Upper and lower limb performance fatigability in people with multiple sclerosis investigated through surface electromyography: a pilot study

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Abstract

Objective: Fatigue experienced by people with multiple sclerosis (pwMS) is multidimensional, consisting of different components, such as perceived, physical and cognitive fatigue and performance fatigability. At present, there is no gold standard to assess performance fatigability in pwMS; therefore, we aimed to determine whether, during a fatiguing task, average rectified value (ARV), mean frequency of the power spectrum (MNF), muscle fiber conduction velocity (CV) and fractal dimension (FD) of surface electromyography (sEMG) may be used as indirect indices of performance fatigability. Moreover, we analyzed whether a three-week rehabilitation program impacts on performance fatigability in pwMS, and whether a relationship between sEMG parameters and trait levels of perceived fatigability, before and after rehabilitation, does exist.

Approach: Twenty-one pwMS performed a 20\% maximal voluntary contraction (MVC) of 1 min, and afterwards a 60\% MVC held until exhaustion. sEMG signals were detected from the biceps brachii, vastus medialis and vastus lateralis. Performance fatigability was determined at entry to (\(t_0\)) and discharge from (\(t_1\)) rehabilitation. Perceived fatigability was measured at \(t_0\) and \(t_2\), one month after rehabilitation. Main results: ARV, MNF, CV and FD rates of change showed significant changes at \(t_0\) and \(t_1\) (\(p < 0.05\)) during the high-level contraction in the BB, but rather limited in the vastii muscles. Moreover, rehabilitation did not induce any reductions in either perceived or performance fatigability. No significant correlations between ARV, MNF, CV and FD rates of change during the 60\% MVC and perceived fatigability, at \(t_0\) and \(t_2\), were found. Significance: Our findings suggest that the sEMG parameters are useful for indirectly assessing performance fatigability in pwMS during sub-maximal fatiguing contractions, particularly in the biceps brachii.

Abbreviations

EMG Electromyography
MS Multiple sclerosis
MVC Maximal voluntary contraction
ARV Average rectified value
MNF Mean frequency of the power spectrum
CV Conduction velocity
FD Fractal dimension
VV Vastus medialis and lateralis
BB Biceps brachii
Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system that affects upper motor neurons (Koch-Henriksen and Sorensen 2010). People with multiple sclerosis (pwMS) progressively develop impaired functional and cognitive capacity and reduced physical activity. Although the clinical progression of MS varies widely between individuals (Lublin and Reingold 1996), one of the most common symptoms is represented by high levels of fatigue, experienced by 50%–80% of patients along the disease course (Penner and Paul 2017). MS fatigue is multidimensional, consisting of different components, such as perceived physical and cognitive fatigue and performance fatigability (Zijdewind et al 2016, Hunter 2018). Recently, Kluger et al (2013) suggested adopting a unified taxonomy to guide the assessment and management of fatigue in neurological populations. The taxonomy distinguished between perceived fatigability, which was assessed by self-report scales under different constructs, such as physical or cognitive, or state versus trait, and performance fatigability.

Abnormal performance fatigability of pwMS is caused by reduced central activation and neural drive to the muscles predominately of the lower limbs (Schwid et al 1999) that results in altered motor unit (MU) recruitment and decreased maximal voluntary MU firing rate (Dorfman et al 1989, Zijdewind et al 2016).

At present, there is no gold standard to assess performance fatigability in pwMS; nonetheless, three categories of outcome measures were identified in the systematic review of Severijns et al (2017): (i) strength-based (directly measuring strength decline during a specific task), (ii) indirect (e.g. the inability to maintain a target force), and (iii) neurophysiological outcomes (e.g. the twitch interpolation technique). sEMG was used in one-fifth of the studies (out of 48), where the twitch interpolation technique along with amplitude and spectral variable analysis were used as indicators of performance fatigability. In particular, the authors used root mean square (RMS) and median frequency of the power spectrum (MDF) to quantify the changes in the amplitude and spectral content of the sEMG signal, respectively.

