2013•2014
FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
master in de revalidatiewetenschappen en de kinesitherapie

Masterproef

Motor fatigue of the shoulder muscles in pwMS and healthy controls during repetitive robot-assisted exercises

Promotor :
Prof. dr. Peter FEYS

Copromotor :
Mevrouw Deborah SEVERIJNS

Yasmine Vanhaelemeesch
Proefschrift ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

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Preface

This is my master thesis, which will contribute to achieving the Master of Rehabilitation Sciences and Physiotherapy at the University of Hasselt. I would like to thank the persons who have contributed to the establishment of this master thesis. First of all, I want to thank my promoter Prof. Dr. Peter Feys, and my co-promoter Dra. Deborah Severijns. I am grateful for their guidance during the experimental research and the writing procedure. I would also like to thank the participants of this study for the effort and for the time they made to participate in the study. I want to thank the Research Center (REVAL), for the research support. I gratefully acknowledge the Rehabilitation and MS Center Overpelt for the recruiting of persons with MS (pwMS). Finally, I want to thank the Expertise Center for Digital Media (EDM) Diepenbeek for the technological support during technology-based training.

Bilzen, 02-06-2014 Y.V.

Research context

This thesis, will contribute to the research of motor fatigue with patients suffering from neurological diseases, especially persons with MS (pwMS), during exercise training.

PwMS suffer from fatigue as a general complaint. Motor fatigue is a subdivision of fatigue. At this time, there is an emerging interest on this topic although there are unresolved problems with the assessment and interpretation of motor fatigue in pwMS. Therefore, this study focuses on experimental research on the occurrence of fatigue during repetitive shoulder anteflexion movements in pwMS and in healthy controls. These repetitive movements are being performed with the Haptic Master. It is important to obtain this information in order to prepare rehabilitation programs.

The proposed master thesis is a work in the field of applied neurological rehabilitation. This research domain updates theoretical knowledge in the rehabilitation of persons with neurologic diseases. The study is supervised by Prof. Dr. Peter Feys and Dra. Deborah Severijns. Prof Dr. Feys is a scientific researcher in the fields of rehabilitation sciences and physiotherapy. He concentrates on neurologic rehabilitation within the education programs of 'Rehabilitation Science and Physiotherapy'. His research focuses on rehabilitation in pwMS.

This thesis topic is a contribution to an ongoing doctoral project of Deborah Severijns, which lasts from 2010 to 2016. The project name is 'Motor fatigue during upper and lower extremity function in Multiple Sclerosis'. It focuses on the occurrence of motor fatigue and its possible impact in persons with neurological diseases. Her research is directed to the prevalence, severity and impact of motor fatigue in the upper limb during activities.

PwMS were recruited from the Rehabilitation and MS Center in Overpelt. Patient testing was performed in collaboration with the Expertise Center for Digital Media (EDM) Diepenbeek. The EDM is related to the University of Hasselt and collaborates with 'I-TRAVLE' an 'Individualized Technology and Robot Assisted Virtual Learning Environment" which is an ongoing follow-up project of 'Revalidatierobitica II', an interreg IV. The EDM developed the I-TRAVLE system. This system is a software package to move the arms of the patient by a virtual environment performed by a robot. The robot is used to give a force feedback to the user. The haptic master and the I-TRAVLE system were used in this experimental research.

This part of the master thesis will contribute to the study of motor fatigue in pwMS and healthy controls, by investigating how motor fatigue can be measured during an exercise protocol of shoulder movements on the Haptic Master and to examine the difference between pwMS and healthy controls. The study design is a cross-sectional case-control. An existing protocol will be used and the data collection has already started in 2011.

This master thesis study will follow the author's guidelines of the Multiple Sclerosis Journal. The contribution of the student in this study design will focus on recruiting healthy participants, data processing, data analysis, statistical analysis and the writing procedure. The recruiting and experimental research of pwMS had already been done.

Motor fatigue of the shoulder muscles in pwMS and healthy controls during repetitive robot-assisted exercises

In accordance with the guidelines of the Multiple Sclerosis Journal: http://msj.sagepub.com.

Hasselt, 2014

Motor fatigue of the shoulder muscles in pwMS and healthy controls during repetitive robot-assisted exercises

Abstract

Background: It is unclear if motor fatigue occurs in the shoulder muscles during a standardized exercise protocol of the shoulder during robot- based rehabilitation and if pwMS are easier fatigued, compared to healthy persons.

Objective: This study aimed to verify whether motor fatigue occurred on the basis of force measurements, surface electromyography and performance measurements and to examine the difference between healthy controls and pwMS during repeated movements.

Methods: Sixteen pwMS and 16 age-and gender-related healthy control subjects were included. The exercise protocol consisted of 6 repeated exercise bouts of 3 minutes of shoulder anteflexion movement, performed with the haptic master. After the fifth exercise bout, there was a recovery period of 15 minutes. Outcome measurements of fatigue were the Visual analogue scale of fatigue which was measured before and after an exercise bout, the maximum force measurements of shoulder anteflexion and abduction were measured before the first, after the fifth exercise bout, and after the recovery period. Surface electromyography was constantly measured, and performance data of the tasks were measured during the task. The assistance and maximal force tests were measured before and after the exercise bout with surface electromyography. The assistance test was measured when the participant held the shoulder in 90° anteflexion for 30 seconds. The maximum force test was measured during the performance of 90° shoulder anteflexion position and was pushed as hard as possible in an upward direction. The performance data of the haptic master included the number of lifting movements during a virtual reality game. Statistical analyses were performed with IBM SPSS statistics 22.

Results: In both groups, the feeling of fatigue increased during progression of prolonged exercises and decreased after a rest period ($p<0.001$). In pwMS, the feeling of fatigue was higher than in healthy controls. PwMS showed less maximal strength than healthy controls. The amplitude and frequency of the surface electromyography of the assistance test showed muscle fatigue (HC;pwMS) before the rest period and force increase (HC) and muscle recovery (pwMS) after the rest period. The surface electromyography data of maximum force showed muscle fatigue (pwMS) before the rest period and force increase (pwMS) after the rest period. Task performance increased with exercise development ($p=0.01$), with no significant changes after a rest period.

Conclusions: The results indicate the appearance of muscle fatigue, the decline of muscle strength, and subjective fatigue during the progression of the feeding task. In contrast, there was no decline of exercise performance. Healthy controls had an overall better performance, more strength and fewer complaints about fatigue in comparison with pwMS.

Keywords

Multiple Sclerosis, motor fatigue, repetitive movements.

Introduction

Multiple Sclerosis (MS) affects 250 per 100.000 people in Europe, it is a chronic and an immune-mediated neurologic disease (1;2). One of the most pronounced symptoms, in pwMS, is fatigue (3). Forty percent of the pwMS consider fatigue as the most impairing symptom (4). The prevalence of fatigue in MS was estimated on 38-83% (5). The origin and the pathophysiology of 'fatigue' are understood insufficiently (5;6). Even the term 'fatigue' had no standard definitions (5). A general definition of fatigue is described as 'an abnormal sense of tiredness or a subjective lack of physical and mental energy, out of proportion to the degree of effort or level of disability, which interferes with usual activities' (7;8).

Several types of fatigue are described in literature. Central fatigue, especially seen in neurological diseases as MS, is defined as an impairment in the central nervous system. On the other hand peripheral fatigue is described as changes in the peripheral nervous system and muscles (6;9). The terms of fatigue were subdivided in 2 domains by Kluger et al. The first domain, 'the perceptions of fatigue' refers to the term subjective fatigue which describes the feeling or impression of tiredness in pwMS during the performance of an activity (5;10). The second domain, 'performance fatigability' including peripheral – and central factors, refers to an objective measurement of fatigue as the decrease of performance during a task (5). Motor – and muscle fatigue are possible objective measurements of the second domain of fatigue. Motor fatigue is described 'as a decline in ability of the persons to practice force during a prolonged motor task performance' (11;12). The decline of the performance is caused by muscle fatigue (12). Muscle fatigue is described 'as a decrease of the maximal force of power that the involved muscles can produce' (13;14).

Our research includes the 2 domains of fatigue, especially subjective – and motor fatigue with more focus on the latter.

PwMS report fatigue during activities of daily living (ADL), which interferes with normal ADL and limits the ability to perform these activities (4). This is not the case in healthy controls, the occurrence of fatigue, as well as perception as performance fatigue, is normal during an intense long-lasting exercise. However, it disappears at rest and doesn't interfere with daily life activities (ADL) (5). Many activities of daily living include repetitive movements of the upper limb (15;16). Therefore, it is important to be aware of the risk factors of developing motor fatigue in the upper limbs during these repetitive movements. In a study of healthy controls, findings suggest that repetitive arm movements cause muscle fatigue and motor fatigue and that these manifestations can lead to musculoskeletal injuries (17;18). Insufficient recovery after muscle and motor fatigue can lead to musculoskeletal pain (19). It is assumed that a change in muscle recruitment during static movements, due to fatigue, can lead to complaints (15;20;21). Therefore, motor fatigue should be taken into account during motor performance.

In an earlier study of pwMS, surface electromyography was used to evaluate muscle fatigue, force decrease, force increase and muscle recovery. The electromyography signals, including the amplitude and frequency, change when fatigue occurs. These changes make it possible to detect the appearance of fatigue (22). A possible indication of the occurrence of fatigue is a decline in muscle

performance and the appearance of weakness during the activity (5;23). Therefore, measuring of muscle strength with a hand-held myometer can be useful (23). In previous literature of MS, it was determined that pwMS demonstrate excess fatigue compared (24) with the healthy control group during repetitive contractions of hand grip for 30 seconds (24). Possibly, pwMS have an impairment in the neuromuscular responses and in the recruitment of motor neurons which can lead to an extensive appearance of motor fatigue (25). In literature, findings in pwMS indicate that the changes in objective cognitive performance during prolonged training can appear independently of changes in the feeling of fatigue (10;26). An important goal is to find an association between the 'perception of fatigue' and 'performance fatigability' (5). Therefore, further research in pwMS is needed about the association of these two domains of fatigue.

