



Force decline after low and high intensity contractions in persons with multiple sclerosis



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HIGHLIGHTS

- Mechanisms underlying force decline differed between controls and persons with MS.
- Force decline during strong contractions is dominated by changes in peripheral (muscle) properties.
- Force decline during weak contractions is associated with sense of fatigue in persons with MS.

ABSTRACT

Objective: Force decline during strong contractions is dominated by changes in the periphery whereas during weaker contraction changes in voluntary activation become more important. We compared force decline and contributing factors in persons with multiple sclerosis (PwMS) during low and high intensity contractions.

Methods: Index finger abduction force, force evoked by electrical stimulation of the ulnar nerve at rest (RTw), and during MVCs were investigated in 19 PwMS and 19 controls. Participants performed contractions in sets of six contractions (7 s-on, 3 s-off) at 25% or 80% MVC. After each set, a 5 s-MVC was performed with superimposed nerve stimulation followed by RTw. Contractions were repeated until MVC dropped below 80% of initial MVC.

Results: Low compared to high intensity contractions caused a greater decline in voluntary activation and a smaller decline in RTw. Compared to controls, PwMS accomplished equal sets of contractions but showed a smaller decline in RTw. Female PwMS showed poorer voluntary activation. The number of low intensity contractions was associated with sense of fatigue in PwMS.

Conclusion: Although, no difference in fatigability was observed, the mechanism contributing to force decline differed between PwMS and controls during submaximal contractions.

Significance: During weak contractions, fatigue and fatigability are associated in PwMS.

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1. Introduction

Fatigue is an often reported symptom (Kluger et al., 2013) in persons with multiple sclerosis (PwMS) and has a major impact on functioning and quality of life (Kratz et al., 2016). Fatigue hin-

ders PwMS to perform paid labor (Bøe Lunde et al., 2014) and to engage in regular physical activity (Asano et al., 2015). A related phenomenon is performance fatigability (Kluger et al., 2013). In the motor domain, one specifies performance fatigability as reduced strength after repeated or sustained contractions (Dobkin, 2008). Previous research on performance fatigability in PwMS heavily relied on maximal voluntary isometric and isokinetic strength measurements (Zijdwind et al., 2016; Severijns et al., 2017). During isometric maximal contractions, research indicates that compared with controls PwMS show greater (Sheean et al., 1997; Schwid et al., 1999; Severijns et al., 2014) or similar (Steens et al., 2012b) force decline. However, in PwMS this force

Abbreviations: EMG, electromyography; EDSS, expanded disability status scale; FDI, first dorsal interosseous; FSS, Fatigue severity scale; HADS, Hospital anxiety and depression scale; MFIS, Modified fatigue impact scale; MS, multiple sclerosis; PwMS, persons with MS; MVC, maximal voluntary contraction; RTw, twitch at rest.

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decline was accompanied by a greater decline in voluntary muscle activation than in control subjects (Sheean et al., 1997; Steens et al., 2012b).

Although the capacity to perform strong muscle contractions are important, activities of daily life most often involve submaximal contractions (Kern et al., 2001). In contrast to strong contractions where muscle properties are the most limiting factor, a larger reduction in the voluntary muscle activation is observed during submaximal contraction in control subjects (Eichelberger and Bilodeau, 2007; Taylor and Gandevia, 2007).

After submaximal contractions PwMS often show similar performance fatigability compared with controls (Thickbroom et al., 2008; White et al., 2009). Whether in PwMS this force decline is also accompanied by a greater decline in voluntary muscle activation is still unknown. So far, no studies compared the contributions of changes in voluntary muscle activation during both low and high intensity exercises in the same group of PwMS. Therefore, we aimed to examine the contributions of changes in voluntary muscle activation versus peripheral changes in muscle properties during intermittent low and high intensity contractions of an intrinsic hand muscle in a group of PwMS.

The standard measure to quantify voluntary muscle activation is the twitch interpolation technique (Merton, 1954; Allen et al., 1995). This technique uses electrical nerve or muscle stimulation, or transcranial magnetic stimulation to add extra input beyond voluntary muscle activation to the muscle fibres (Gandevia, 2001). If all muscle fibres are maximally activated during the MVC no extra force is evoked by the interpolated stimulus; if extra force is evoked, however, the amplitude of the evoked force is inversely related to the voluntary muscle activation.

To assess the relative importance of mechanisms responsible for the force decline during low and high intensity contractions, we used two experimental sessions. The contribution of changes in voluntary muscle activation versus muscle properties were

addressed by means of the twitch interpolation technique given during short-lasting MVCs mixed in between low- and high intensity contractions.

The following research questions will be answered: (1) Do PwMS differ from controls in the time course of the decline in muscle force (fatigability) after submaximal intermittent isometric contractions of the first dorsal interosseous (FDI) muscle at different intensities? (2) Is there a difference in the mechanisms underlying force decline for the intermittent contractions at a low versus high intensity in controls and PwMS?

2. Methods

2.1. Participants

In this cross-sectional study, 19 PwMS were recruited in REVAL, the rehabilitation research center of Hasselt University. PwMS were included if they (a) were diagnosed with multiple sclerosis according to McDonald criteria, (b) were >18 years, (c) had no known orthopaedic conditions or pain in the upper limb impeding participation, (d) did not experience any MS relapse in the past month, (e) were right handed as determined by the Oldfield handedness inventory (score >40). Additionally, age- and sex-matched controls were recruited. The ethics committees of UZ KU Leuven, Hasselt University and The Rehabilitation and MS Centre Overpelt approved the study. All participants provided written informed consent before participation.

