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**Motor fatigability after low-intensity hand grip exercises in persons with multiple sclerosis.**

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## Abstract

### *Introduction*

During maximal, sustained contractions, persons with multiple sclerosis (PwMS) show higher motor fatigability in comparison with healthy persons. It is not known if motor fatigability is also different between PwMS and healthy persons during low-intensity exercises. Thus, the aim of this study was to determine the difference in hand grip fatigability between healthy persons and PwMS for both hands during low-intensity hand grip exercises.

### *Methods*

19 PwMS and 19 healthy controls performed 18 minutes of hand grip exercises at a maximum of 25% of the maximal voluntary strength, with an electronic hand dynamometer. Perceived fatigability, maximal hand grip strength and muscle activity (electromyography) of the wrist flexors and extensors were recorded in between these exercises for the dominant and non-dominant hand.

### *Results and discussion*

There was a significant decrease in maximal hand grip strength after exercising in both groups and for both hands, mainly situated in the first 6 minutes. In contrast to what was hypothesized, PwMS did not show more decline in strength than healthy controls, neither in the dominant nor the non-dominant hand. There was no group difference in the increase of the perceived fatigability in the dominant hand. However, for the non-dominant hand, the perceived fatigability after exercising increased more in PwMS than in healthy controls. Additionally, there was no relation between fatigue indices, as assessed with short maximal contractions and the strength decline after low-intensity repetitive exercises.


Keywords: hand strength, fatigability, multiple sclerosis, motor fatigue

## 1. Introduction

Multiple sclerosis (MS) is a neurodegenerative disease, causing symptoms such as muscle weakness and fatigue,(Kister et al., 2013) with a large impact on daily life (Fernandez-Munoz et al., 2015). Fatigue can be described as “ a subjective lack of physical and/or mental energy is perceived by the individual or caregiver to interfere with usual and desired activities (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998).Fatigability, on the other hand, is “the magnitude or rate of change in a performance criterion relative to a reference value over a given time of task performance or measure of mechanical output” (Kluger et al., 2013). The change in perception of fatigue after exercising is called perceived fatigability (Enoka and Duchateau, 2016).

Persons with MS (PwMS) experience problems in daily life, for example with grasping or lifting an object, due to upper limb dysfunction (Lamers et al., 2013) . The capacity to fulfil activities in daily living (ADL) is related to maximal hand grip strength (Chen et al., 2007) . It could thus be hypothesized that PwMS will experience even more problems in their ADL if their maximal hand grip strength would decrease further due to pathological motor fatigability.

Indices based on sustained or repetitive maximal contractions (Schwid et al., 1999; Severijns et al., 2015) are mostly described to assess motor fatigability. The assessment with these indices showed that PwMS have more motor fatigability (Djaldetti et al., 1996; Severijns et al., 2015). It is not clear if these indices, based on short maximal isometric strength, are representative for the fatigability after ADL. In daily life, one usually uses repetitive submaximal contractions at a low intensity (Iyengar et al., 2009) and the development of motor fatigability is specific to the demands of the task (Enoka, 1995). There is, however, only limited information available in PwMS on motor fatigability during low-intensity contractions in the upper limb. One study showed that the motor fatigability, measured with a decline in strength after repetitive contractions at 40% of the maximal strength, is not higher in PwMS (Thickbroom et al., 2006), in contrast to the motor fatigability, as assessed with maximal contractions. In contrast, in the lower limbs, submaximal intermittent exercises are able to elicit more strength decline (Thickbroom et al., 2008), which might be related to the different degree of impairment in lower vs. upper limbs (Schwid et al., 1999).

To assess motor fatigability clinically, it was recommended to record maximal strength before and after an exercise protocol (Dobkin, 2008) . In line with this advice, maximal hand grip strength assessments before and after submaximal exercises have been found to be a reliable parameter in healthy persons to document hand grip endurance(Reuter et al., 2011) . The influence of a low intensity exercise protocol on the maximal hand grip strength, as an outcome for motor fatigability in PwMS, has not been studied so far. Previously, it was reported that there was no difference in motor fatigability between the dominant and non-dominant hand during maximal sustained isometric contractions in PwMS (Severijns et al., 2015), but it is not known if this is also the case during low-intensity exercises. Besides maximal strength measures, also electromyography (EMG) parameters are used to indirectly document the presence of motor fatigability in the muscle groups under investigation. EMG assessment of forearm muscles has already been used in healthy subjects to detect signs of muscle fatigue, underlying motor fatigability, both in wrist flexors and wrist extensors after a gripping task (Hagg and Milerad, 1997). There is, however, no report on the use of EMG parameters during a low-intensity hand grip exercise in PwMS.