Recently, publications in the MS literature showed the effect of a robot-assistive training of the upper limbs (16;27). One study performed rehabilitation training with the Armeo Spring. This study suggests that technology based physical rehabilitation of the functionality of the upper limbs can be positive in high-level disability pwMS (16). Performance of repeated movements and an interactive virtual screen are applications in the technology based treatments (16) which is a surplus value in the performance of an exercise program. The study of Carpinella et al. showed that 'pwMS have the ability to adapt to the robot-generated forces' (27). The results of previous studies give the ability to investigate the various robot-assistive training programs in the rehabilitation of the upper limbs and the appearance of motor fatigue during a prolonged robot-assistive exercise program in pwMS. One of the questions is whether fatigue appears during an exercise bout with a robotic device and disappears during a rest period in pwMS in comparison with healthy controls.

In order to examine if fatigue occurs during a standardized exercise protocol, performed with a robotic device, a cross-sectional case-control study was designed (1) to verify whether motor fatigue occurs on the basis of force measurements, sEMG and performance measurements and (2) to examine the difference between healthy controls and pwMS.

Methods

Participants

PwMS were recruited from the MS rehabilitation center in Overpelt. PwMS were included, if they had a diagnosis of MS, according to the McDonald criteria. We selected 16 subjects diagnosed with MS. The control group contained 16 age-and gender-related control subjects. There were no exclusion criteria based on the type of MS, the EDSS score and their age. Exclusion criteria for pwMS were exacerbations or a treatment with corticosteroids injection in the last months prior to the study. Patients also needed to be able to understand instructions and needed to be able to actively use their upper limb. PwMS and healthy controls with orthopedic and/or cognitive problems which impeded participation in the study were excluded.

All participants were asked to sign a 'written informed consent' prepared by the researchers. The study was approved by the Ethical Commission of the University Hospitals Leuven, the University of Hasselt and the Rehabilitation and MS center in Overpelt.

Study design

The study was designed as a cross-sectional case-control study. Both groups were exposed to a repeated exercise of the dominant shoulder. The dominant shoulder was in accordance to the side of the preferred hand. All participants performed one session of exercise bouts. During these exercises different parameters which can point out the presence of motor fatigue were recorded. No dropouts occurred during the session.

Experimental protocol

All participants performed one session of exercise bouts with a custom-made software on the haptic master (MOOG Inc.). The haptic master is a robot and is illustrated in figure 1.The fatigue protocol consists of 5 repeated exercise bouts of 3 minutes of shoulder anteflexion movement. The fruit is located at the top of the screen. The aim is to take the fruit at a shoulder position of 90°-100° of anteflexion to hold it briefly and move to the figure at the bottom of the screen. This is shown in figure 2. These exercise bouts are repeated six times. After the fifth exercise bout, there is a recovery period of 15 minutes. Two tests were performed before the exercise bouts of 3 minutes. Test one (1) to hold the shoulder in 90° anteflexion for 30 seconds, which is shown on the screen to keep the ball between two lines. Test two: (2) to bring the shoulder in 90° anteflexion position and push as hard as possible in an upward direction, to determine the maximal voluntary anteflexion. Before the first and after the fifth exercise bout, an isometric contraction of 90° anteflexion and abduction was measured with the Microfet to determine the force. This is also asked before and after the sixth exercise bout. While performing the exercise bouts, there was a continuous sEMG registration of M. biceps, M. upper trapezius and the M. deltoid anterior and middle.

Figure 1: The haptic master and interaction within a virtual learning environment

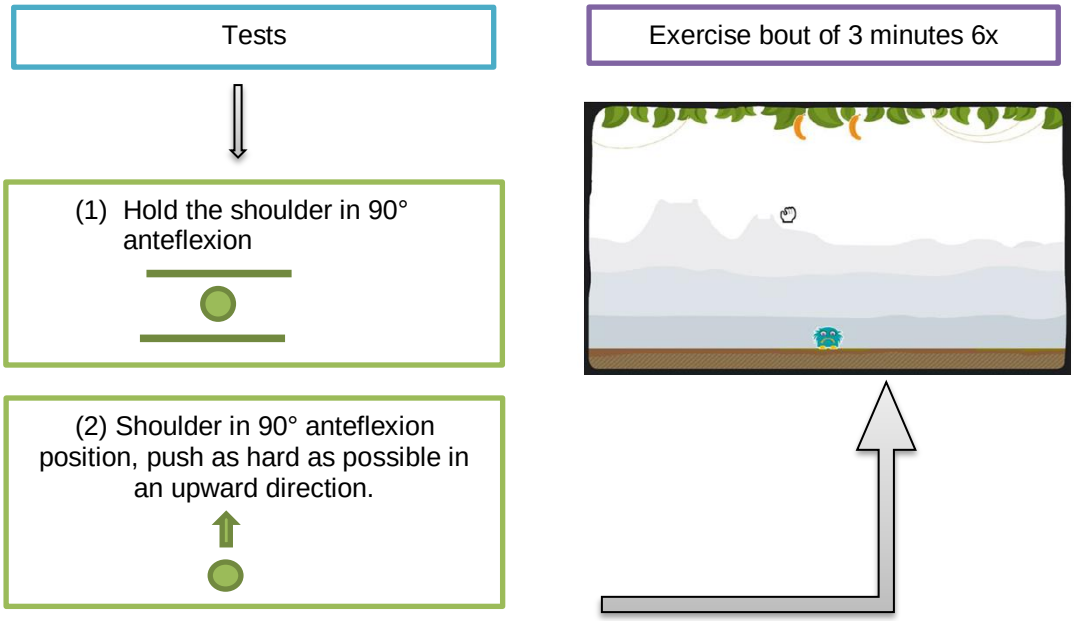

Figure 2: Tests and exercise bout of the haptic master

Timetable of tests, exercise bouts and outcome measurements						
Tests before exercise bouts			**Exercise bouts**	**Tests after exercise bout 5 and 6**		
VAS fatigue	Tests	Microfet	**EB1 (3min.)**			
VAS fatigue	Tests		**EB2 (3min.)**			
VAS fatigue	Tests		**EB3 (3min.)**			
VAS fatigue	Tests		**EB4 (3min.)**			
VAS fatigue	Tests		**EB5 (3min.)**	Tests	VAS fatigue	Microfet
Recovery 15 min. MFIS/FSMC						
VAS fatigue	Tests	Microfet	**EB6 (3min.)**	Tests	VAS fatigue	Microfet
Continuous sEMG registration						

Tests (figure 2), EB: Exercise bout (figure 2), Microfet anteflexion/abduction, VAS fatigue: Visual Analogue Scale of fatigue, MFIS: Modified fatigue impaired scale, FSMC: Fatigue scale for motor and cognitive function

Figure 3: Exercise protocol

Outcome measurements

A distinction is made between 3 types of outcome measurements: descriptive outcomes, clinical outcome measures, and haptic master-based outcome measures.

The descriptive outcome measurements. The descriptive outcome measurements used in the experimental search were age, gender, hand preference and the outcomes of the fatigue questionnaires.
During the recovery period, two subjective questionnaires were completed by the participants: the modified fatigue impaired scale (MFIS) (28) and the fatigue scale for motor and cognitive function (FSMC) (29). These scales are ordinal scales and detect general subjective fatigue of the subjects.

The MFIS scale experienced 21 items due to fatigue with individual subscale scores for physical (9-items), cognitive (10-items), and psychosocial (2-items) functioning, during the last month. Each item was scored with a likert scale (range 0-4) (30;31). The minimal score of each item is 0 (fatigue had no influence on daily living) and a maximum score is 4 (fatigue had a maximum influence on daily living). The study of Kos D. et al. reflected about the Dutch version of the MFIS and concludes that 'The MFIS is a valid, reliable and responsive tool to assess the impact of MS-related fatigue on daily life'(30).

The FSMC has 20-items with individual subscale scores for motor (10-items) and cognitive (10-items) function. The reliability of the FSMC total scale was 0.87. The FSMC is highly sensitive and specific in the detection of fatigued pwMS(29).

The clinical outcome measurements. The clinical outcome measurements used in the cross-sectional case-control study were the development of force generation, the feeling of fatigue and the possible occurrence of motor fatigue during the performance task. The systems used to determine the clinical outcome measurements were the Microfet 2 hand-held dynamometer, the VAS fatigue scale and the sEMG.

The Microfet 2 hand-held dynamometer was used to measure the shoulder abduction and anteflexion strength in Newton. Microfet 2 had a good to excellent reliability in normal, healthy, young people. The lever to provide resistance and stabilization of the nontest extremity seems to determine the result of the intrarater and interrater reliability (32).

The visual analogue scale (VAS) of fatigue was used to determine the subjective fatigue of the participants. The VAS fatigue scale was taken before and after each exercise part. The VAS fatigue scale suggested the following question: 'Is your arm fatigued?'. The fatigue VAS scale consists of a 10 cm horizontal line, from 0 (no fatigue) to 10 (person is extremely fatigued). Subjects were asked to mark on the line the point that they feel represents their perception of their current state. One study used almost a similar scale for fatigue and suggested a good validity, responsiveness and reliability for this scale (33).

The system used to determine the possible occurrence of muscle fatigue was the sEMG signal collecting system. Surface EMG was used to measure the changes in the level of electrical activity at the muscle surface during muscle contractions (Delsys Trigno Wireless system) (34). sEMG was measured in the following muscles: M. deltoid anterior and middle, M. biceps and M. upper trapezius. In further data-analysis, we only used the sEMG signals of assistance and maximal force of the anterior deltoid, since this is the prime mover of shoulder anteflexion. The sEMG measurement of assistance was measured during the following test: to hold the shoulder in 90° anteflexion for 30 seconds. The sEMG measurement of maximum force was measured during the following test: bring the shoulder in 90° anteflexion position and push as hard as possible in an upward direction. Electrode placement was done according to the SENIAM guidelines. The sEMG analyses were done on the basis of the Root Mean Square (RMS) and MF (Median frequency). As muscle fatigue occurred, changes in the amplitude (RMS) and frequency (MF) appeared which can be used to quantify the rate of fatigue. The study De Luca et al. states that an increase of the EMG amplitude and a decrease of the frequency are an indication for the appearance of muscle fatigue (35). Joint Analysis of EMG spectrum and amplitude were developed for the determination of motor phenomena in surface EMG (36;37). The following motor phenomena are described: muscle recovery, force decrease, force increase, and muscle fatigue as previous described. Muscle recovery occurs when the amplitude decreases and the frequency increases. During force decrease, the amplitude and frequency decrease. Both, amplitude and frequency increase during force increase. These analyses have been validated in normal subjects (36;38).