2.2. Experimental set-up

Participants held a strain gauge based force transducer (Van Duinen et al., 2007) in their right hand with a support underneath their forearms (Fig. 1A). The proximal interphalangeal joint of the

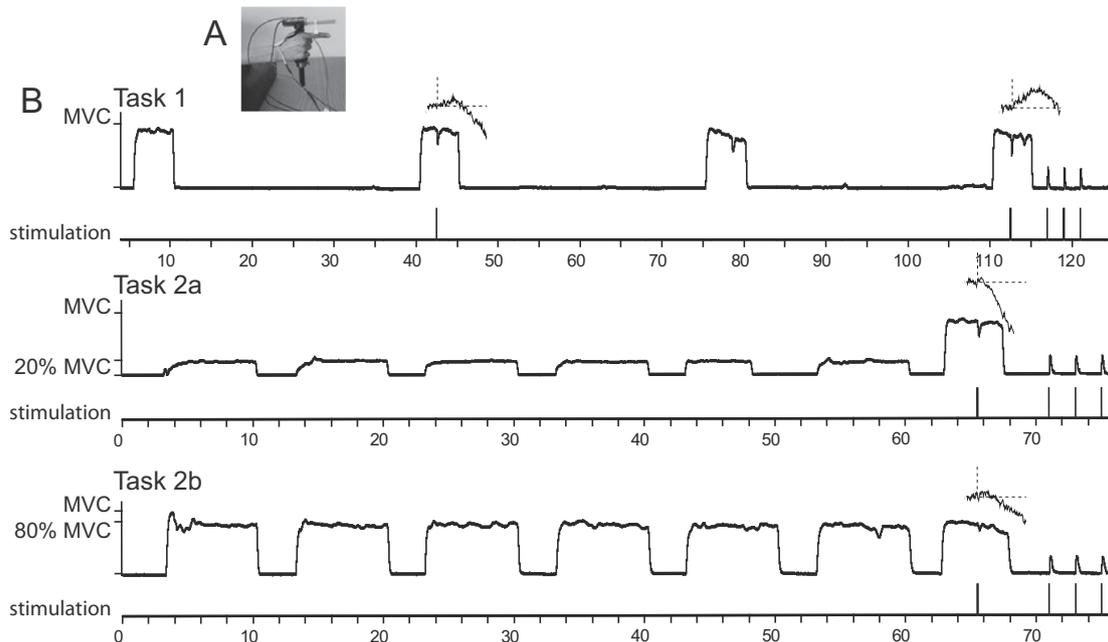


Fig. 1. (A) The hand position while holding the force transducer. (B) Illustration of the experimental tasks. Task 1 consisted of four 5 s maximal contractions (MVC's). In the middle of the second and fourth MVC a supramaximal double pulse stimulation is given. After the last MVC, three stimulations were given to determine the twitch at rest with 2 s between stimuli. This task represents the baseline in session 1 and 2. Task 2a illustrates one block of intermittent contractions at 25% of the MVC (session 1) and task 2b illustrates one block of intermittent contractions at 80% of the MVC (session 2). Both task 2a and 2b were followed by a 5 s MVC with electrical stimulus in the middle of the contractions, followed by three stimuli at rest with 2 s between stimuli. The interpolated twitch is presented at higher amplification above the index finger abduction force recording; the interrupted line presents the voluntary force at the moment of stimulation.

index finger was taped to a wedge which was connected to the transducer. The fingers and the thumb were also taped to prevent movements of the hand. Electromyographic signals of the right FDI were measured using a desktop electromyography (EMG) system (Bagnoli-16, Delsys Inc., Natick, MA, USA). The recorded force and EMG signals were digitized at 2 kHz (Power 1401 and Signal v4.11, CED, Cambridge, UK) and stored on a laptop for offline analysis.

2.3. Electrical nerve stimulation

To determine the voluntary activation of the FDI, the right ulnar nerve was stimulated (pulse width: 200 μ s, Digitimer DS7A, Welwyn Garden City, UK) with two Ag-AgCl surface electrodes over the nerve just proximal of the wrist. For each participant, the stimulation intensity was determined as the lowest intensity where no further increase in M-wave of the FDI was seen. Therefore, current intensity was increased in steps of 5 mA, until a maximal M-wave was detected without further increase with increasing current intensity. During the experiment, all presented stimuli were doublet stimulation with an interstimulus interval of 10 ms at an intensity of 130% of the maximal M-wave intensity.

2.4. Protocol

All participants were tested on three days, with a minimum of three days in between sessions. On the first test day, clinical arm function was assessed with an elaborate clinical testing battery and questionnaires on fatigue and depression were filled out (see Table 1). Further, participants were familiarized with the experimental set-up. On the following two days, the experimental protocol was performed in two sessions. Each session consisted of two tasks, as visualized in Fig. 1. Task 1 comprised four maximal voluntary contractions (MVC) (5 s, with 30 s rest). During the second and fourth MVC, a superimposed doublet stimulus was given after 2.5 s. The twitch on top of the highest force was used as the reference superimposed twitch (SIT_r). After the last MVC, three doublet stimulations were given at rest (the largest twitch was used as reference twitch at rest, RT_r). For task 2, participants performed intermittent contractions for blocks of one minute (six cycles of 7 s

contraction, followed by 3 s rest). An auditory stimulus paced the contractions. Based on the highest MVC of task 1, the exercise intensity was set at 25% of MVC in session 1, and 80% of MVC in session 2. After each block, participants performed a 5 s-MVC (MVC_n), with a superimposed stimulation at 2.5 s (SIT_n), followed by three stimuli at rest (RT_n). Participants received continuous online visual feedback of the generated force on a computer screen. In both sessions, the participants had to continue until the MVC_n performed at the end of each minute dropped below 80% of MVC in two consecutive blocks or after 30 bouts of contractions. For the comparisons between the two conditions, data obtained during the first MVC smaller than 80% of the initial MVC or during the MVC after 30 bouts of contractions.