Therefore we designed a study to determine, both in dominant and non-dominant hands 1) whether PwMS have different motor fatigability from healthy controls (HC), where the hypothesis is that PwMS have more motor fatigability and thus show a larger decline in hand grip strength and 2) whether there is a relation between the short fatigue indices, based on maximal contractions and the strength decline after low-intensity exercises.

## 2. Methods

### ***2.1*** *Participants*

PwMS with a clinical diagnosis of MS according to the McDonald criteria without any exacerbation one month before testing were recruited in the Rehabilitation and MS center Overpelt, Belgium without any specific inclusion criteria for the type of MS, disability level or level of hand function. Age and gender-matched control subjects were recruited within acquaintances of the researchers. Participants who were unable to understand the test instructions or complained of pain in the hands hampering participation in the experiment were excluded. Each participant gave an informed consent before participation in the study. The study was approved by the Ethical committees of the University Hospitals Leuven, Hasselt University and the rehabilitation and MS center Overpelt.

### ***2.2*** *Apparatus*

Both the hand grip strength testing and the hand grip exercises were performed with the digital E-link hand dynamometer (E-link, Biometrics Ltd, Newport, UK), with the handle placed in the second position (Trampisch et al., 2012). The hand grip strength was recorded with arms adducted in the shoulders, elbows flexed at 90°, wrist positioned in the midrange of pronation and supination and neutral wrist posture, according to the recommendations of the American Society of Hand Therapists (ASHT) (Fess, 1982).

To record muscle activity, a wireless electromyography (EMG) system was used. Bipolar and pre-amplified surface electrodes with a fixed distance of 1.0 cm (Trigno wireless system, Delsys Inc., Natick, MA, USA) were used. sEMG was sampled at 2000 Hz, with a bandwidth of 20-450Hz. The common mode rejection rate was >80dB. Delsys EMG Works software, version 4.0.2 (Delsys, Inc., Natick, MA, USA) was used for signal acquisition. Data-analysis was done with custom-made software (using Labview, National Instruments Cooperation, Austin, TX).

### **2.3** Experimental design and protocol

The participants were tested on three days. On the first day, arm function was assessed, the subjects filled out questionnaires and baseline maximal hand grip strength and fatigue indices were recorded.

First, the skin over the muscle bellies under investigation was shaved and wiped with alcohol. EMG electrodes were placed on the m. extensor carpi radialis longus and brevis and on m. flexor carpi radialis (Cram et al., 1998). Hereafter, two maximal hand grips of five seconds were recorded. Then, the participants sustained a 30-seconds maximal hand grip. After two minutes of rest, the participants performed 30 repetitive hand grip contractions. To familiarize the participants with the protocol of the next test days, four times two maximal hand grip contractions of five seconds were done with the dominant hand and the non-dominant hand at T0, T1, T2 and T3, with 10 minutes of rest in-between tests.

On the second and third test-day, the protocol was repeated. However, instead of a rest period in between T0, T1, T2, and T3, the participants performed instrumented hand grip exercises with the E-link activity modules (E-link, Biometrics Ltd, Newport, UK), with three different virtual exercises. The exercise intensity was set at a maximum of 25% of the maximal hand grip strength, determined at T0 on the first testing day. The first exercise was a tracking exercise, where the patients had to follow an object on the computer screen by increasing or decreasing the isometric hand grip strength from 15-25% MVC. The second exercise was a repetitive squeezing exercise with a frequency of 0.5 Hz, where an avatar moved to the bottom of the screen if no strength was delivered and to the top of the screen if the 25% MVC was reached. With the third exercise, the subjects controlled the movement of a basket on the screen, where the right side of the computer screen was reached when squeezing at 25% of the MVC. The three exercises took 2 minutes each, giving a total exercise duration of 6 minutes per bout. In total, after three bouts, participants therefore exercised 18 minutes. The dominant hand (DH) exercised on day two, the non-dominant hand (NDH) exercised on day three. On day two and three, an additional test moment, T4 was added, to see if 10 minutes of rest influenced the maximal hand grip strength.