The haptic master-based outcome measures. Data of the haptic master recorded during the exercise bouts, determined whether the task performance is reduced. The following performance measurements were recorded: the time per cycle, distance traveled per cycle, maximal force and number of feeding. The time per cycle measures the time the participant needed to start from the bottom of the screen, pick up the fruit on the top of the screen and travel back to the bottom of the screen (figure 2). The distance traveled per cycle measures the distance traveled from the bottom to the top of the screen and the other way round. The maximal force measures the force generation during the prolonged exercise. Number of feeding measures the number of picked fruit during the 3 minutes of an exercise bout. If there is a decrease of performance, which includes abnormalities in the motion track, decline of the maximal force, decline in the number of picked fruit, and increase of the time per cycle, there will be an appearance of motor fatigue (5;23).

Statistical Analysis

All results were analyzed using the software package IBM SPSS Statistics 22. Normality of the data was examined graphically (histograms, Q-Q plots) and statistically using the Shapiro-Wilk test.

Descriptive data analyses were performed for the collected varieties of the participants: age, gender, hand dominance, MS duration, MS type and EDSS score. The two subjective questionnaires (FSMC, MFIS) were analyzed by means of descriptive data analysis. For the data of the VAS fatigue scale, the

Microfet 2-hand held dynamometer, the sEMG, and the 3 domains of the haptic master, non-parametric statistics were used, including the Friedman test to determine the differences between the test moments in each group separately. Post hoc test was performed with the Wilcoxon signed-rank tests to examine where the differences actually occur within the group. Post hoc analysis with the Wilcoxon signed-rank tests was applied with a Bonferroni correction. The differences between the groups on each moment were analyzed by means of a Mann-Whitney U test. Non-parametric tests were used because some data of the Microfet2, the sEMG, and the haptic master cannot assume normal distribution. Non-parametric tests are more stringent and the results are less likely to be significant. The data of the number of feeding had a normal distribution and were analyzed with parametric tests, including the one-way repeated measures Anova to determine the differences between the test moments in each group separately. Post hoc test was performed with the paired sample t-test to examine within the group were the differences actually occur. The paired sample t-test was applied with a Bonferroni correction. The differences between the groups were analyzed by means of an independent samples t-test. The level of statistical significance was set to $p < 0.05$ two-sided.

Results

Participants

Sixteen pwMS (mean age = 54.9, SD = 7.5 years) and 16 healthy controls (mean age= 53.9, SD = 9.5 years) participated in our experimental study (Table 1). The mean disease duration of MS was 14.9 years (SD = 9.3) (Table 1). The pwMS had a mean EDSS score of 5.9 (SD=1.9). No significant differences were found between groups concerning age, gender and hand dominance between the groups. The total score of the MFIS and the FSMC was higher in pwMS in comparison with healthy controls (Table 1; appendix 1). PwMS, complained more about fatigue than healthy controls.

Table 1. Descriptive characteristics of both MS and healthy control groups: mean ± SD and frequency

Group item	MS group (n=16)	Healthy control group (n=16)
Mean Age ± SD (years)	54.9 ± 7.5	53.9 ± 9.5
Gender: m/f (n)	6 / 10	5 / 11
Dominant hand (right/left) (n)	13 / 3	16 / 0
Total score MFIS ± SD (84)	42.31 ± 17.83	16.31 ± 13.13
Total score of FSMC ± SD (84)	47.75 ± 13.53	16.25 ± 11.83
Mean Disease duration ± SD (years)	14.9 ± 9.3	NA
MS type (PP/SP/RR) (n)	3 / 10 / 3	NA
Mean EDSS ± SD	5.9 ± 1.9	NA
Mean ARAT dominant hand ± SD (right/left)	47.2 ± 13.8 / 41,3 ± 16.6	NA
Mean Jamar dominant hand ± SD (right/left)	21.2 ± 11.0 / 18.8 ± 5.1	NA
Mean MI dominant hand ± SD (right/left)	79.2 ± 14.9 / 69.3 ± 5.8	NA

SD: standard deviation; MFIS: Modified fatigue impact scale; FSMC: fatigue scale for motor and cognitive functions, EDSS: Expanded Disability Status Scale; MI: Motricity Index.

Differences within and between the groups

At baseline, no significant differences were found between groups concerning age, gender and hand dominance.

The feeling of fatigue during progression of the performance task

VAS scale of fatigue - differences within the group. Within the groups there was a significant difference between the repeated measurements of the VAS fatigue scale ($p<0.01$ for both groups) (Table 2). There was a significant difference between the measurement before the first exercise (Test 1) and the measurement after the fifth exercise (Test 6) ($p<0.001$ for both groups). In both groups, the score of the VAS fatigue scale was increased after the fifth exercise in comparison with the measurement of test 1. The measurement after the fifth exercise (Test 6), before the recovery period started, was compared with the measurement after the recovery period (Test 7) ($p<0.001$ for both groups). In both groups, the score of the VAS fatigue scale was decreased after the rest period (Table 2).

VAS scale of fatigue – differences between the groups. The outcomes of the VAS fatigue scale showed that test 2 and test 4 were significant different between the two groups (Table 2). Graphical difference showed that pwMS had an overall higher score, on the VAS fatigue scale, than the healthy control group (figure 4). The VAS fatigue scale decreased in both groups after the recovery period. After the last exercise the score of the VAS fatigue scale increased more in pwMS in comparison with healthy controls.

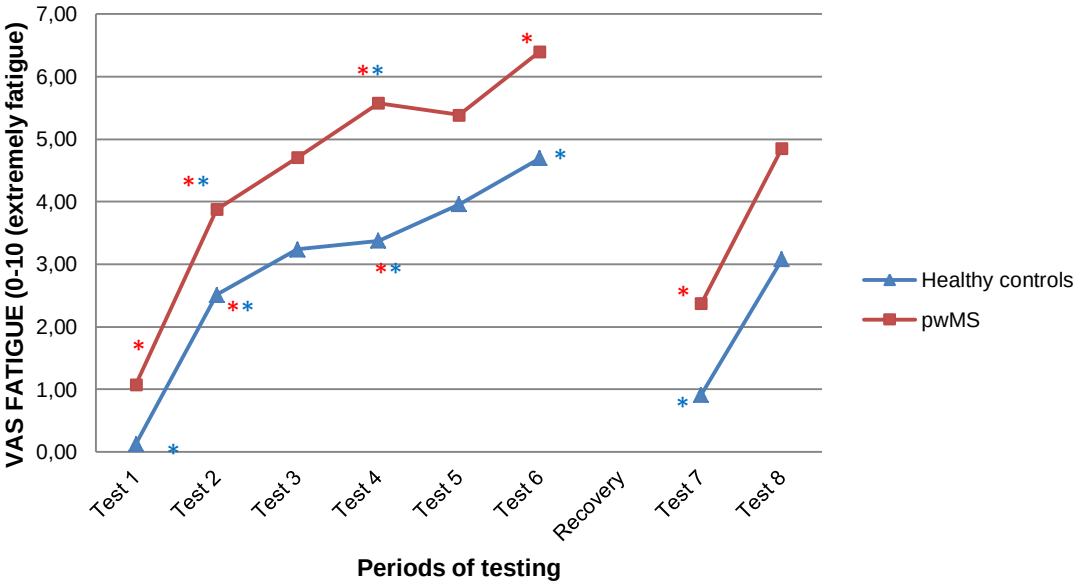

Figure 4: The mean of the VAS fatigue scale for each test period in both groups. */ * *A significant difference: between test 1 and test 6 in both groups.* */ * *A significant difference: between test 6 and test 7 in both groups.* ** *A significant difference: between the pwMS and the healthy control group in the score of the VAS fatigue scale (0-10) for test period 2 and 4.*

Table 2. Mean ± SD of the VAS fatigue scale in both MS and healthy control groups and the associated P-values

Repeated measurements	Before exercise 1 Test 1	After exercise 1 Test 2	After exercise 2 Test 3	After exercise 3 Test 4	After exercise 4 Test 5	After exercise 5 Test 6	Recovery period	Before exercise 6 Test 7	After exercise 6 Test 8	Friedman Test $	P-value Test 1 – Test 6 $$	P-value Test 6 – Test 7 $$
pwMS (n=16)	1,08 ± 1.77	3,88 ± 2.36	4,71 ± 2.23	5,58 ± 2.46	5,39 ± 2.66	6,40 ± 2.77		2,38 ± 3.03	4,86 ± 3.41	<0.001*	<0.001*	<0.001*
HC (n=16)	0,13 ± 0.24	2,51 ± 2.58	3,24 ± 2.54	3,38 ± 2.62	3,96 ± 2.79	4,70 ± 2.91		0,91 ± 1.23	3,08 ± 2.42	<0.001*	<0.001*	<0.001*
P-value $$$	0.06	0.04*	0.06	0.02*	0.13	0.12		0.29	0.09			

SD: standard deviation; HC: healthy controls; $ Friedman test; $$ Wilcoxon-signed rank test (p=0.05/3=0.017); $$$ Mann-Whitney U test (p=0.05); *Significant difference.

The force generation during progression of the performance task

Microfet - differences within the group. In both groups, no significant difference was noticed between the repeated measurements of anteflexion (pwMS: p=0.07; Healthy controls: p=0.23) (Table 3). In pwMS and healthy controls, there was no significant difference between the anteflexion measurements before the first exercise (Test 1 AF) and the measurements after the fifth exercise (Test 2 AF) (pwMS: p=0.09; healthy controls: p=0.04). In both cases, the maximal anteflexion strength had a tendency to decrease after the fifth exercise (Test 2) in comparison with test 1. No significant difference was noticed in the comparison between the anteflexion measurements after the fifth exercise (Test 2 AF) and the measurements after the recovery period (Test 3 AF) (pwMS: p=0.03; healthy controls: p=0.44) (Table 3). In both groups, the maximal anteflexion strength had a tendency to increase after the recovery period (Test 3) in comparison with the last measurement before the recovery period (Test 2).