However, to overcome the twitch interpolation technique limitations (e.g. discomfort from stimulation, impossibility to test the neuromuscular function in physiological conditions, contribution of intramuscular processes to superimposed force with fatigue (Gandevia 2001, Beretta-Piccoli et al 2013)), and the low reliability of sEMG amplitude characteristics (Dideriksen et al 2011), the indirect assessment of performance fatigability might be explored using other indicators, such as muscle fiber conduction velocity (CV) or non-linear parameters (Gonzalez-Izal et al 2012). In fact, during isometric constant force contractions, fatigability may be observed through the decay in CV, mainly related to a decrease of the intracellular pH (Komi and Tesch 1979). Moreover, non-linear analysis has proven useful for investigating a variety of physiological time series, such as to detect changes in the complexity of a myoelectric signal during fatiguing contractions using e.g. fuzzy approximate entropy (Xie et al 2010, Chen et al 2018), percentage of determinism (Felici et al 2001) or detrended fluctuation analysis (Hernandez and Camic 2019). In particular, a decrease in the fractal dimension (FD) was associated with fatigability, ageing and disease (Goldberger et al 2002, Gonzalez-Izal et al 2012, Arjunan and Kumar 2013). Findings suggest a possible benefit of the fractal analysis of the sEMG signal as a complementary tool for the evaluation of fatigability during a performance test.

Therefore, the primary aim of this pilot study was to evaluate whether linear and non-linear sEMG parameters are suitable as indirect indicators of performance fatigability in pwMS, during isometric fatiguing contractions of the biceps brachii (BB), vastus medialis (VM) and vastus lateralis (VL) muscles. Moreover, the secondary aims were as follows:

1. to identify whether a three-week rehabilitation program impacts on performance fatigability in pwMS;
2. to evaluate the relationship between sEMG parameters and trait levels of perceived fatigability, measured through the Fatigue Scale of Motor and Cognitive functions (FSMC, Penner et al 2009), before and after rehabilitation. The FSMC assess fatigue symptoms in general during daily life activities, thus it is not intended to be used during inpatient rehabilitation.

The hypothesis was that in both muscle groups, but in particular in VM and VL, the signs of performance fatigability were detectable through the parameters extracted from the sEMG signal, as recently assessed in healthy subjects (Boccia et al 2016, Beretta-Piccoli et al 2017). Moreover, after rehabilitation significant changes in the sEMG fatigue parameters were expected.

Methods

Participants

Inpatients assigned for rehabilitation at the Valens clinic (Switzerland) holding a definite MS diagnosis according to the McDonald criteria (Polman et al 2005), were screened for inclusion on the day of clinical admission
over an eight-month period. Participants underwent general medical screening for study eligibility and were excluded if persistent infections or cardiovascular or pulmonary diseases persisted, they were diagnosed with neurodegenerative disorders other than MS, or had severe disease progression or relapses the day prior to the day of assessment.

Twenty-one participants fulfilled the main study criteria and had an expanded disability status scale (EDSS) score between 1.0 and 5.5. Study participants’ characteristics are listed in Table 1.

All participants had physician clearance, were informed about the study, and gave their written consent before the study started. The study was approved through the regional ethics committee (BASEC Nr. 2016-01002/EKOS 16/080) and was performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

Experimental procedures
Performance fatigability was assessed twice, at entry to (t0) and discharge from (t1) a three-week rehabilitation program in 21 pwMS. Evaluation of perceived fatigability was collected twice under resting conditions: at t0, and at t2, four weeks after rehabilitation (follow-up). Assessments were performed out of the normal rehabilitation program that consisted of two physical therapy and occupational therapy interventions per day and one session of neuropsychological training. Physical therapy consisted of progressive resistance training (45 min) and one low-intensity physiotherapeutic session (30 min). Progressive resistance training focused more on lower limb muscles and consisted of seven exercise sequences held equally for all the participants, four for the lower limbs and three for the upper limbs. Occupational therapy focused on activities of daily living functions (30 min). Neuropsychological training was performed daily for 30 min. The experimental design and patients included are shown in figure 1.

Perceived fatigability
Trait levels of fatigue experienced by participants were quantified using the German version of the FSMC that considers mental and physical factors influencing perceived fatigability (Penner et al 2009). The pwMS were asked to report if fatigue had an impact in general, on 20 different daily functioning situations (not relevant and appropriate to a rehabilitation context). According to the cutoff values of ≥43, ≥53, and ≥63, pwMS may be categorized as mildly, moderately or severely fatigued, respectively.