### ***2.4*** *Descriptive outcome measures*

Age, gender, weight and height were recorded on day one. The score on the Expanded Disability Status Scale (EDSS)(Kurtzke, 1983) was obtained from the treating neurologist. To describe arm function, the Motricity index (Collin and Wade, 1990) and the Box and block test (Mathiowetz et al., 1985) were used. Spasticity in the wrist flexors and extensors was assessed with the Modified Ashworth scale.(Bohannon and Smith, 1987) The Modified Fatigue Impact Scale (MFIS) assessed the perceived impact of fatigue on daily life functioning(Fisk et al., 1994). The Neurological fatigue index for Multiple Sclerosis (NFI-MS)(Mills et al., 2010), was used to document the severity of fatigue in the PwMS.

Furthermore, to assess motor fatigability during maximal contractions, two fatigue indices were calculated, the static fatigue index (SFI) (Surakka et al., 2004) and the dynamic fatigue index (DFI) (Schwid et al., 1999). The SFI is the ratio between the area under the strength curve and the hypothetical area, when no strength decline would occur during 30 seconds maximal grip (Severijns et al., 2015). The DFI, based on 30 intermittent maximal hand grip contractions, is the ratio between the average of the first and the last three contractions, and expressed as a percentage. The rhythm for the 30 intermittent contractions was set at 0.5 Hz, with verbal cueing (contract/release).

### ***2.5*** *Experimental outcomes*

The maximal hand grip strength in kilogram (MVC) was the maximum of two maximal hand grip contractions on T0, T1, T2, T3 and T4. A visual analogue scale (VAS) assessed the perceived fatigability on the same moments as the maximal hand grip contractions, with the question: “How fatigued is your arm at this moment?”, and this on a scale from 0-10. The median frequency (MF) and the Root Mean Square (RMS) of the EMG of the wrist flexors and wrist extensors were calculated during a period of one second around the maximal peak in the EMG signal, sampled during maximal hand grip contractions.

### ***2.6*** *Statistical analysis*

All statistical analyses were performed using SAS JMP Pro 11.2.0 (2013, SAS Institute inc.), with a significance level at 5%. The baseline MVC, static and dynamic fatigue indices were compared between the HC and PwMS with an unpaired student t-test or a Fisher’s exact test for nominal variables.

The experimental outcome measures (MVC, VAS and EMG outcomes) were analyzed with a linear mixed model. Time, referring to test moment (T0-T3) and group (HC vs. PwMS) and the group*time interaction effect were included as fixed effects. A random subject effect was added to the model. To investigate the recovery after 10 minutes of rest, the same model was used, for T3 and T4.

To investigate the potential impact of muscle weakness on motor fatigability during low-intensity hand grip exercises, a subgroup analysis was done in the PwMS. A mixed model was used to analyze the possible different patterns in the decline of maximal strength over time between hands with normal strength and weak hands (group*time effect), according to age and gender matched norm values (Werle et al., 2009).

Further, a correlation analysis was performed between the SFI and the decline in strength after 18 minutes of exercise, to investigate if there is a relation between fatigability during maximal contractions and low-intensity repetitive contractions. To this end, a Pearson product-moment correlation coefficient was calculated between the delta score for the maximal hand grip strength between T0 and T3 and the SFI for both the dominant and non-dominant hand.

## 3. Results

19 PwMS and 19 HC completed the protocol. An overview of the descriptive outcome measures can be found in Table 1.Six PwMS had no clinical impairment of the upper limbs. 4 PwMS did not score below norms for hand grip strength, but had minor problems in one or two upper limbs, shown by a motricity index (MI) below 100 (n=3) and/or the presence of mild tremor (n=2). Four PwMS had a bilateral impairment of the upper limbs, with a weak hand grip (Werle et al., 2009) and a MI below 100. 2 PwMS scored bilaterally below norms for hand grip strength only. 2 PwMS had unilateral impairment (NDH) with a weak hand grip, low MI and mild signs of spasticity. One PwMS had a unilateral impairment (NDH) with moderate tremor and dysmetria.