Within the MS group there was a significant difference between the repeated measurements of the abduction test (pwMS: p=0.01) (Table 3). Also, no significant difference was established between the repeated measurements of the abduction test in healthy controls (p=0.49) (Table 3). In both groups, there was no significant difference between the measurements before the first exercise (Test 1 ABD) and the measurements after the fifth exercise (Test 2 ABD) (pwMS: p=0.87; healthy controls p=0.50). In pwMS, the abduction force tended to decline as the testing session progressed. An exception was noticed in the healthy control group, the abduction force tended to increase as the testing session progressed. Within the MS group there was a small significant difference between the abduction measurements after the fifth exercise (Test 2 ABD) and the measurements after the recovery period (Test 3 ABD) (pwMS: p=0.01). In pwMS, the abduction force tended to increase after the recovery period. No significant difference was established in the healthy control group (healthy controls: p=0.57) (Table 3). But, the abduction force tended to decrease after the rest period.

Microfet – differences between the groups. For the anteflexion test, all measurements were significant different between the two groups. For the abduction test, test 1 and test 2 were significant different between both groups (Table 3). Graphical difference showed that pwMS had an overall lower strength for shoulder anteflexion and abduction than the healthy control group (figure 5).

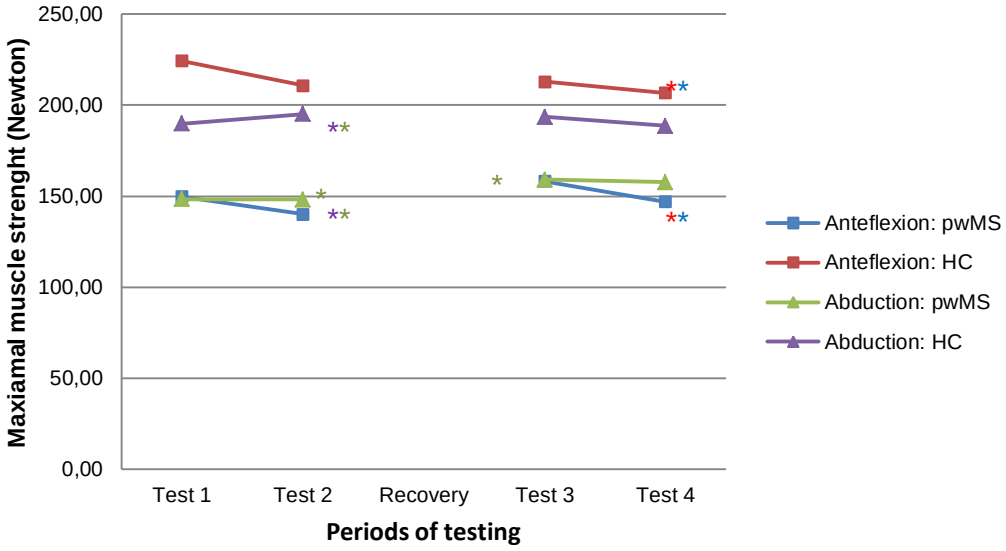

*Figure 5: The mean of the maximal muscle strength for each test period in both groups. *A significant difference: between the abduction test 2 and test 3 in the pwMS group. ** A significant difference: in anteflexion force (N) for each test period between pwMS and healthy controls. ** A significant difference: in abduction force (N) for test period 1 and 2 between both groups.*

Table 3. Mean ± SD of the maximal muscle strength in both MS and healthy control groups and the associated P-values

Repeated measurements	Before exercise 1 Test 1	After exercise 5 Test 2°°	Recovery period	Before exercise 6 Test 3	After exercise 6 Test 4	Friedman Test $	P-value Test 1 – Test 2 $$	P-value Test 2 – Test 3 $$	P-value Test 3 – Test 4 $$
Anteflexion									
pwMS (n=16)	149.83 ± 56.86	140.09 ± 49.88		158.28 ± 61.05	146.97 ± 49.93	0.07	0.09	0.03	0.12
HC (n=16)	224.29 ± 67.04	210.80 ± 54.48		212.96 ± 57.48	206.76 ± 50.78	0.23	0.04	0.44	0.55
Abduction									
pwMS (n=16)	148.43 ± 43.52	148.18 ± 34.94		159.14 ± 44.78	157.71 ± 47.16	0.01*	0.87	0.01*	0.44
HC (n=16)	189.88 ± 40.97	195.13 ± 48.20		193.54 ± 51.89	188.60 ± 50.38	0.49	0.50	0.57	0.20
P-value AF $$$	<0.001*	<0.001*		0.02*	<0.001*				
P-value ABD $$$	<0.001*	<0.001*		0.07	0.08				

SD: standard deviation; HC: healthy controls; AF: antefelxion; ABD; abduction, °° n= 15, $Friedman test; $$ Wilcoxon-signed rank test (p=0.05/4=0.0125), $$$ Mann-Whitney U test (p=0.05); *Significant difference.

Haptic master, maximal muscle strength - differences within the group. In the healthy control group was a significant difference between the repeated measurements (healthy controls: p<0.001) (Table 5). No significant difference was noticed between the repeated measurements in the MS group (pwMS: p=0.75) (Table 5). In both groups, there was no significant difference between the measurement before exercise 1 (test 1) and the measurement after exercise 5 (Test 6) (pwMS: p=0.88; healthy controls: p=0.03). In both cases, the maximal force was decreased after exercise 5 relative to the measurement before exercise 1. The measurement after exercise 5 (Test 6) was compared with the measurement after the recovery period (Test 7). In both groups, no significant difference was established between these measurements (pwMS: p=0.68; healthy controls: p=0.96) (Table 5).

Haptic master, maximal muscle strength – differences between the groups. All the measurements of maximal forces from test 1 to 8 were significant different between the two groups. Graphical difference showed that pwMS had an overall lower maximal force performance than the healthy control group (figure 6). The performance of the healthy control group was better in comparison with the MS group.

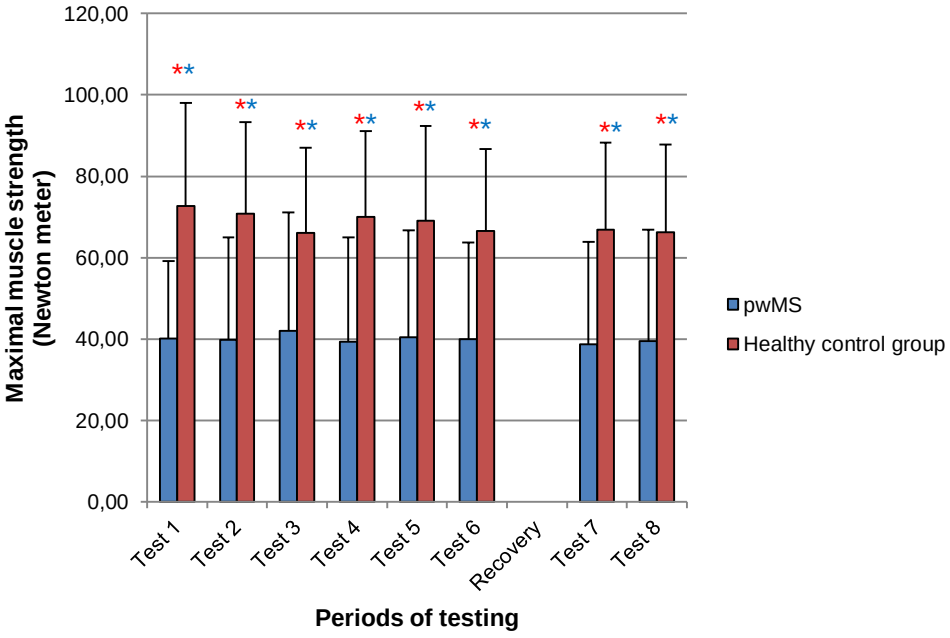

Figure 6: The mean of the maximal muscle strength, measured with the haptic master, for each test period in both groups. ** *A significant difference: in maximal muscle strength (Nm) for each test period between pwMS and healthy controls.SD: Standard deviation.*

The occurrence of motor fatigue during progression of the performance task

EMG Assistance anterior Deltoid – differences within the group. In the healthy control group, was a significant difference between the repeated measurements of the RMS and the MF (HC: $p<0.001$; HC: $p<0.001$) (Table 4). Within the MS group, no significant difference was noticed between the repeated measurements of the RMS and the MF (pwMS: $p=0.81$; pwMS: $p=0.06$) (Table 4). In pwMS, no significant difference was established between the measurements before the first exercise and after the fifth exercise (MF;RMS). In pwMS, the MF had a tendency to decrease after the fifth exercise in comparison with the first. The RMS had a tendency to increase after the fifth exercise in comparison with the first. These changes showed the appearance of muscle fatigue after the performance of the repeated exercises. In healthy controls, significant difference was established between measurements before the first exercise (Test 1) in comparison with the measurement before the recovery period (Test 6) (MF; RMS; $p<0.01$). The MF score decreased after the fifth exercise in comparison with the first. The RMS increased after the fifth exercise in comparison with the first. These changes showed the appearance of muscle fatigue after the performance of the repeated exercises. In both groups, a significant difference was noticed between the MF measurement just before the recovery period in comparison with the MF measurement after the recovery period (HC; pwMS; $p=0.01$). In both groups, the MF score increased after the recovery period. In pwMS and healthy controls, no significant difference was established between the RMS measurements just before the recovery period in comparison with the RMS measurement after the recovery period (HC: $p=0.22$: pwMS: $p=0.31$). In pwMS, the RMS score had a tendency to decrease which caused muscle recovery after the rest period. In healthy controls, the RMS score had a tendency to increase which caused force increase after the rest period (Table 4). In both groups, the scores of the MF were higher than the scores of the RMS (figure 7).