2.5. Outcome measures

Age and sex were documented. For the PwMS, the expanded disability status scale (EDSS), MS phenotype and disease duration was retrieved from the treating neurologist. The Symbol digit modalities test was used to assess information processing speed. Clinical arm function was assessed with the motricity index (MI) to evaluate muscle strength, the Modified Ashworth scale (MAS) for spasticity, the Nine Hole Peg Test (NHPT) for manual dexterity.

Participants filled out four questionnaires: the Modified fatigue impact scale (MFIS) and Fatigue Severity scale (FSS) for the impact and severity of fatigue, the Hospital anxiety and depression scale (HADS) and the Manual Abilities Measure-36 (MAM-36) for the perceived difficulty that a person experiences during upper limb related activities of daily living.

2.6. Experimental outcome measures

Index finger abduction MVC was calculated as the average force over 0.5 s window around maximal force (task 1). During task 2, an MVC was performed after each set of six contractions (one-minute block); maximal force (MVC_n) was averaged over a 0.5 s time window around peak force, before the supramaximal doublet stimulus was given. For task 2, the number of blocks performed until MVC_n decreased to less than 80% of MVC_1 was determined. The decline in MVC force was calculated for each consecutive minute: $100 * [1 - (MVC_n/MVC_1)]$. The decline in twitch force was calculated according to the following formula: $100 * [1 - (RT_n/RT_r)]$.

The voluntary activation and the central activation ratio were calculated based on the superimposed twitch during the MVCs. Voluntary activation (VA) was calculated as: $VA = 100 * [1 - (SIT_n/RT_n)]$; central activation ratio (CAR) as: $CAR = MVC_n / (MVC_n + SIT_n)$.

2.7. Data processing and statistical analysis

All force data were visually checked for artefacts. The offset was removed before data processing using Matlab (MATLAB 2015a, The MathWorks Inc., Natick, MA, USA). Statistical analyses were performed with SAS JMP and MLWIN. Baseline variables (MVC_1 , VA, CAR, RT_r) were compared between PwMS and controls with linear mixed-models. The advantage of these models is that data of both sessions can be used even though the data is not independent (most subjects contribute more than one data point). Group (controls and PwMS), sex (males and females) and the interaction between group and sex were (stepwise) included as fixed factor. The model that included the interaction effect was only retained when this model had significantly better likelihood values. Normality of residuals was tested with quantile-quantile plots. Both VA and CAR were log-transformed to meet the criteria of normally distributed residuals.

Linear regression was used to identify parameters which could explain differences in number of contractions that could be per-

Table 1
Descriptive variables of the subjects.

Variable	PwMS	Controls	p-value
Age, years, mean (SD)	52 (9.3)	52 (9.2)	0.94
Gender (F/M)	12/7	12/7	
Type MS (RR/SP/PP)	13/5/1	NA	
Disease duration, years, mean (SD)	15.6 (9.2)	NA	
EDSS score, median (range)	3 (1.5–6.5)	NA	
SDMT, mean (SD)	45.6 (10.9)	53.3 (8.7)	0.02
NHPT, seconds, mean (SD)	21.6 (5.8)	17.0 (2.2)	0.003
MI (0–100), mean (SD)	94 (8)	100 (0)	0.006
Intention tremor, score (0/1)	15/4	NA	
Dysmetria, score (0/1/2)	7/11/1	NA	
Postural tremor, score (0/1)	17/2	NA	
MAS (0–4), mean (SD)	0	NA	
MAM score, mean (SD)	67.4 (14.2)	89.7 (12.1)	<0.001
HADS depression subscale	4.9 (3.2)	1.5 (2.3)	<0.001
FSS, mean (SD)	4.55 (1.60)	2.29 (0.80)	<0.001
MFIS, mean (SD)	42.79 (16.78)	13.63 (12.71)	<0.001

PwMS: persons with Multiple Sclerosis; P-value: p value of the unpaired student t-test or non-parametric equivalent; RR, Relapsing Remitting type of MS; PP: primary progressive type of MS; SP: secondary progressive type of MS; EDSS: Expanded Disability Status Scale; SDMT: Symbol Digit Modalities Test; NHPT: Nine Hole Peg Test; MI: Motricity Index; MAM: Manual Ability Measure; HADS: Hospital Anxiety and Depression Scale; FSS: Fatigue Severity Scale; MFIS: Modified Fatigue Impact Scale.

formed during the submaximal contractions. For each group (controls and PwMS) forward regression models were designed in which MVC, VA, decline in resting twitch and FSS or the MFIS were used as explanatory variables.

Since we observed that FFS and MFIS scores could be explained by the number of contractions in the 25% condition, we included an additional regression analysis to test whether the scores on the questionnaires could be explained even better by including HADS depression scores.

Changes in MVC, resting twitch, VA and CAR data during the submaximal contractions (task 2) were analysed by linear mixed-effect models. An advantage is that these models can handle missing data points; in the present set-up the number of contractions differ between subjects. Furthermore, these models take into account dependence between data points obtained in a subject at different time points and conditions (Prescott, 2018). Baseline values of task 1 were included (as measurements at time zero) in the analysis of task 2 (data from all MVCs/time points were included in the analysis). We started with a model containing random intercepts for each individual and we added random effects for each individual on the slope of the model. Diagnostics were calculated for each model to check model fit and only models with significant better likelihood values were retained. We first added MVC number (centered) and intensity (25% and 80%) as factors nested within individuals, group (PwMS and controls) and sex were added as a fixed factors. Models were extended by including interactions among MVC number, intensity, group and sex. The results showed that models including random effects of individuals on both inter-

cept and slope were superior for all outcome measures. Statistical significance was set at $p < 0.05$.