The maximal hand grip strength was lower in the PwMS, compared to the HC, both for the dominant and the non-dominant hands (DH: $p<0.01$; NDH: $p=0.01$). The SFI was significantly higher in the PwMS compared to the HC for both hands (DH: $p<0.001$ and NDH: $p< 0.01$). The DFI was only higher in PwMS in the non-dominant hand ($p<0.05$).

**Table 1. Descriptive outcome measures**

| Parameter | Healthy controls | Persons with multiple sclerosis | p-value |
|---|---|---|---|
| Age (yrs.) | 56±13 | 56±12 | NS |
| Gender (F/M) | 13/6 | 13/6 | na |
| Weight (kg) | 72.7±17.4 | 69.8±10.2 | NS |
| Height (cm) | 169±9 | 168±7 | NS |
| Disease duration (yrs.) | NA | 15.2±14.3 | na |
| Type of MS (RR/SP/PP) | NA | 8/8/3 | na |
| EDSS score (median, range) | NA | 5 (1.5-7.5) | na |
| Handedness (R/L) | 17/2 | 19/0 | NS |
| MFIS (0-84) | 12±9.3 | 42.6±16.6 | <0.001 |
| NFI-MS summary scale(0-30) | 3.4±3.2 | 10.5±2.1 | <0.001 |
| Motricity index DH (0-100) | 99±2 | 94±10 | 0.03 |
| Motricity index NDH(0-100) | 98±4 | 89±12 | 0.0066 |
| Modified Ashworth Score (median summary score, range) | NA | 0 , 0-1 | na |
| Box and block test DH (# blocks) | 65±9 | 49±11 | <0.001 |
| Box and block test NDH (# blocks) | 65±8 | 47±14 | <0.001 |
| Maximal hand grip strength (Kg) DH | 35±10.1 | 25.7±9.8 | 0.0062 |
| Maximal hand grip strength (Kg) NDH | 32.5±10.2 | 22.9±9.4 | 0.0094 |
| Static fatigue index (%) DH | 29.5±10.0 | 41.6±10.1 | 0.0007 |
| Static fatigue index (%) NDH | 30.7±10.9 | 41.7±9.4 | 0.002 |
| Dynamic fatigue index (%) DH | 22.2±9.9 | 26.3±11.4 | NS |
| Dynamic fatigue index (%) NDH | 24.8±9.2 | 33.3±10.8 | 0.0167 |

NS: Not significant; na: not applicable; RR: relapsing remitting MS; SP: secondary progressive MS, PP: primary progressive MS; DH: dominant hand; NDH: non-dominant hand

### *3.1 Fatigability due to low-intensity exercises in the dominant hand*

The strength at which the PwMS exercised was 6.42±2.4 kg. For the healthy controls, this was 8.8±2.6 kg. The experimental outcomes are shown in Table 2 and are represented schematically in Figure 1, panel A and B.

**Table 2. Strength and perceived fatigability in the upper limb in means and standard deviations for PwMS and healthy controls.**

| | | T0 | T1 | T2 | T3 | T4 |
|---|---|---|---|---|---|---|
| MVC dominant hand (Kg) | HC | 33.9±8.8 | 27.9±6.9 | 27.1±8.1 | 27.1±7.8 | 29.4±7.9 |
| | MS | 26.0±9.6 | 23.4±9.6 | 21.4±10.0 | 21.6±9.9 | 23.1±9.6 |
| %MVC of the dominant hand (in % of the initial MVC) | HC | 96.4±9.9 | 79.2±11.6 | 76.2±10.5 | 77.5±15.9 | 83.4±7.9 |
| | MS | 100.5±13.3 | 89.7±11.9 | 81.6±17.9 | 81.6±15.0 | 87.8±12.7 |
| VAS dominant hand | HC | 1.6±1.8 | 2.3±2.0 | 3.3±2.2 | 3.5±2.3 | 3.0±2.2 |
| | MS | 1.8±1.6 | 4.2±2.5 | 4.6±2.9 | 6.1±3 | 4.9±2.5 |
| MVC non-dominant hand (Kg) | HC | 30.6±10.5 | 29±10.6 | 26.5±9.5 | 25.6±9.8 | 27.9±9.9 |
| | MS | 22.5±9.3 | 19.4±7.9 | 18.6±8.5 | 18.1±8.1 | 21.2±10.1 |
| %MVC of the non-dominant hand (in % of the initial MVC) | HC | 93.6±9.2 | 88.4±19.6 | 80.2±11.9 | 77.3±12.8 | 84.9±9.9 |
| | MS | 96.4±15.7 | 82.3±18.9 | 80.3±23.9 | 77.3±16.4 | 87.9±20.1 |
| VAS non-dominant hand | HC | 0.8±1.3 | 1.9±1.8 | 2.8±2.2 | 3.5±2.6 | 2.2±1.8 |
| | MS | 1.4±1.3 | 3.1±2.1 | 3.3±2.2 | 4.4±2.4 | 3.9±2.4 |