EMG Assistance anterior Deltoid – differences between the groups. For the MF and the RMS, no significant difference was noticed in the outcomes of each test period between both groups (Appendix 2;3). Graphical difference showed that pwMS had an overall lower score, on the scores of the MF measurements in comparison with the healthy control group (figure 6). No major differences were noticed between the RMS scores (figure 7).

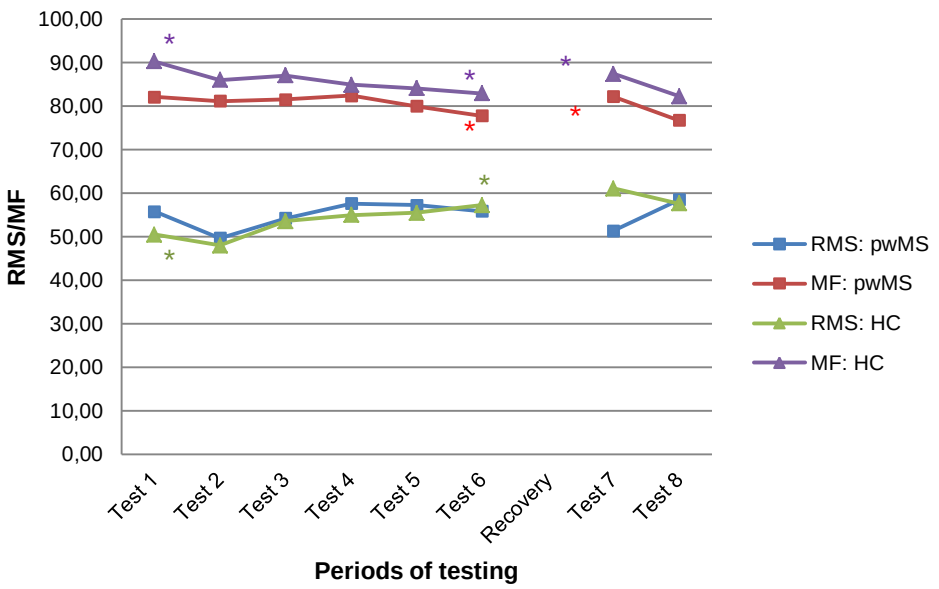

*Figure 7: The mean of the EMG signals of the anterior Deltoid for each test period in both groups- assistance. *A significant difference: between the RMS test 1 and test 6 in the healthy control group. * A significant difference: between the MF test 1 and 6 in healthy controls. * / * A significant difference: between the MF test 6 and 7 in the both groups.*

EMG maximum force anterior Deltoid - differences within the group. In both groups, no significant difference was noticed between the repeated measurements of the MF scores (Table 4). In the healthy control group, a significant difference was established between the repeated measurements of the RMS scores (Table 4). In pwMS, no significant difference was noticed between the repeated measurements of the RMS scores (Table 4). Within both groups, no significant difference was established between the repeated measurements before the first exercise (Test 1 MF; Test 1 RMS) and the measurements after the fifth exercise (Test 6 MF; Test 6 RMS) (Table 4). In pwMS, MF had a tendency to decrease after the fifth exercise in comparison with the first. The RMS had a tendency to increase after the fifth exercise in comparison with the first. These changes showed the appearance of muscle fatigue after the performance of repeated exercises. In healthy controls, the MF had a tendency to increase after the fifth exercise in comparison with the first. The RMS had a tendency to decrease after the fifth exercise in comparison with the first. These changes showed the appearance of muscle recovery which was an uncommon phenomenon. In both groups, no significant difference was noticed between the measurements after the fifth exercise in comparison with the measurements after the recovery period (MF; RMS). In pwMS, the MF and the RMS had a tendency to increase after the rest period. These changes showed the appearance of force increase. In healthy controls, the MF had a tendency to decrease after the rest period. The RMS had a tendency to increase after the rest period. These changes showed the appearance of muscle fatigue which was uncommon. In both groups, the scores of the RMS were higher than the scores of the MF (figure 8).

EMG Assistance anterior Deltoid – differences between the groups. The outcomes of the RMS, of most of the test periods, were different in both groups (Appendix 5). For the MF, no significant difference was established in the outcomes of each test period between the two groups (Appendix 4). Graphical difference showed that pwMS had an overall lower score, on the scores of the MF and the RMS measurements, in comparison with the healthy control group (figure 8).

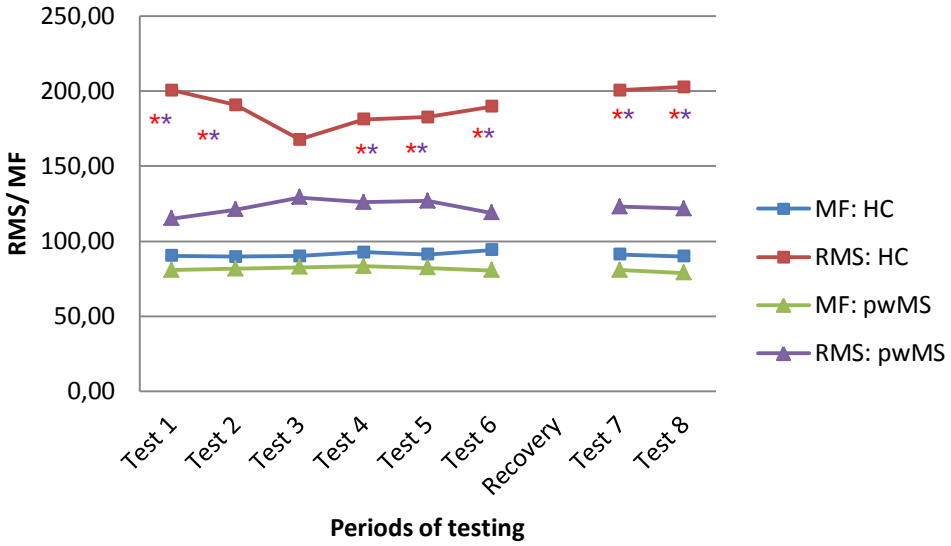

*Figure 8: The mean of the EMG signals of the anterior Deltoid for each test period in both groups - maximal force. ** A significant difference: in RMS for each test period (except test 3) between pwMS and healthy controls.*

Table 4. Mean ± SD of the EMG analyses of the anterior Deltoid in both MS and healthy control groups and the associated P-values

Repeated measurements	Before exercise 1 Test 1	Before exercise 2 Test 2	Before exercise 3 Test 3	Before exercise 4 Test 4	Before exercise 5 Test 5	After exercise 5 Test 6	Recovery	Before exercise 6 Test 7	After exercise 6 Test 8	Friedman Test $	P-value Test 1 – Test 6 $$	P-value Test 6 – Test 7 $$
Assistance anterior Deltoid												
Healthy controls												
RMS	50.51 ± 16.97	48.03 ± 13.67	53.57 ± 19.22	54.99 ± 18.69	55.52 ± 16.38	57,30 ± 16.14		61.09 ± 15.46	57.62 ± 19.21	<0.001*	0.01*	0.22
MF	90.33 ± 15.39	86.06 ± 15.64	87.03 ± 15.67	84.94 ± 15.50	84.14 ± 15.19	82.93 ± 14.54		87.41 ± 15.39	82.32 ± 14.87	<0.001*	<0.001*	0.01*
PwMS												
RMS	55.77 ± 23.77	49.66 ± 24.61	54.27°° ± 24.46	57.66°° ± 23.27	57.30 ± 23.44	55.89 ± 22.37		51.40 ± 20.00	58.54 ± 22.18	0.81	0.76	0.31
MF	82.14 ± 12.15	81.16 ± 12.40	81.54°° ± 12.24	82.45°° ± 13.97	79.98 ± 14.05	77.76 ± 14.06		82.24 ± 15.99	76.80 ± 17.83	0.06	0.04	0.01*
Maximum anterior Deltoid												
Healthy controls												
RMS	200.56 ± 102.33	190.72 ± 95.02	167.65 ± 84.93	181.19 ± 68.17	182.66 ± 64.81	189.62 ± 73.71		200.66 ± 71.41	202.78 ± 91.01	0.01*	0.03	0.26
MF	90.32 ± 24.75	89.83 ± 17.08	90.06 ± 35.87	92.69 ± 25.60	91.20 ± 24.14	94.17 ± 29.90		91.20 ± 22.78	90.04 ± 23.01	0.38	0.33	0.72
PwMS												
RMS	115.14°° ± 47.65	121.12 ± 55.69	129.0°° ± 58.48	126.04 ± 57.93	126.87 ± 49.21	118.94 ± 40.39		122.93 ± 51.97	121.79 ± 47.05	0.90	0.36	0.33
MF	80.87°° ± 14.76	81.66 ± 16.87	82.72°° ± 17.89	83.41 ± 18.30	82.19 ± 17.74	80.67 ± 16.52		80.82 ± 18.13	78.76 ± 17.98	0.42	0.39	0.96

SD: Standard deviation; RMS: Root Mean Square (mean); MF: Median frequency (mean); AD: anterior deltoid; $ Friedman test; $$ Wilcoxon signed-rank test (p=0.05/3=0.017); n=15°°.

Task performance during progression of the task

Time per cycle - differences within the group. Within both groups there was a significant decrease between the repeated measurements ($p<0.001$ for both groups) (Table 5). More specific, between the measurement of the first exercise (Test 1) and the measurement of the fifth exercise (Test 5) ($p<0.001$ for both groups). The measurement of test 5 was compared with the measurement after the recovery period (Test 6). In both groups, no significant difference was noticed between these measurements. (pwMS: $p=0.73$; healthy controls: $p=0.03$) (Table 5).

Time per cycle – differences between the groups. All the test periods from test 1 to 6 were significant different between the two groups. Graphical difference showed that pwMS had an overall higher time performance per cycle than the healthy control group (figure 9).

Distance traveled per cycle – differences within the group. Within both groups there was a significant difference between the repeated measurements (pwMS: $p=0.04$; healthy controls: $p<0.001$) (Table 5). In both groups, There was a significant difference between the measurement of the first exercise (Test 1) in comparison with the measurements of the fifth exercise (Test 5) (pwMS: $p=0.01$; healthy controls: $p<0.001$). The distance traveled per cycle decreased in test 5 relatively to test 1 in pwMS and healthy controls. The measurement of test 5 was compared with the measurement after the recovery period (test 6). In both groups, no significant difference was noticed between these measurements (pwMS: $p=0.69$; healthy controls: $p=0.07$) (Table 5).