The questionnaires were handed over to patients by the physical therapists who were also available for explanations and support. Additionally, participants were asked to report the state level of fatigue after the low-intensity contraction, using the modified Borg scale, ranging from 6 to 20 (Borg 1982). The scale was anchored with 6 representing rest or no exertion, and 20 corresponding to the strongest possible effort.

Performance fatigability
The protocol has been shown to induce fatigability in the knee extensor and elbow flexor muscles in healthy subjects, and has been described in detail elsewhere (Beretta-Piccoli et al 2015, 2017). Briefly, participants were asked to perform two maximal voluntary contractions (MVC), separated by 2 min rest, followed by a 20% MVC contraction lasting 1 min and a 60% MVC contraction until the end of endurance. During the contraction participants were verbally encouraged to keep the force level for as long as possible, until the force value decreased below 90% of the target (endurance time, i.e. the time for which a subject is able to maintain the requested mechanical task). The two sub-maximal contractions were separated by 5 min rest.

EMG signals were detected from the right VL, VM, and BB. Due to the fact that upper and lower limb muscles show different degrees of impairment (Schwid et al 1999), and that upper limb disability, on average, develops later in the disease progression (Kister et al 2013), the vastii muscles were chosen as more affected, and the BB as less affected by MS.

Table 1. Patient characteristics.

| Characteristics                  | Values          |
|----------------------------------|-----------------|
| Gender (M/F)                     | 9/12            |
| Age (y)                          | 47 ± 11         |
| Body mass (kg)                   | 68 ± 15         |
| Height (cm)                      | 171 ± 10        |
| EDSS                             | 4.3 ± 1.0       |
| MS phenotype (PP/SP/RR)          | 3/6/12          |

M: male; F: female; EDSS: expanded disability status scale; MS: multiple sclerosis; PP: primary progressive; SP: secondary progressive; RR: relapsing remitting.
Vastus lateralis and medialis
Participants were seated on an ergometer chair (COR1, OT-Bioelettronica, Turin, Italy) equipped with a load cell (Model TF022, CCT Transducers, Turin, Italy), with their knee flexed at 60° and their leg fixed with a strap attached to the chair, 2–3 cm above the lateral malleolus. An adhesive matrix of 64 electrodes (3 mm diameter, 8 × 8 grid, 10 mm interelectrode distance; model ELSCH064NM3; OT-Bioelettronica) was cut into two identical portions along the midline to obtain two arrays of 32 electrodes, which were applied along the direction of the muscle fibers, away from the innervation zone, according to Barbero et al (2012) (figure 2(A)). The ground electrode was placed on the contralateral ankle.

To assure the repeatability of the measurements between t₀ and t₁, at t₀ the positions of the arrays with respect to anatomical references were reported on a transparent sheet. The base of the patella and iliac crest were identified and the line between the two anatomical landmarks was marked on the skin. The repositioning error was estimated to be less than 2 mm.

Biceps brachii
Participants were seated in a height-adjustable chair with their arm positioned on an isometric ergometer (MUC1, OT-Bioelettronica), equipped with an identical load cell (CCT Transducers) as described above. In order to isolate the action of the BB, the wrist was fastened to the ergometer, with the elbow at 120°. To detect the EMG signals, another adhesive matrix of 64 electrodes (OT-Bioelettronica) was positioned, according to Barbero et al (2012), with its distal edge close to the cubital fossa and the midline of the array aligned with the midline of the BB along a line from the cubital fossa to the acromion (figure 2(B)). The ground electrode was placed on the contralateral ankle.

Elbow and knee torque were assessed using a torque meter operating linearly in the range 0–1000 Nm. The torque signals were amplified (MISO II; OT-Bioelettronica) and saved on a computer. The EMG signals, acquired in monopolar configuration, were amplified by a variable factor ranging from 2000 to 5000 (10–750 Hz bandwidth amplifier; EMG-USB2; OT-Bioelettronica). EMGs and the torque signal were digitized synchronously at 2048 samples/s using a 12-bit A/D converter, with 5 V dynamic range, and stored on a computer.