3. Results

Nineteen PwMS and age and sex-matched healthy persons were recruited. Table 1 shows the descriptive characteristics of both groups. The majority of the PwMS and none of the controls experienced pathological fatigue, with 12 out of 19 PwMS scoring higher than the cut-off score of 4 on the FSS and 38 on the MFIS. The scores on the HADS depression subscale indicated that five PwMS had mild symptoms of depression, while one HC had mild symptoms of depression.

Three PwMS were excluded from the statistical analysis for both session 1 and 2. One PwMS could not adhere to the protocols as required given a marked variability in force production. A second PwMS had difficulties performing the reference contractions (MVC_n) in between the exercises and the voluntary activation deviated with more than two standard deviations from of the rest of the sample. In the third PwMS, the experimental set-up unfortunately did not function correctly. Additionally, data of two PwMS were excluded for the high intensity exercises (session 2) only. One PwMS could not perform the 80% contractions as required and one PwMS was excluded after a first statistical analysis, as this person showed behaviour that was outside two standard deviations for the number of exercise blocks and influenced model fit significantly.

Table 2
Comparison between persons with MS and control at baseline.

			Session 1		Session 2		Group	Sex	Group ^a sex
			Controls (7/12)	PwMS (7/9)	Controls (7/12)	PwMS (7/7)			
MVC (N)	Mean	♂	39.6	35.4	42.2	38.6	Z	-1.25	-2.83
		♀	31.5	29.0	33.3	28.9			
	SD	♂	9.8	14.3	11.6	14.0	P	0.21	0.005
		♀	6.2	5.5	5.5	7.7			
		♂	39.0	32.3	41.6	36.3			
P 25th–P 75th	♂	31.0	29.7	33.1	29.6				
	♀	35.2–40.9	29.7–36.6	37.9–43.6	32.8–42.4				
Resting twitch (N)	Mean	♂	12.2	9.7	12.8	13.2	Z	-0.98	-1.49
		♀	10.3	9.8	11.5	10.1			
	SD	♂	3.5	4.7	4.2	5.4	P	0.33	0.14
		♀	2.2	2.6	1.3	2.7			
		♂	10.5	10.0	11.2	12.3			
P 25th–P 75th	♂	10.9	10.1	11.6	10.4				
	♀	9.6–15.5	6.1–13.8	10.5–15.1	9.0–17.4				
VA, % [†]	Mean	♂	94.8	96.8	94.6	96.6	Z	-1.08	-0.28
		♀	95.6	87.8	95.5	92.8			
	SD	♂	5.4	2.9	2.6	2.9	P	0.28	0.78
		♀	3.7	7.5	2.7	5.4			
		♂	98.6	98.0	94.1	97.5			
P 25th–P 75th	♂	97.0	84.7	96.0	92.3				
	♀	90.7–98.7	95.6–98.4	92.8–95.9	95.6–98.1				
CAR, (0–1) [†]	Mean	♂	94.4–98.0	82.3–96.3	94.6–97.2	89.9–96.9			
		♀	0.98	0.99	0.98	0.99	Z	-1.00	-0.12
	SD	♂	0.99	0.96	0.98	0.98			
		♀	0.02	0.01	0.01	0.01	P	0.32	0.91
		♂	0.01	0.03	0.01	0.02			
P 25th–P 75th	♂	1.00	0.99	0.98	0.99				
	♀	0.99	0.95	0.99	0.98				
		♂	0.97–1.00	0.99–1.00	0.98–0.99	0.99–0.99			
		♀	0.98–0.99	0.93–0.99	0.98–0.99	0.97–0.99			

Abbreviations: PwMS: persons with multiple sclerosis; MVC: maximal voluntary contraction. Z: Z-ratio and P: P-value. Linear mixed models were used to address group (control = reference) and sex (male = reference) differences.

[†] In the statistical model the data was log-transformed to obtain normally distributed residuals. The interaction effect is only presented for models which explained variance significantly better than only main effects. Bold values indicate statistical significance.

3.1. Baseline strength and voluntary activation

Baseline results are shown in Table 2. The MVC differed between male and female individuals ($P = 0.005$) but not between PwMS and controls. There was a significant interaction between group and sex for VA and CAR ($P = 0.015$, $P = 0.028$); female patients showing a lower VA and CAR (Table 2). Although VA and CAR were highly correlated with a correlation coefficient between 0.95 and 0.97 ($p < 0.0001$ for both sessions), CAR was always three to five percent higher than the VA ($p < 0.001$). Since VA and CAR were so similar only the data for the VA is presented in the text (actual values for both parameters are presented in the Tables and Figures).

3.2. Exercise duration, the number of exercise sets

Although the number of exercise bouts that could be accomplished differed between low and high intensity contractions (z -ratio: -12.52; $p < 0.001$, Table 3), no difference was observed between PwMS and controls. On average, controls performed 23 sets and PwMS performed 20 sets for the low intensity contractions. Eight controls and five PwMS completed all 30 sets of contractions. Three PwMS stopped quite early during the low intensity exercises: after four, five or seven sets.

Both groups performed on average three sets for the high intensity contractions. In total, eight participants (two PwMS) could maintain only one set of 80% contractions before their MVC declined to below 80% of MVC_1 . One of these PwMS also showed a very fast decline in the low intensity contractions (five sets).