Distance traveled per cycle – differences between the groups. The distance traveled per cycle in test period 3, 4, 5 and 6 were significant different between both groups (Table 5). Graphical difference showed that pwMS had an overall higher distance performance per cycle than the healthy control group (Appendix 8).

Number of feeding - differences within the group. Within both groups there was a significant difference between the repeated measurements (pwMS: $p<0.001$; healthy controls: $p<0.001$) (Table 5). In pwMS and the healthy control group, was a significant difference between the measurement of test 1 and the measurement of test 5 (pwMS: $p<0.001$; healthy controls: $p<0.001$). In both groups, the number of feeding increased in the fifth exercise relative to the first exercise. The measurement of test 5 was compared with the measurement after the recovery period (test 6). In the MS group, no significant difference was established between these measurements (pwMS: $p=0.90$). In contrary to the healthy control group were a significant increase was noticed ($p=0.01$) (Table 5).

Number of feeding – differences between the groups. All the measurements of the number of feeding from test 1 to 6 were significantly different between the two groups. Graphical difference showed that pwMS had an overall lower number of feeding compared with the healthy control group (figure 9).

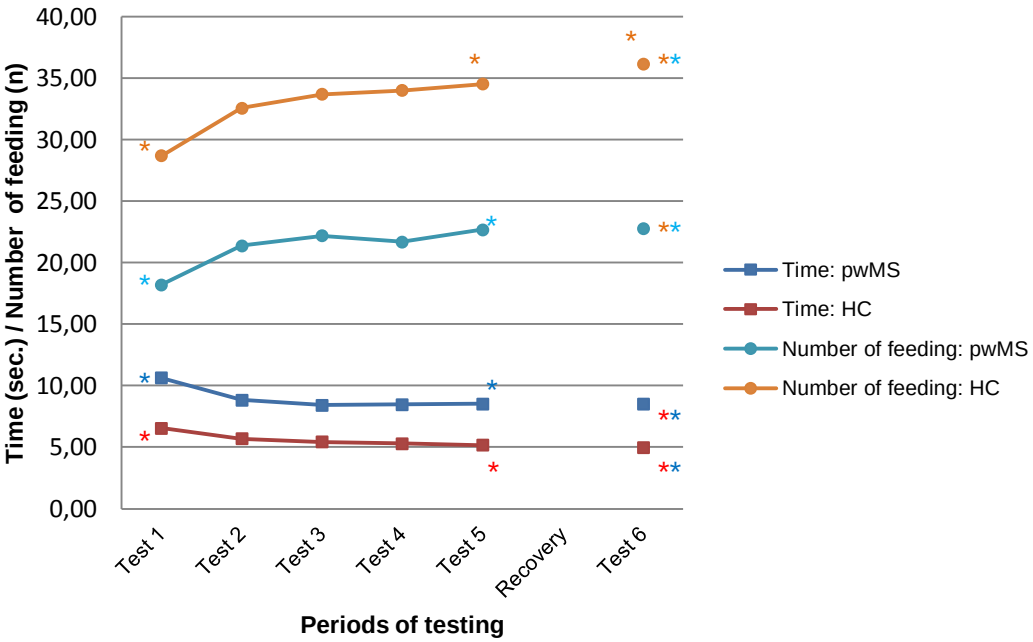

*Figure 9: The mean of the time per cycle and the number of feeding for each test period in both groups. * / * A significant difference: between time test 1 and test 5 in both groups. **A significant difference: in time for each test period between pwMS and healthy controls. * / * A significant difference: between number of feeding test 1 and test 5 in both groups. * A significant difference: between number of feeding test 5 and test 6 in the healthy control group. **A significant difference: in time for each test period between pwMS and healthy controls.*

Table 5. Mean ± SD of the performance data in both MS and healthy control groups and the associated P-values

Repeated measurements	Test 1	Test 2	Test 3	Test 4	Test 5	Recovery period	Test 6	Friedman Test $ - One-way repeated measures ANOVA #	P-value Test 1 – Test 5 $$ - ##	P-value Test 5 – Test 6 $$ - ##
Time during the feeding task (sec.)										
pwMS (n=16)	10.64 ± 3.66	8.85 ± 2.71	8.43 ± 2.40	8.48 ± 2.44	8.53 ± 2.86	Recovery period	8.52 ± 2.87	<0.001*	<0.001*	0.73
HC (n=16)	6.55 ± 2.07	5.68 ± 1.39	5.43 ± 1.05	5.30 ± 0.66	5.17 ± 0.52		4.98 ± 0.54	<0.001*	<0.001*	0.03
P-value $$$	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*		<0.001*			
Distance travelled during the feeding task (m)										
pwMS (n=16)	1.09 ± 0.29	0.98 ± 0.17	0.98 ± 0.16	0.99 ± 0.16	0.96 ± 0.16	Recovery period	0.97 ± 0.16	0.04	0.01*	0.69
HC (n=16)	0.93 ± 0.13	0.90 ± 0.12	0.89 ± 0.07	0.88 ± 0.05	0.87 ± 0.05		0.86 ± 0.05	<0.001*	<0.001*	0.07
P-value $$$	0.09	0.07	0.03	0.01	0.02		0.01			
Number of feeding during the feeding task (n)										
pwMS (n=16)	18.19 ± 6.77	21.38 ± 5.55	22.19 ± 6.02	21.69 ± 5.39	22.69 ± 7.34	Recovery period	22.75 ± 7.06	<0.001* #	<0.001* ##	0.90 ##
HC (n=16)	28.69 ± 5.88	32.56 ± 6.46	33.69 ± 5.69	34.00 ± 4.43	34.50 ± 3.81		36.13 ± 4.05	<0.001* #	<0.001* ##	0.01* ##
P-value ###	<0.001*	<0.001*	0.02*	<0.001*	0.02*		<0.001*			

SD: Standard deviation; $ Friedman test, $$ Wilcoxon signed – rank test (p=0.05/3=0.017), $$$ Mann-Whitney U test (p=0.05); # One-way repeated measures ANOVA, ## Paired samples t-test (p= 0.05/3=0.017), ### Independent Samples t-test (p=0.05); *Significant difference.

Discussion

The present study examined the impact of repeated lifting exercises in a virtual learning environment on muscle strength, perceived fatigue and game performance and investigated the difference between pwMS and healthy controls. Based on these 3 previous outcomes, we determine the occurrence of motor fatigue in pwMS and healthy controls.
The outcomes indicated the appearance of muscle fatigue, the decline of muscle strength, and subjective fatigue during the progression of the feeding task. In contrast, there was no decline of exercise performance.

Force decline during the exercise protocol

Maximal force measurements were performed with the Microfet 2 hand-held dynamometer and the haptic master. The results of maximal anteflexion strength, for both measurement systems, were in accordance with each other. In both groups, the maximal anteflexion strength had a tendency to decrease when the number of exercises increased indicating that the exercise protocol was fatiguing. These changes could be expected. Muscle fatigue occurs after repeated exercise performance (18) which leads to an alternation of the mechanisms involved in force production and these alternations lead to a decrease in force production (39). This phenomenon may be clarified by several different physiological phenomena. One study suggested that central- and peripheral fatigue contributes to the occurrence of force decline. 'Central fatigue' 'which constitutes a decrease in voluntary activation of the muscle which is in accordance with a decrease in the number and discharge rates of the motor units recruited at the start of the muscle strength generation'. 'Peripheral fatigue' 'indicates a decrease in the contractile strength of the muscle fibres and changes in the underlying mechanisms of transmission of muscle action potentials'(39). Several adaptation mechanisms were developed in order to sustain force generation. Main muscle mechanism for dealing with fatigue is a combination of increased motor unit recruitment and the modulation of the motor unit discharge rate (39). Possibly, pwMS have an impairment in the neuromuscular responses and in the recruitment of motor neurons which can lead to an extensive appearance of muscle – and motor fatigue and a decline in adaptation mechanisms (25). Unexpectedly, no greater force decline was seen in pwMS in comparison with healthy controls but the overall anteflexion strength of pwMS was significant lower in comparison with the healthy controls.

In both groups, the maximal anteflexion strength measured with the Microfet showed an increase in maximal strength after the recovery period, but no significant differences were present. An exception was noticed in pwMS during the maximal force measurement of the haptic master. Remarkably, the strength had a tendency to decrease after the recovery period which was in contrast with the previous reports, were normally an increase in muscle strength was seen after rest.

Furthermore, abduction strength was measured with the Microfet while the performance task only consisted of anteflexion movements. In pwMS, the results of the abduction strength were in

accordance with the results of the anteflexion strength and agreed with the predetermined hypothesis (18;39). Albeit surprising, an exception was seen at the healthy control group for the abduction strength which increased when the number of exercises increased. No significant difference was present but the tendency of this outcome was not immediately expected. Maybe, this is caused by the exercise, which only included anteflexion movements. Therefore, there was probably no occurrence of force decline and motor fatigue during the performance of the maximal abduction strength test. Maybe, pwMS compensated during the performance task and used more shoulder abduction force in comparison with the healthy controls. Therefore, a possible hypothesis is that pwMS develop more force decline during the performance test of the maximal abduction strength. In pwMS, the maximal abduction increased significantly after the recovery period. These changes could be expected. Maybe, pwMS used more abduction force during the performance task and the rest period allowed the muscles to recover, resulted in an increasing of muscular strength.

Performance and muscular signs of fatigue (sEMG)

In both groups, the sEMG measurement of assistance showed muscle fatigue/ force decreases in the deltoid anterior muscle after the performance of the repeated exercise bouts. In pwMS, muscle recovery was seen after the recovery period. In healthy controls, a force increase was seen after the recovery period. All these changes could be expected. An earlier study also suggested the appearance of muscle fatigue, in the fatigue period, by analyzing electromyography signals, during the performance of a prolonged typewriting task but the authors suggested that the sEMG parameters did not recover completely during the rest period while our study showed an acceptable recovery after the rest period(40).