VAS: Visual Analogue Scale; MVC: maximal hand grip strength; %MVC is the relative strength, compared to the baseline maximal strength, assessed on day 1; T0-4: test moments, where T1-3 are assessed after 6 minutes of exercise and T4 is assessed after 10 minutes of rest.

After 18 minutes of hand grip exercises, both groups showed a decline in maximal hand grip strength, with a significant group ($p<0.05$), time ($<0.0001$) and group*time ($p<0.05$) interaction effect. The post hoc tests showed that there was a difference between T0, and T1-2-3 for both PwMS and healthy controls. There was no significant difference between the other time moments, which indicates that the strength decline was mainly situated in the first bout of exercises (T0 vs. T1) and remained stable afterwards. The absolute strength decline was larger in the control group, compared to the PwMS. Both groups showed a similar recovery pattern, since there was no significant group*time interaction effect. The hand grip strength recovered incompletely after 10 minutes of rest. The percentage of strength after 10 minutes of rest (T4) compared to baseline (T0) is 86.9±7.8% for the healthy control group and 89.3 ± 16.2% for the PWMS. The subjective feelings of fatigue increased after exercising ($p<0.0001$) in both groups. The EMG of the forearm extensors and flexors during the maximal contractions, showed a decline in RMS value over time (both: p=<0.0001), without any group or interaction effect. The median frequency of the extensors and flexors showed an increase after exercising, with $p<0.0001$. As shown by the post hoc tests, this increase was mainly situated in the first 6 minutes, since T0 was significantly different from the consequent test moments in both groups (T0 vs T1, 2 and 3) and for both muscles. Average values for all EMG parameters are shown in Table 3.

Although there was a baseline strength difference between weak hands and hands with normal strength in the PwMS (Werle et al., 2009), the subgroups did not respond differently after exercising with their dominant hands, shown by a non-significant group*time interaction effect ($p=0.8422$). As such, PwMS with weak dominant hands did not show a different pattern in the decline of the MVC over time.

**Table 3. EMG parameters from wrist extensors and flexors in means and standard deviations for persons with MS (PwMS) and healthy controls (HC).**

| | | | | | |
|---|---|---|---|---|---|
| | **Root Mean Square (Microvolts)** | | | | |
| | **wrist extensors** | | | | |
| | T0 | T1 | T2 | T3 | T4 |
| HC DH | 129.11±47.83 | 113.2±46.90 | 103.6±41.71 | 104.24±40.71 | 118.85±41.89 |
| PwMS DH | 118.13±84.97 | 88.04±61.74 | 85.11±57.86 | 84.23±51.35 | 89.72±76.81 |
| HC NDH | 101.57±88.41 | 86.11±101.19 | 80.86±78.11 | 79.58±82.85 | 94.76±111.02 |
| PwMS NDH | 99.60±53.44 | 86.39±43.93 | 76.92±32.27 | 83.02±44.91 | 91.74±47.16 |
| | **wrist flexors** | | | | |
| | T0 | T1 | T2 | T3 | T4 |
| HC DH | 123.93±68.68 | 103.88±61.77 | 96.18±50.91 | 101.54±53.20 | 117.19±64.05 |
| PwMS DH | 91.24±59.79 | 77.22±44.64 | 78.24±47.67 | 77.56±50.21 | 81.52±51.14 |
| HC NDH | 55.91±38.80 | 50.55±40.19 | 51.69±44.52 | 55.57±53.64 | 53.30±43.44 |
| PwMS NDH | 90.14±57.06 | 79.58±38.45 | 72.80±36.45 | 75.99±39.71 | 80.49±38.86 |
| | **Median Frequency (Hz)** | | | | |
| | **wrist extensors** | | | | |
| | T0 | T1 | T2 | T3 | T4 |
| HC DH | 94.63±13.59 | 110.75±17.30 | 107.88±21.21 | 107.12±17.67 | 102.30±20.87 |
| PwMS DH | 109.78±17.11 | 113.52±19.61 | 114.67±16.69 | 116.90±23.46 | 113.12±22.62 |
| HC NDH | 92.07±27.51 | 102.62±22.72 | 102.90±24.99 | 100.34±25.04 | 99.31±21.51 |
| PwMS NDH | 89.39±20.76 | 102.32±20.25 | 102.82±25.37 | 100.49±22.20 | 95.14±18.28 |
| | **wrist flexors** | | | | |
| | T0 | T1 | T2 | T3 | T4 |
| HC DH | 72.54±14.51 | 81.54±16.32 | 81.81±17.36 | 82.98±18.26 | 81.80±18.80 |
| PwMS DH | 83.20±24.87 | 87.38±25.16 | 91.86±21.95 | 92.73±26.42 | 87.42±23.00 |
| HC NDH | 86.13±24.25 | 90.11±26.56 | 84.83±22.47 | 89.77±20.73 | 81.79±19.72 |
| PwMS NDH | 70.74±17.82 | 77.92±15.25 | 80.27±22.90 | 77.96±13.15 | 76.87±15.71 |