Linear regression analysis (forward regression) revealed that the variation in the number of exercise bouts that subjects could maintain in the 25% condition was negatively associated with the FSS or MFIS score (Fig. 2), but this was especially true for PwMS

(R^2 : 0.39, $p = 0.010$ and R^2 : 0.31, $p = 0.025$ for MFIS and FSS, respectively) whereas no association was found for controls (FSS, R^2 : 0.002; MFIS, R^2 : 0.11). The number of contractions in the 80% MVC condition was negatively associated with VA and MVC for controls (R^2 : 0.44, $p = 0.009$) but not for PwMS (R^2 : 0.24, $p = 0.22$).

Both MFIS and FSS were associated with the depression score of the HADS (MFIS: controls: $R = 0.62$, $p = 0.03$; PwMS: $R = 0.63$, $p = 0.005$; FSS: controls: $R = 0.41$, $p = 0.04$; PwMS: $R = 0.54$, $p = 0.015$). Inclusion of both the number of contractions in the 25% condition and the HADS depression score in the model to explain variation in fatigue showed that for the PwMS significantly more of the variation in the MFIS (R^2 : 0.58, $p = 0.004$, F-change, $p = 0.033$) could be explained. For the FSS both HADS and the number of contraction were associated but combining the two variables could not explain significantly more variation (R^2 : 0.45, $p = 0.022$, F-change, $p = 0.098$).

3.3. Submaximal contractions: Voluntary activation and muscle fatigue

The outcomes obtained during the last MVC (i.e. the first MVC smaller than 80% of MVC_1 or MVC_{30}) of the two sessions are shown in Table 3.

The model explaining most of the variance in the MVCs included significant main and interaction effects of contraction number and intensity, but no significant main or interaction effect of group (Table 3, Fig. 3). Both intensities resulted in a significant decline in MVCs over time ($z = 7.7$, $p < 0.001$). The decline in MVCs was faster in the 80% condition than in the 25% MVC condition (interaction effect, $z = 12.1$; $p < 0.001$) but no difference was observed between PwMS and controls. This was to be expected, since all subjects were stopped when the MVC_n was lower than 80% MVC_1 or after 30 sets.

Table 3

Values obtained during the first MVC smaller than 80% of the initial MVC or the last MVC ($n = 30$) after intermittent contractions at low and high intensity.

		Low intensity		High intensity		Mixed model statistics						
		C (19)	PwMS (16)	C (19)	PwMS (14)	C-number	group	intensity	sex	C-number* intensity	C-number* group	Group* sex
Number of blocks	Mean	22.8	19.9	2.9	2.9	z-ratio						
	SD	10.1	7.7	2.0	1.7							
	Median	25.0	23.5	2.0	2.0							
	25th	18.0	11.0	1.0	2.0							
	75th	30.0	30.0	3.5	4.0							
Decline in MVC, %	Mean	17.4	19.0	24.3	27.8	z-ratio	7.69		14.31		12.10	
	SD	8.1	8.6	3.7	9.0							
	Median	20.3	21.1	23.4	25.2							
	25th	16.6	18.1	21.5	22.7							
	75th	20.9	22.9	25.8	26.6							
Decline in twitch force, %	Mean	20.6	5.9	20.0	19.5	z-ratio	9.89	-3.25	15.75		14.48	-4.74
	SD	7.2	11.6	12.2	9.1							
	Median	19.5	4.1	19.9	19.3							
	25th	16.0	-1.8	12.0	14.2							
	75th	20.9	11.2	26.3	22.4							
VA*, %	Mean	88.8	83.9	93.8	89.4	z-ratio	5.56	-0.48	2.79	-0.58	2.93	2.09
	SD	10.4	12.5	5.0	5.5							
	Median	91.0	88.6	95.0	88.3							
	25th	84.8	78.7	92.8	85.8							
	75th	95.3	92.3	97.6	93.3							
CAR*, (0–1)	Mean	0.96	0.94	0.98	0.95	z-ratio	5.14	-0.06	2.76	-0.05	2.85	2.07
	SD	0.04	0.05	0.02	0.03							
	Median	0.97	0.95	0.98	0.95							
	25th	0.96	0.91	0.97	0.94							
	75th	0.98	0.98	0.99	0.96							

CAR: Central activation ratio; Med: median; MVC: maximal voluntary contraction; SD: standard deviation; VA: voluntary activation; C-number: contraction number. Decline in MVC is calculated as $[100 - MVC (\% \text{ initial})]$ and twitch force as $[100 - \text{twitch force } (\% \text{ initial})]$. VA and CAR are presented as actual values.

Results of multilevel model are only presented for models that explained significantly more variance. *Statistical analysis were performed on log transformed data. Bold values indicate statistical significance.