Signal processing
The channels used for CV estimation were selected on the basis of visual inspection of single differential signals, along one of the array columns as previously described (Beretta-Piccoli et al 2017), and their number usually ranged between four and seven (according to Farina et al (2004)). CV was estimated using a multichannel...
algorithm (Farina and Merletti 2003) on single differential signals, based on the matching between signals filtered in the temporal and spatial domains, using non-overlapping signal epochs of 1 s, on the selected channels. Each of the selected signal epochs was used for the estimation of average rectified value (ARV), mean frequency of the power spectrum (MNF) and FD; these variables were averaged across all the selected channels. ARV (a measure of the amplitude) and MNF (a parameter used to quantify the changes in the spectral content of the sEMG signal based on the Fourier transform), were computed offline with numerical algorithms (Merletti et al 1990) using the following calculation formula (Gonzalez-Izal et al 2012):

\[
ARV = \frac{1}{n} \sum_{n} |x_n|
\]

where \(x_n\) are the values of the sEMG signal, and \(n\) is the number of samples.

\[
F = \frac{\int_{f_1}^{f_2} f \cdot PS(f) \cdot df}{\int_{f_1}^{f_2} PS(f) \cdot df}
\]

where \(PS(f)\) is the sEMG power spectrum calculated using Fourier transform, and \(f_1\) and \(f_2\) determine the bandwidth of the surface electromyography (\(f_1 = \) lowest frequency and \(f_2 = \) highest frequency of the bandwidth). FD was estimated using the box-counting method as previously reported (Gitter and Czerniecki 1995). Briefly, a grid of square boxes is used to cover the EMG signal and the number of boxes that the signal passes through is counted. When decreasing the sides of the boxes in a dichotomic process, the number of boxes that are counted increases exponentially. However, by plotting the logarithm of the number of boxes required to cover the signal versus the logarithm of the inverse of the box area, an approximately linear relation is obtained. The slope of the interpolation line (estimated in the least mean squares procedure) is the FD (Mesin et al 2009). Therefore, the following expression defines the FD of the sEMG signal:

\[
FD = \log \frac{N}{\log (1/L)}
\]

with \(N\) the number of boxes required to cover the signal, \(L\) the box side length, and the ratio indicating the slope of the interpolation line.

Performance fatigability was quantified indirectly as the slopes of the considered sEMG variables during the endurance contractions.

Statistics
Linear regression over time was applied to ARV, MNF, CV and FD in order to extract the slopes, which were normalized with respect to their initial values. A Shapiro–Wilk test revealed that the variable distributions deviated from normality; consequently, a non-parametric Wilcoxon signed–rank test was run to determine whether normalized slopes of the considered EMG variables changed between 20% and 60% MVC, and from \(t_0\) to \(t_1\). Moreover, the same test was used to identify differences across the values of MVC, rate of perceived exertion during the 20% MVC and endurance time during the 60% MVC at \(t_0\) compared to \(t_1\). The normalized slopes of the EMG variables from the VL were analyzed together and averaged with data from the VM (VV). In addition, a Pearson’s product-moment correlation was run to assess the relationship between the FSMC score and the sEMG parameters during the endurance contraction.

Finally, to verify whether in pwMS a correlation between the normalized slopes of CV and FD exists, a Spearman’s correlation coefficient (\(r_s\)) test was used. Statistical analysis was performed using SPSS Version 24.0 (SPSS
Inc, Chicago, IL, USA), and significance was set to $\alpha = 0.05$. The results are reported as median and interquartile range.

Results

Twenty-one patients were included and ($n = 20$) completed the study, resulting in a completion rate of 95%. One patient was dismissed before the completion of the full rehabilitation program. No adverse events (relapses) occurred. Two participants were lost to $t_2$.

sEMG parameters

Time courses of FD, CV, MNF and ARV during 20% and 60% MVC are shown in figure 3 for one representative subject. In the BB, both at $t_0$ and $t_1$, the ARV normalized slope was significantly higher at 60% MVC than at 20% MVC ($p \leq 0.05$), whereas significant negative slopes for MNF, CV and FD were observed during the sustained 60% MVC compared with the lower-intensity contraction ($p < 0.001$) (table 2). In contrast, in the VV, only the MNF and CV normalized slopes showed a significant decrease at 60% MVC, respectively at $t_0$ and $t_1$, and at $t_1$ only ($p < 0.005$) (figure 4(A)).

In addition, no significant correlation was observed between FD and CV normalized slopes during the 60% MVC contraction in both muscle groups (BB, $r_s = 0.42$, $p = 0.11$; VV, $r_s = 0.46$, $p = 0.06$).

