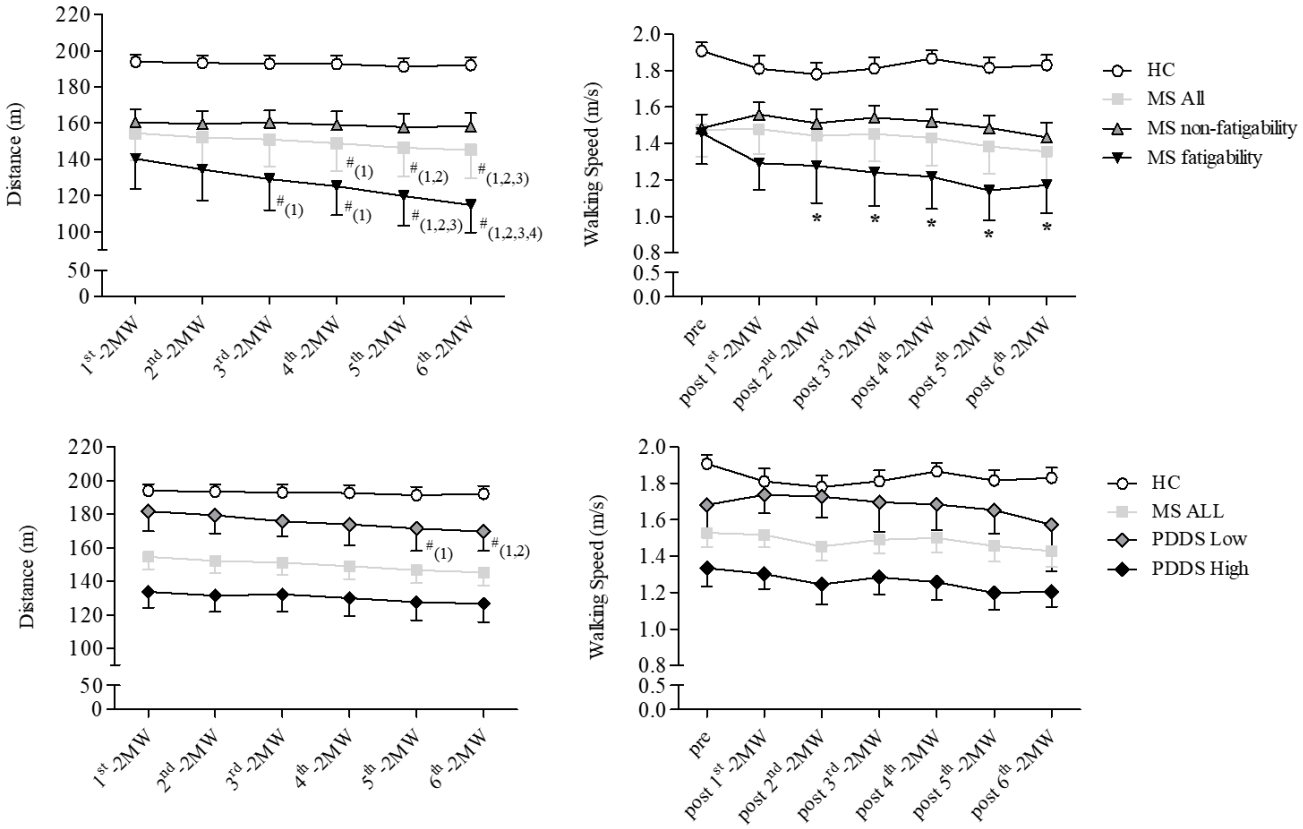

Figure 3. Course of the distance walked and the walking speed over the 12-minutes intermittent walking. HC, healthy controls. MS All, total sample of multiple sclerosis (MS) participants. MS non-fatigability, MS participants not presenting walking-fatigability. MS fatigability, MS participants presenting walking-fatigability. PDDS Low, MS participants with a score equal to zero in the Patient Determined Disease Step. PDDS High, MS participants with a score equal or higher than 1 in the Patient Determined Disease Step. Results are presented as mean and standard error. Statistical significances ($p \leq 0.05$) are denoted by $^{\#}(1)$: different from the first 2-minute walk (1st -2MW); $^{\#}(1,2)$: different from the 1st - and the 2nd -2MW; $^{\#}(1,2,3)$: different from 1st -, 2nd - and 3rd -2MW; $^{\#}(1,2,3,4)$: different from 1st -, 2nd -, 3rd and 4th -2MW. *, denotes statistical significance from the moment pre (walking speed performed before the entire 12-minutes walking).