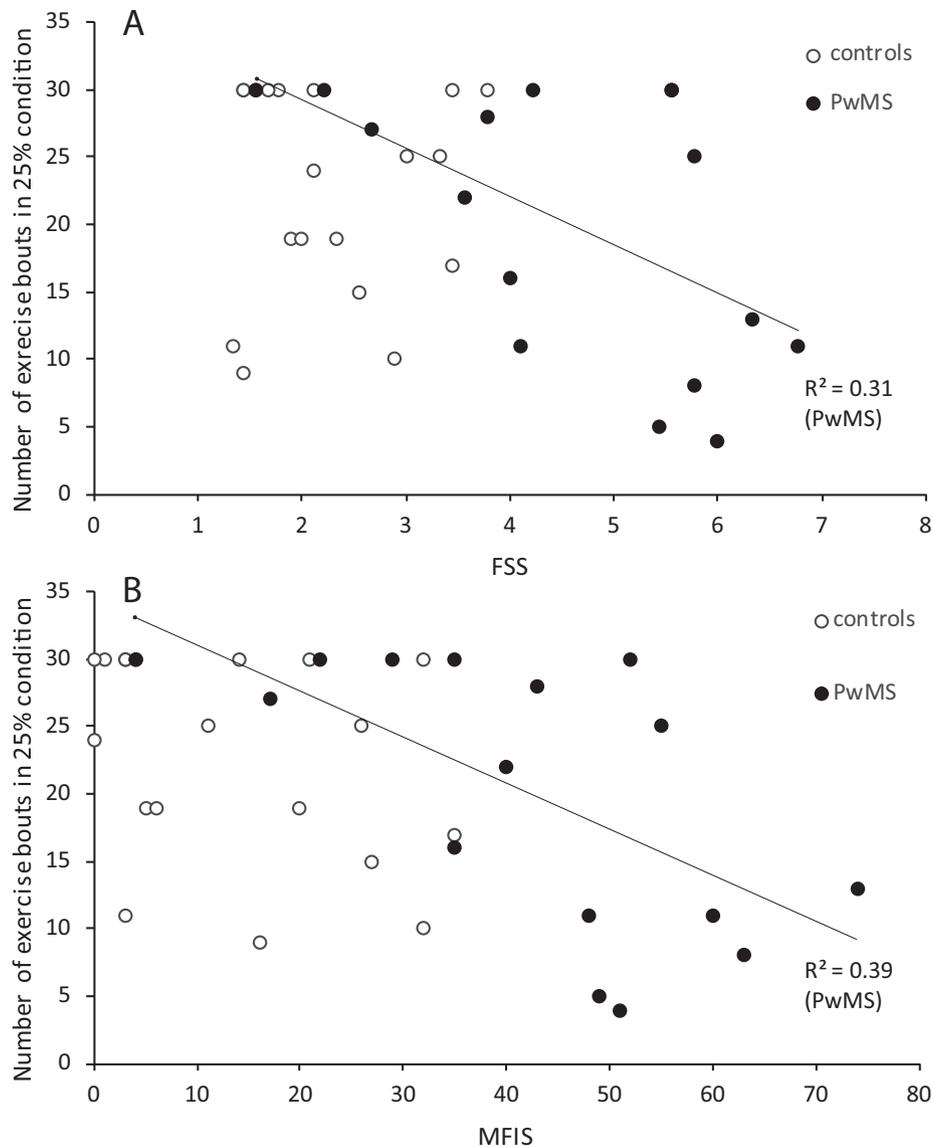


Fig. 2. Associations between number of exercise bouts in the 25% condition and FSS (A), and MFIS (B). Open circles represent controls, closed circles PwMS. The regression line reflects the association in PwMS; no significant association was found for controls. (Some data points are not visible due to overlap.)

For the twitches at rest the model that included contraction number, intensity, group and the interaction between contraction number and intensity, and contraction number and group fitted the data best (Table 3, Fig. 3). The twitch at rest declined over time ($z = 9.9$; $P < 0.001$). This decline over time was greater during the high compared with low intensity contractions (interaction effect, $z = 14.5$; $p < 0.001$), and was greater in control subjects than in PwMS (interaction effect, $z = -4.7$; $p < 0.01$).

The VA, as quantified by the twitch superimposed on the MVCs was best explained by contraction number and intensity, together with the interaction between contraction number and intensity (Fig. 3), and between group and sex (Table 3). Overall, voluntary activation was poorer in female PwMS ($z = 2.1$, $p = 0.04$) and during the 25% condition ($z = 2.6$; $p = 0.006$). Over time the voluntary activation decreased significantly ($z = 5.1$; $p < 0.001$) and this decrease was smaller during the 80% condition ($z = 2.7$; $p = 0.007$). The decline in VA over time was, however, not significantly different between the groups. Thus, female PwMS showed poorer activation but the decline in activation over time did not differ from the decline observed in control subjects.

4. Discussion

This study investigated mechanisms which contribute to the force decline during repeated low and high intensity contractions in PwMS. The number of exercise bouts that could be performed by PwMS did not differ from control subjects in both intensity conditions. However, the between-subject variation in the number of exercise bouts in the two exercise conditions could be explained best by different parameters. In PwMS, the variation in the low intensity condition was explained best by subjective fatigue scores (MFIS or FSS); that is, individuals with lower fatigue scores were more likely to complete more exercise sets. Whereas, in controls, the variation in the high intensity condition could be explained best by a combination of initial MVC and VA; stronger individuals and individuals with better voluntary activation performed less exercise bouts.

During the performance of the submaximal exercise bouts, the main differences between PwMS and control subjects were poorer voluntary activation in female PwMS and smaller decline in resting twitch in PwMS. In general, compared with the high intensity con-