In pwMS, the sEMG measurement of maximal force showed muscle fatigue after the performance of the repeated exercise bouts. These changes were expected. Remarkably, the healthy control group showed no muscle fatigue after the repeated measurements while we expected the appearance of muscle fatigue. These results were in contrast with the study of Kimura et al.(40). In our study, force increase was noticed in pwMS after the recovery period which was in accordance with our assumptions. Another exception was noticed in healthy controls which showed no force increase after the recovery period. This modification was not expected after a recovery period. The study of Kimura et al. suggested an uncompleted recovery of sEMG measurements after the recovery period, but muscle fatigue was partially restored (40). No restoration seems unlikely. The overall scores of the sEMG findings could be expected, except the sEMG measurements of maximal force in healthy controls.

In contrast to the findings, based on the sEMG, the findings of the performance data of the haptic master suggested no decline of the performance of the feeding task while the task was in progression. A decline in performance was however expected (5;23). Albeit surprising, the current findings are in line with an earlier study, of 30 healthy women, that found that neuromuscular fatigue induces by 1h

strength training session of the upper limbs had no effect on the motor performance of the hand(41). In our study, the time the participant needed, to start from the bottom of the screen, pick up the fruit on the top of the screen and travel back to the bottom of the screen, was not increased. In fact, the time decreased while the test session progressed. There was, unexpectedly, a better performance on the end of the repeated measures than in the beginning. The traveled distance, from the bottom to the top of the screen, was not increased after the repeated measurements. In fact, the results of the travelled distance were decreased after the repeated measurements. The study of Gates et al. included 10 healthy controls which performed a repetitive sawing task until volitional exhaustion (15-20min.). The participants performed the task on sternum height ('low') and shoulder height ('high'). The study suggested that fatigue occurred quicker while working on a shoulder height. Muscle fatigue causes more variability at high height, but did not lead to greater instability. People adapt their movement strategies in multi-joint redundant tasks and maintain stability (42). In our study no significant variability was seen in the travelled distance during the repeated exercises. This can be related to one study, included 18 healthy controls, which perform a repetitive pointing task at shoulder height. The study suggests: 'that healthy individuals are able to develop strategies to compensate for fatigue-induced deficits at one joint to maintain the endpoint accuracy of a multi-joint task constant'(18). The latter study also found that the subjects perform the movements in less time while fatigued (18) which is in accordance with our findings. The last performance test was the number of feeding that measures the number of picked fruit during the 3 minutes of an exercise bout. The number of picked fruit increased as the exercise progressed.

Our findings suggested a possible appearance of motor fatigue during the exercise progression but there was no decline in exercise performance. These outcomes were against our expectations that suggested decreasing levels of performance in accordance with increasing levels of motor and muscle fatigue as the testing progressed (5;23).

Subjective signs of fatigue (VAS fatigue scale)

In both groups, the score of the VAS fatigue scale increased during prolonged exercise repetitions. In pwMS and the healthy controls, the score of the VAS fatigue scale decreased after the recovery period. Remarkably, the feeling of fatigue was not in accordance with the performance of the exercise. Findings in pwMS, indicate that the changes in objective cognitive performance during prolonged training can appear independently of changes in the feeling of fatigue (10;26). The pwMS reported a greater increase in the level of subjective fatigue, than healthy controls. No significant correlation was seen between the changes in subjective fatigue and the changes in cognitive fatigue (10). Another study included persons with Parkinson Disease, suggests that objective decrements in motor performance did not significantly correlate with perceived fatigue which was in accordance with our findings (43). The subjective ratings of fatigue were mirrored by changes in sEMG parameters indicating muscular fatigue, which was in accordance with the study of Kimura et al.(40), despite the stable performance of the feeding exercise.

Limitations and further research

In considering the results from this cross-sectional case-control study, it is important to consider the limitations. This present study included a small sample (n=32) of individuals with MS (n=16) and another group of healthy controls (n=16). Some methodological procedures must be taken into account. First, it is important to notice some missing values in the Microfet and sEMG data. Findings may be disturbed because of the missing values. Second, the activities performed on the testing day, before the performance of the test, were not taken into account. Maybe, these earlier performed activities can affect the appearance of fatigue. Because, repetitive movements generate fatigue (18), earlier performed repetitive tasks can affect the appearance of fatigue during the feeding task. Third, several mechanisms on 'central' and peripheral' level can be affected by muscle fatigue and can cause a decrease in force generation. Some changes on peripheral level are changes in the intracellular environment and changes within the muscle fibres (i.e. changes in the sarcoplasm, inhibition of the calcium release, decrease in glycogen reserves, a drop in blood glucose, and a drop in nerve action potentials as a result of biochemical changes inside and around the muscle fibres). Possibly, pwMS have impairments in the neuromuscular responses and in the recruitment of motor neurons (25). Hence, there may be other internal changes in the muscles of pwMS. These changes were not examined in our study and that might indicate a limitation. Fourth, the differences between the MS type and the EDSS scores were not taken into account. Finally, there was no distinction in the results between males and females, however, we note that we had similar sex distribution in our two groups.

Further research is important to overcome these limitations. The results of the study indicate that the subjective ratings of fatigue were mirrored by changes in sEMG parameters and maximal force decline, despite a better performance of the feeding task. The latter seems to be a contradiction that needs further investigation. It may be useful to take a muscle biopsy to detect a possible objective measurement of fatigue. This additional measurement can help us to detect the changes within the muscle composition.

Conclusion

These results indicate that the subjective ratings of fatigue were mirrored by changes in sEMG parameters and changes in maximal muscle strength indicating muscular fatigue and force decline, despite the stable or better performance of the feeding exercise. Healthy controls had an overall better performance, more strength and fewer complaints about fatigue in comparison with pwMS.

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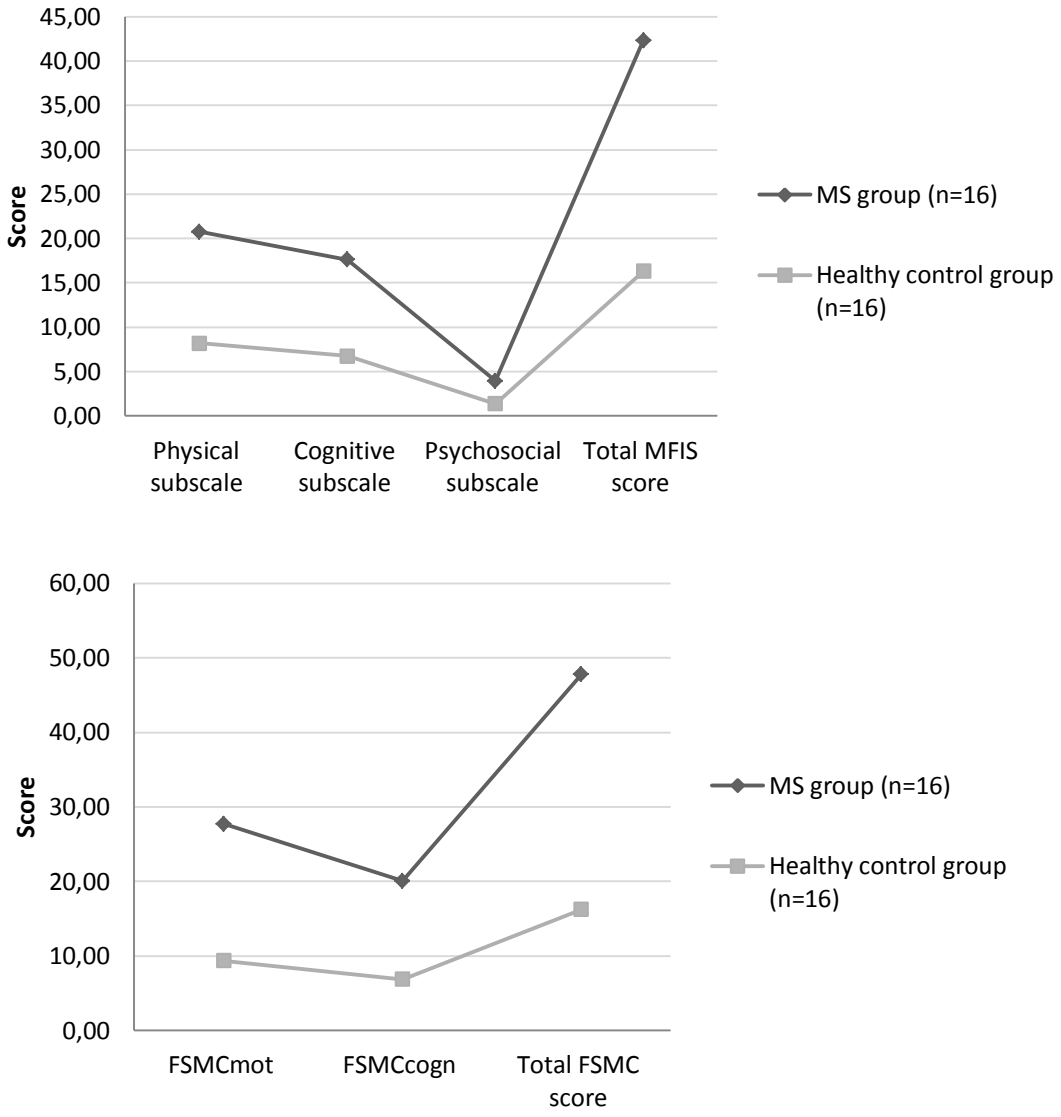
APPENDIX

1. Appendix 1: graphic of the subscales and the total score of the MFIS and the FSMC.
2. Appendix 2. Difference between the groups in the outcomes of each test period (P-value) – EMG data assistance median frequency.
3. Appendix 3. Difference between the groups in the outcomes of each test period (P-value) – EMG data assistance Root Mean Square.
4. Appendix 4. Difference between the groups in the outcomes of the values of each test period (P-value) – EMG data Maximum median frequency.
5. Appendix 5. Difference between the groups in the outcomes of the values of each test period (P-value) – EMG data Maximum Root Mean Square.
6. Appendix 6. Mean ± SD of the EMG analyses of the anterior Deltoid – Assistance anterior Deltoid.
7. Appendix 7. Mean ± SD of the EMG analyses of the anterior Deltoid – Maximum anterior Deltoid.
8. Appendix 8. The mean of the distance traveled per cycle for each test period in both groups.