DH: dominant hand; NDH: non-dominant hand; T0-4: test moments, where T1-3 is assessed after 6 minutes of exercise and T4 is assessed after 10 minutes of rest.

*3.2 Fatigability due to low-intensity exercises in the non-dominant hand*

The maximal strength at which the PwMS exercised was 5.8±2.3 kg. For the healthy controls, this was 8.2±2.5 kg. Average values for strength and perceived fatigability can be found in table 2 and are schematically shown in Figure 1, panel C and D. After 18 minutes of exercises, there was a similar significant decline in both groups (time effect, $p<0.0001$). There was a significant recovery of hand grip strength in both groups after rest (time effect, $p<0.05$). The hand grip strength of the healthy controls recovered to 91.06±11.16%, of the PwMS to 91.7±17.8 % of the initial hand grip strength (T0). The subjective feelings of fatigue in the arm increased over time ($p<0.001$), where PwMS perceived more fatigue over time (group*time interaction: $p<0.01$). After rest, the feelings of fatigue recovered, with the same pattern in healthy controls and PwMS. The EMG amplitude (RMS) of the extensors decreased over time (p<0.0001), and the MDF of the extensors increased over time (p<0.0001). For the flexors, there was no significant time, nor group effect.

Also for the non-dominant hands, a subgroup analysis was performed, to analyze the differences in strength decline over time between weak hands and hands without muscle weakness (Werle et al., 2009). In accordance with the dominant hands, no significant interaction effect was found (group*time effect: p=0.0873), thus weak hands did not show more decline in strength after exercising at 25% of the MVC.