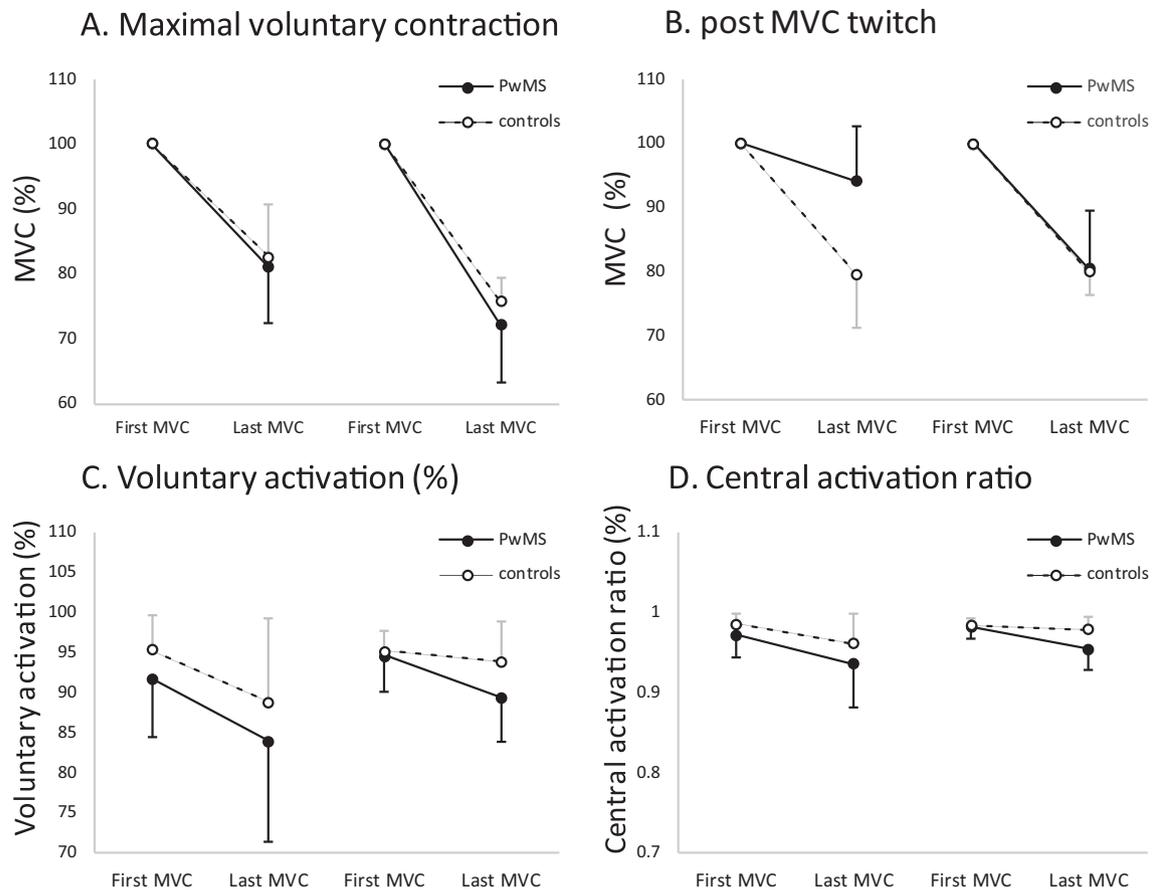


Fig. 3. Changes in maximal voluntary contraction (MVC), double pulse twitch at rest, voluntary activation and central activation ratio from baseline to the end of the exercises. Session 1 with contractions at 25% of the maximal voluntary contraction is represented on the left side of the panels (low intensity). Session 2 with contractions at 80% of the maximal voluntary contraction is represented on the right-side of the panels (high intensity).

dition, during the low intensity condition the voluntary activation was poorer and showed a larger decline with time.

The combined results suggest that in PwMS fatigue is an important contributor to performance fatigability especially at low forces whereas in control individuals and at high forces factors related to initial muscle force determine performance fatigability. Additionally, voluntary activation seemed to be less affected in male than in female PwMS, and in high versus low intensity contractions.

4.1. Relation between fatigue and fatigability in PwMS

Fatigue is a symptom affected by interactions between perceptions of fatigability and performance fatigability and can be quantified as trait or a state characteristic (Kluger et al., 2013; Enoka and Duchateau, 2016). Both FSS and MFIS questionnaires assess the impact of fatigue on daily life and are methods to quantify fatigue as a trait characteristic. The term perceptions of fatigability (quantified by e.g. a visual analogue scale) reflects the psychological state of the individual and the physiological capacity of the body to maintenance homeostasis whereas performance fatigability reflects the use-dependent decline in performance (Enoka and Duchateau, 2016). Several modulating factors (e.g. blood glucose or core temperature) do not only contribute to changes in perceptions of fatigability or to changes in performance fatigability but can also modulate the interaction between perceptions of fatigability and performance fatigability (Enoka and Duchateau, 2016).

Also, in the present study scores on the MFIS could be explained best by a combination of a modulator of perceived fatigability (HADS depression) and performance fatigability (number of contractions during the 25% condition).

The data obtained during the low intensity contractions propose an association between fatigue (as measured with the questionnaires) and performance fatigability (number of exercise bouts) in PwMS. Although performance of PwMS was not significantly different from controls (Severijns et al., 2014; Thickbroom et al., 2006) and about half of the participants in both groups achieved the maximal number of 30 exercise bouts in the 25% MVC condition, differences in the number of exercise bouts were nevertheless associated with fatigue in PwMS; PwMS with high fatigue scores performed less well. This observation corroborates previous results obtained in sustained maximal contractions (Steens et al., 2012a; Wolkorte et al., 2016) in which fatigue and measures of performance fatigability were shown to be associated in PwMS. In contrast, other authors (Sheean et al., 1997; Thickbroom et al., 2006; see for review, Loy et al., 2017) failed to find associations between measures of fatigue and fatigability, which is supported by the current data obtained during the high intensity contractions. An important difference between the sustained maximal contractions and the high intensity contractions in the present experiment is the fact that in the present experiment subjects were stopped when the MVC dropped below 80% of the initial MVC. During sustained contractions subjects are pushed to maintain maximal effort for a longer time. Although, it is difficult

to differentiate between time- and force-related changes during weak and strong contractions previous data suggests that contraction duration is an important contributor to reduced voluntary activation (Sogaard et al., 2006; Eichelberger and Bilodeau, 2007).