Appendix 1: the subscales and the total score of the MFIS and the FSMC in both groups.

Appendix 2. Difference between the groups in the outcomes of each test period (P-value) – EMG data assistance median frequency

Repeated measurements	Before exercise 1 Test 1	Before exercise 2 Test 2	Before exercise 3 Test 3	Before exercise 4 Test 4	Before exercise 5 Test 5	After exercise 5 Test 6	Recovery period	Before exercise 6 Test 7	After exercise 6 Test 8
P-value	0.12	0.79	0.60	0.98	0.67	0.78		0.45	0.26

Mann-Whitney U test (p=0.05)

Appendix 3. Difference between the groups in the outcomes of each test period (P-value) – EMG data assistance Root Mean Square

Repeated measurements	Before exercise 1 Test 1	Before exercise 2 Test 2	Before exercise 3 Test 3	Before exercise 4 Test 4	Before exercise 5 Test 5	After exercise 5 Test 6	Recovery period	Before exercise 6 Test 7	After exercise 6 Test 8
P-value	0.96	0.99	0.95	0.77	0.96	0.81		0.13	1.00

Mann-Whitney U test (p=0.05)

Appendix 4. Difference between the groups in the outcomes of each test period (P-value) – EMG data Maximum median frequency

Repeated measurements	Before exercise 1 Test 1	Before exercise 2 Test 2	Before exercise 3 Test 3	Before exercise 4 Test 4	Before exercise 5 Test 5	After exercise 5 Test 6	Recovery period	Before exercise 6 Test 7	After exercise 6 Test 8
P-value	0.50	0.18	0.45	0.47	0.31	0.17		0.25	0.13

Mann-Whitney U test (p=0.05)

Appendix 5. Difference between the groups in the outcomes of each test period (P-value) – EMG data Maximum Root Mean Square

Repeated measurements	Before exercise 1 Test 1	Before exercise 2 Test 2	Before exercise 3 Test 3	Before exercise 4 Test 4	Before exercise 5 Test 5	After exercise 5 Test 6	Recovery period	Before exercise 6 Test 7	After exercise 6 Test 8
P-value	0.01	0.02	0.09	0.04	0.02	<0.001		<0.001	<0.001

Mann-Whitney U test (p=0.05)

Appendix 6. Mean ± SD of the EMG analyses of the anterior Deltoid in both MS and healthy control groups and the associated P-values – Assistance anterior Deltoid

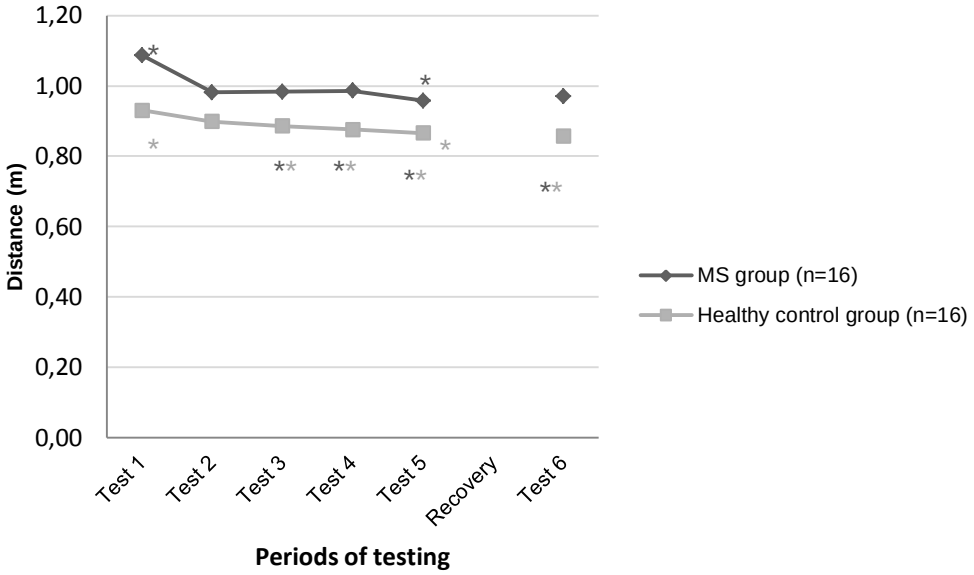
Healthy controls												
Repeated measurements	Before exercise 1 Test 1	Before exercise 2 Test 2	Before exercise 3 Test 3	Before exercise 4 Test 4	Before exercise 5 Test 5	After exercise 5 Test 6	Recovery	Before exercise 6 Test 7	After exercise 6 Test 8	Friedman Test $	P-value Test 1 – Test 6 $$	P-value Test 6 – Test 7 $$
RMS	50.51 ± 16.97	48.03 ± 13.67	53.57 ± 19.22	54.99 ± 18.69	55.52 ± 16.38	57,30 ± 16.14		61.09 ± 15.46	57.62 ± 19.21	<0.001 *	0.01 *	0.22
MF	90.33 ± 15.39	86.06 ± 15.64	87.03 ± 15.67	84.94 ± 15.50	84.14 ± 15.19	82.93 ± 14.54		87.41 ± 15.39	82.32 ± 14.87	<0.001 *	<0.001 *	0.01 *
Comparison of RMS and MF with the test before												
RMS vs MF	Start	MF↓ RMS↓	MF↑ RMS↑	MF↓ RMS↑	MF↓ RMS↑	MF↓ RMS↑		MF↑ RMS↑	MF↓ RMS↓			
Fatigue interpretation	Start number	Force decrease	Force increase	Muscle fatigue	Muscle fatigue	Muscle fatigue	Recovery	Force increase	Force decrease			
PwMS												
RMS	55.77 ± 23.77	49.66 ± 24.61	54.27 °° ± 24.46	57.66 °° ± 23.27	57.30 ± 23.44	55.89 ± 22.37		51.40 ± 20.00	58.54 ± 22.18	0.81	0.76	0.31
MF	82.14 ± 12.15	81.16 ± 12.40	81.54 °° ± 12.24	82.45 °° ± 13.97	79.98 ± 14.05	77.76 ± 14.06		82.24 ± 15.99	76.80 ± 17.83	0.06	0.04	0.01 *
Comparison of RMS and MF with the test before												
RMS vs MF	Start	MF↓ RMS↓	MF↑ RMS↑	MF↑ RMS↑	MF↓ RMS↓	MF↓ RMS↓		MF↑ RMS↓	MF↓ RMS↑			
Fatigue interpretation	Start	Force decrease	Force increase	Force increase	Force decrease	Force decrease	Recovery	Muscle recovery	Muscle fatigue			

SD: Standard deviation; RMS: Root Mean Square (mean); MF: Median frequency (mean); AD: anterior deltoid; $ Friedman test; $$ Wilcoxon signed-rank test (p=0.05/3=0.017); n=15°°; *Significant, RMS vs MF (36).

Appendix 7. Mean ± SD of the EMG analyses of the anterior Deltoid in both MS and healthy control groups and the associated P-values – Maximum anterior Deltoid

Healthy controls												
Repeated measurements	Before exercise 1 Test 1	Before exercise 2 Test 2	Before exercise 3 Test 3	Before exercise 4 Test 4	Before exercise 5 Test 5	After exercise 5 Test 6	Recovery	Before exercise 6 Test 7	After exercise 6 Test 8	Friedman Test $	P-value Test 1 – Test 6 $$	P-value Test 6 – Test 7 $$
RMS	200.56 ± 102.33	190.72 ± 95.02	167.65 ± 84.93	181.19 ± 68.17	182.66 ± 64.81	189.62 ± 73.71		200.66 ± 71.41	202.78 ± 91.01	0.01*	0.03	0.26
MF	90.32 ± 24.75	89.83 ± 17.08	90.06 ± 35.87	92.69 ± 25.60	91.20 ± 24.14	94.17 ± 29.90		91.20 ± 22.78	90.04 ± 23.01	0.38	0.33	0.72
Comparison of RMS and MF with the test before												
RMS vs MF	Start	MF↓ RMS↓	MF↑ RMS↓	MF↑ RMS↑	MF↓ RMS↑	MF↑ RMS↑		MF↓ RMS↑	MF↓ RMS↑			
Fatigue interpretation	Start	Force decrease	Muscle recovery	Force increase	Muscle fatigue	Force increase	Recovery	Muscle fatigue	Muscle fatigue			
PwMS												
RMS	115.14 °° ± 47.65	121.12 ± 55.69	129.06 °° ± 58.48	126.04 ± 57.93	126.87 ± 49.21	118.94 ± 40.39		122.93 ± 51.97	121.79 ± 47.05	0.90	0.36	0.33
MF	80.87 °° ± 14.76	81.66 ± 16.87	82.72 °° ± 17.89	83.41 ± 18.30	82.19 ± 17.74	80.67 ± 16.52		80.82 ± 18.13	78.76 ± 17.98	0.42	0.39	0.96
Comparison of RMS and MF with the test before												
RMS vs MF	Start	MF↑ RMS↑	MF↑ RMS↑	MF↑ RMS↓	MF↓ RMS↑	MF↓ RMS↓		MF↑ RMS↑	MF↓ RMS↓			
Fatigue interpretation	Start	Force increase	Force increase	Muscle recovery	Muscle fatigue	Force decrease	Recovery	Force increase	Force decrease			

SD: Standard deviation; RMS: Root Mean Square (mean); MF: Median frequency (mean); AD: anterior deltoid; $ Friedman test; $$ Wilcoxon signed-rank test (p=0.05/3=0.017); n=15°°; *Significant; RMS vs MF (36).



*Appendix 8: The mean of the distance traveled per cycle for each test period in both groups. */*A significant difference: between distance test 1 and test 5 in both groups. ** A significant difference: in distance for each test period (except period 1 and 2) between pwMS and healthy controls.*

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