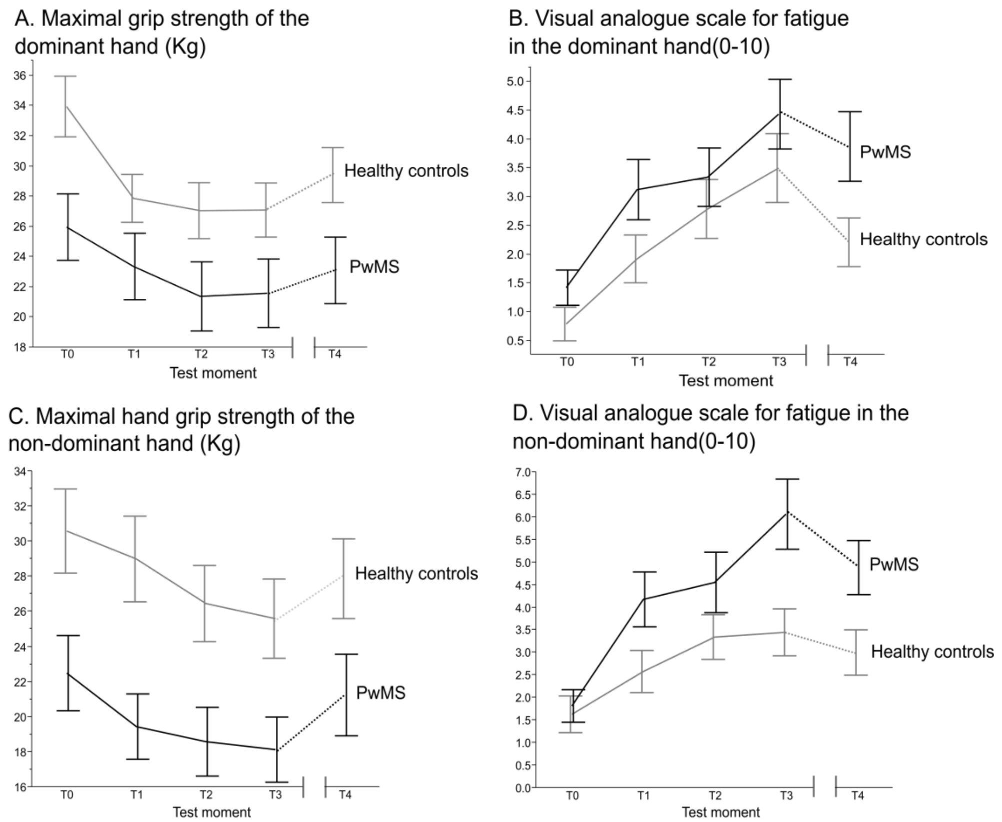


*Figure 1. The strength and perceived fatigability of the dominant and non-dominant hand, shown as means and standard errors. The dashed lines represent a rest period of 10 minutes. Panel A and B show that the decline in strength and increase in perceived fatigability shows the same patterns in PwMS and healthy controls for the dominant hand. Panel C and D show that, although the decline in strength has the same pattern in PwMS and healthy controls, the PwMS experience more perceived fatigability in the non-dominant hand. Kg: kilogram; T0-T4: test 0 to 4.*

*3.3 Correlations between fatigue indices, based on maximal contractions and the strength decline after low-intensity exercises.*

There was no significant correlation between the fatigue indices, based on sustained maximal or intermittent contractions (SFI and DFI) and the delta scores of the strength decline after low-intensity exercises, in healthy controls and for the dominant hand of the PwMS. In the non-dominant hand of the PwMS, there was a significant positive relation between the SFI and the decline in strength after exercising, where a higher SFI correlated with less strength loss during low-intensity exercises ($r=0.53$, $p<0.05$).

## 4. Discussion

In the present study, we investigated fatigability during 18 minutes of hand grip exercises at maximal 25% of the MVC in PwMS and we compared this with HC. In contrast to what was hypothesized, based on previous results during maximal sustained exercises, PwMS did not show more motor fatigability during low-intensity repetitive exercises, based on the decline in maximal strength and EMG parameters. We only found a group difference for the perceived fatigability in the non-dominant hand. PwMS were, however, different from HC, for fatigability during maximal sustained contractions (SFI). PwMS with a wide range of overall disability levels were included and about half of our patients showed reduced hand grip strength in either one or both arms compared to normative data. This confirms the previously reported high prevalence in hand impairment in PwMS in the MS population (Bertoni et al., 2015) where even in PwMS without obvious clinical involvement, hand grip strength is lower than in healthy controls (Iriarte and de Castro, 1998).

To determine motor fatigability, we compared maximal contractions, before and after consecutive exercise bouts of six minutes. This approach has been used before in healthy subjects(Reuter et al., 2011). The significant, although small, strength decline in both healthy controls and PwMS indicates that a short period of low-intensity hand grip exercises can elicit fatigability in both the dominant and non-dominant hand. PwMS did not show more loss of strength during low-intensity exercises, which is in accordance with Thickbroom et al., who reported no difference in force loss between healthy controls and PwMS after repetitive contractions of the first dorsal interosseous muscle at 40% of the MVC for 20 minutes (Thickbroom et al., 2006). For the dominant hand, we even found that the decline in maximal muscle strength in PwMS was significantly smaller than in healthy controls. Since healthy controls exercised with higher absolute hand grip strength, given their higher baseline strength, they might have had more blood flow occlusion in the muscles of the forearm and therefore more peripheral muscle fatigue. This was already stated as an explanation for the difference in endurance between women and men when both groups exercise at the same relative intensity, but men exercise at a greater absolute force(Gonzales and Scheuermann, 2007). The different strength decline between groups disappeared, however, when the absolute values in kilograms were converted to percentages relative to the first MVC. The decrease in maximal strength was mainly situated in the first minutes, where after the strength levelled off, which might be explained by the fact that there is a plateau phase after certain duration of exercises, as was already shown in repetitive maximal isokinetic exercises of the knee (Larsson et al., 2003). The rate of recovery of maximal muscle strength after 10 minutes of rest was the same in HC and PwMS. This confirms previous results after maximal hand grip exercises (Ickmans et al., 2014; Iriarte and de Castro, 1998), showing that recovery capacity of muscle strength in PwMS is not different from HC.