4.2. Different mechanisms affect force decline in PwMS compared to controls

Previous studies have shown that during sustained maximal contractions PwMS have greater difficulty activating their muscle maximally and /or to maintain maximal activation (Sheean et al., 1997; Steens et al., 2012a; Wolkorte et al., 2016). However, only limited data is available on the quality of the voluntary muscle activation during repeated submaximal contractions (Thickbroom et al., 2006). During submaximal contractions, voluntary force is controlled by modulating the number of active motoneurons (i.e. motor units) and the firing rate of these neurons. During weak submaximal contractions the number of motor units is the main control variable whereas during moderate to strong contractions it is modulation of the firing rates (Duchateau and Enoka, 2011). This is especially true for hand-muscles in which all motor units are recruited at or below 50% MVC (Kukulka and Clamann, 1981). Therefore, it is expected that to perform repeated contractions at 25% of MVC, both recruitment and rate gradation are important to maintain the required target force. Research using submaximal contractions at 30% of MVC demonstrated that in control subjects sustaining voluntary muscle activation was difficult and as such, that a larger decline in voluntary activity was seen than during maximal or high intensity contractions (Sogaard et al., 2006; Eichelberger and Bilodeau, 2007). This was confirmed in the present study, in which the voluntary activation was lower and decreased more in the low than in the high intensity condition. The slightly lower voluntary activation would preferentially affect activation of high threshold motor units since these units need the greatest synaptic input to be activated (Kernell, 2003). Therefore, during the 25% condition these units will probably be active only during the intermittent MVCs. During the low intensity condition and in female PwMS reduced voluntary activation will diminish the chance that a high threshold unit becomes active (and thus becomes fatigued). The lower muscle activation during the MVCs would thus result in a smaller decline in intrinsic muscle force. This was visible as a smaller decline in twitch force at rest during the low force condition and in PwMS (Albertas et al., 2011). Similar findings were reported in persons with weakened muscles due to a spinal cord injury (Prak et al., 2015).

During the repeated 80% MVC contractions it is expected that all motor units are active from the start (Kukulka and Clamann, 1981) and that compensation for fatigue-related changes in the muscle fibres comes from rate gradation. Overall the voluntary activation was slightly higher during the 80% condition than the 25% condition which confirms earlier data obtained in control subjects (Sogaard et al., 2006; Eichelberger and Bilodeau, 2007; Taylor and Gandevia, 2007).

Female PwMS had a poorer voluntary activation, however no interaction effect between time or intensity, and group was found. The poorer activation will probably result in a smaller force decline and thus result in a difference in doublet force between (female) PwMS and controls.

4.3. Larger variability between PwMS

Although no differences in the number of exercise sets was observed between PwMS and controls, and about half of both

groups could perform the 25% condition for 30 sets of contractions, it should be noted that three PwMS stopped very early. Additionally, three PwMS were excluded because they were unable to perform the tasks adequately; these results clearly indicate that performing strong repetitive contractions is a difficult task for PwMS. Also, the observation that models which fitted the data best always included random subject effects for both intercept and slope underline the large variability in performance between subjects.

4.4. Limitations and future perspectives

Since membrane properties of active muscle fibres and also the behaviour of motor units within the motoneuron pool change over time, EMG recordings are not capable to capture all fatigue-related changes in the voluntary activation (Dideriksen et al., 2011). Although the twitch superimposition technique has its disadvantages, this technique is more valid than EMG recordings to address voluntary muscle activation during fatiguing contractions (Allen et al., 2004; de Haan et al., 2009; Taylor, 2009; Dideriksen et al., 2011). One disadvantage is that this technique requires maximal voluntary contractions; therefore, we included MVCs after each block of six contractions. Although MVCs were essential to address changes in VA they might have influenced the time course of the force decline.

It is shown that VA declines as a consequence of sedentary behaviour (Shield and Zhou, 2004). A small number of recent studies suggest that resistance training may result in improved VA in controls and in PwMS (Chang et al., 2011). Physical activities in leisure time or amount and type of physical therapy that PwMS engaged in might have confounded results.

One may comment on the different duration of exercising on the individual level. It was chosen to exercise until strength dropped below 80% of the initial MVC. Previous studies, which used a fixed number of exercises (Andreassen et al., 2009), stated that an end point defined by a relative reduction in baseline MVC force could be a better alternative. This made it possible to compare the end data of the 25% and 80% trial.

Further, the characteristics of the sample need to be taken into account. It is known that both the type of MS and the EDSS score, influence voluntary activation, where PwMS with SPMS and a higher EDSS score, show poorer voluntary activation (Sheean et al., 1997; Wolkorte et al., 2016). In our study, the majority of the participants had RRMS and an EDSS score below three, thus mild disability. This might explain the small differences at baseline. Furthermore, our data showed differences in voluntary activation between male and female PwMS. Although there is some data showing sex-related differences in voluntary activation in control subjects (Russ and Kent-Braun, 2003; Martin and Rattey, 2007), we were unable to reproduce this finding (present data; Sars et al., 2018). The observation that voluntary activation differed between male and female PwMS was not presented previously (Albertas et al., 2011); yet the present data demonstrate the need to include sex as a modulating parameter in fatigability studies in both control and clinical populations.

5. Conclusion

Poorer performance in PwMS during low intensity contractions was associated with the symptom of fatigue whereas no association was found during the high intensity contractions. Low intensity contractions were performed for a longer period suggesting that the symptom of fatigue affect performance in PwMS especially during long-lasting or repeated contractions.

Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

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