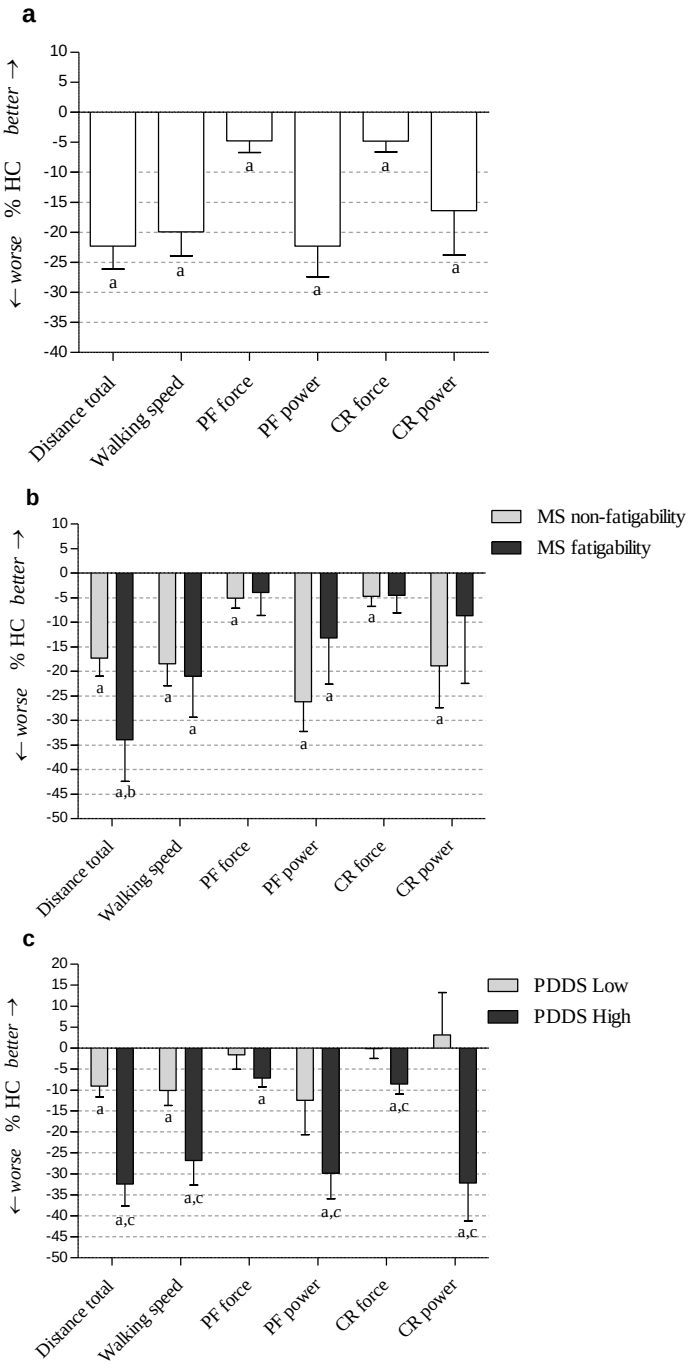

Figure 4. Deficits in physical functions regarding to walking capacity and lower extremity muscle power/force calculated as the percentage of the mean values from the healthy control (HC) group. Results are presented as mean and standard error. **a**, deficits are presented for the entire sample of persons with multiple sclerosis (MS). **b**, deficits presented for the MS non-fatigability group and MS fatigability group. **c**, deficits presented according to the PDDS (Patient Determined Disease Step) score, Low (= 0) or High (≥ 1). PF, plantar flexion. CR, chair rise. Statistical significance ($p \leq 0.05$) and trends ($0.05 < p < 0.10$, shown in italic) are denoted by "a": different from healthy controls (HC), "b": different from Non-Fatigable persons with MS, and "c": different from PDDS Low.