All participants experienced an increased fatigability in the arm during the low-intensity exercises. Previously, PwMS scored the subjective rate of effort higher than controls during a repetitive finger abduction task (Thickbroom et al., 2006). This was only confirmed in the non-dominant hand, where the perceived fatigability increased more in PwMS compared to HC. This might be due to disuse of the non-dominant hand in PwMS (Lamers et al., 2013), which could alter the muscle fiber composition

(Kent-Braun et al., 1997; Wens et al., 2014) and possibly the neural correlates of this hand, or by the fact that the non-dominant hand is the most affected hand in several PwMS.

EMG outcomes were included to detect if the strength decline is caused by muscle fatigue. The RMS, as a measure for the amplitude and the median frequency are most often reported to document muscle fatigue(De Luca, 1984) . In the present study, EMG was sampled during the maximal hand grip contractions, performed in between the exercises. Instead of finding the typical pattern of a decrease in median frequency over time, EMG median frequency of the wrist flexors and extensors increased from the first to the second measurement, where after no changes are seen. These unexpected findings might be explained by the fact that muscle warm-up can alter the frequency of the surface EMG, as already shown during cycling and running exercises, where an initial increase is seen when the activity is not preceded by other exercises (Stewart et al., 2003) . To eliminate this, future research with EMG measures could include a warm-up period. Alternatively, it might be that type 1 fibers, that are recruited during low-intensity exercises and which twitch at a lower frequency, are fatigued after 6 minutes, leading to more recruitment of type 2 fibers during the maximal contractions, twitching at higher frequencies during the following maximal contractions (Goswami et al., 2001). These findings add to the debate on the use of the mean frequency during low-intensity dynamic exercises, where previous reports have concluded that this parameter can increase, decrease or stay stable throughout dynamic exercises (Gerdle et al., 2000). The question remains whether there would have been a decrease when participants exercised more than 18 minutes or when exercises would have been performed at higher workload.

PwMS had, however, more fatigability when assessed with fatigue indices, based on sustained maximal contractions, which confirms previous results (Schwid et al., 1999; Severijns et al., 2015). The group differences during maximal thus high-intensity contractions, but not after low-intensity exercises, might be explained by the fact that during maximal fatiguing contractions, different central mechanisms are used in PwMS compared to healthy controls(White et al., 2009). It might be that PwMS are able to compensate for the reduced neural reserve due to white matter damage during low-intensity exercises, but not during high intensity exercises. Further, it could be related to the fact that other muscle fibers are used. During low-intensity exercises, most likely Type I fibers are recruited, which are fatigue resistant. During maximal contractions, Type II fibers are recruited, with less resistance to fatigue. This confirms that fatigability is task dependent (Enoka, 1995) and that the detection of increased levels of fatigability in PwMS is probably also intensity dependent. This task specificity is also shown by the fact that there were no significant correlations between the fatigue indices (based on maximal contractions) and the delta scores of the MVC after exercising at low intensity.

In conclusion, we did not find more strength loss during low-intensity repetitive exercises of the hand in PwMS, compared to HC. The increase in rating of perceived fatigability was not different between groups for the dominant hand, but it was for the non-dominant hand, which might be caused by less neural reserve for the non-dominant side in PwMS. During 18 minutes of exercise, PwMS can keep up performance as good as healthy controls; therefore, prolonged training with low-intensity exercises is not expected to cause severe fatigability. This is important when, for example, using task-oriented training (Bonzano et al., 2014) by repeating several sets of light weight repetitions. However, further research is necessary to determine the most optimal exercise intensity to avoid excessive fatigability but improve functionality and possibly improve neural plasticity.

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