Effects of rehabilitation on performance fatigability

No statistically significant differences between $t_0$ and $t_1$ in maximal force, rate of perceived exertion or endurance time were assessed for either muscle group (table 3). Significant differences pre- and post-rehabilitation were observed only for normalized slopes of ARV and CV at 20% MVC for the BB ($p = 0.03$) and VV ($p = 0.02$), respectively (figure 4(B)).

Relationship between performance and perceived fatigability

Trait levels of perceived fatigability, as measured with the FSMC questionnaire, were reported as severe, both at $t_0$ and $t_1$ (70.0 ± 15.9 and 65.9 ± 9.0; table 3). At 20% MVC contraction (at $t_0$ and $t_1$), participants estimated their state levels of perceived fatigability through the Borg scale as between fairly light and somewhat hard perceived exertion (table 3). Moreover, no significant correlations were found between the FSMC score and the normalized slopes of ARV, MNF, CV and FD during the 60% MVC at $t_0$ and $t_2$.

Discussion

This pilot study investigated performance fatigability of pwMS through sEMG and perceived fatigability. In contrast to what was hypothesized, the normalized slope of the sEMG variables during the fatiguing contractions were lower in the VV compared to the BB. In addition, although a reduction in the symptoms of fatigue was expected, the rehabilitation program did not induce any relevant changes in the considered outcomes.

Perceived fatigability

Self-reported fatigability remained severe after rehabilitation (table 2). This result is consistent with a previous study on pre-fatigued pwMS at admission that showed no significant changes in perceived fatigability, after a comparable rehabilitation period (Bansi et al 2013).

Performance fatigability

Participants rated their state levels of perceived exertion after the 20% MVC as fairly light to somewhat hard both at $t_0$ and $t_1$. This result was paralleled by the sEMG measurements, which did not show evident signs of fatigability (MNF, CV and FD normalized slopes; table 3) in either the BB or the VV. Surprisingly, during the 60% MVC in the VV, the ARV and FD normalized slopes were no different to those at 20% MVC. Since upper-limb disability on average develops later in MS progression compared to that in lower limbs (Schwid et al 1999), and the included pwMS had an average EDSS of 4.3, we would have expected greater signs of fatigability in the VV. However, it is reasonable to assume that the reduced neural drive led to limited force production and, during the course of contraction, to small changes in the EMG variables in the VV. To the best of our knowledge, only one study has investigated sub-maximal isometric contractions of lower limb muscles in pwMS (average EDSS 3.7), although this was using electrical stimulation (Latash et al 1996). Interestingly, the authors did not find any sign of fatigue at 25% and 50% MVC, hypothesizing that the inability to produce an MVC with the quadriceps muscle was related to the early stages of the demyelination process. Reduced performance fatigability may be also a consequence of less occlusion of blood flow in the VV, due to reduced force production (Sjogaard et al 1988).
Conversely, during the 60% MVC contraction in the BB evident signs of muscle fatigue were measured (i.e. decrease of MNF, CV and FD, and increase in ARV slopes) (Gonzalez-Izal et al 2012). In addition, the MNF and CV slopes (at $t_1$) showed significant differences between the two contraction levels also in the VV (table 3).

Spectral variables were used in several studies as indirect indicators of fatigability in pwMS (Jonkers et al 2004, Korkmaz et al 2011, Severijns et al 2015, Severijns et al 2016), whereas analysis of the behavior of CV was performed only once in pwMS (Scott et al 2011), although it is extensively used in physiological and clinical studies. A possible explanation may be the need for specific operator expertise to estimate CV or the use of multichannel electrodes (Beretta-Piccoli et al 2019).

In the literature, only a few studies have used sEMG parameters to indirectly evaluate performance fatigability in pwMS during or after sub-maximal fatiguing contractions (10% to 40% MVC) (Thickbroom et al 2006, Severijns et al 2015, Wolkorte et al 2015a, Gould et al 2018), although this procedure has been widely used in healthy subjects.

In contrast, the decline in MVC torque has generally been used as index of performance fatigability, although one could question that this procedure may not be representative of fatigability after activities in daily living, where mainly sub-maximal contractions are performed. However, in the study of Severijns et al (2016) isometric

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**Table 2. Results of the sEMG variables.**

| Biceps brachii | $t_0$ (baseline) | $t_1$ (discharge) | $t_0$ (baseline) | $t_1$ (discharge) |
|----------------|------------------|------------------|------------------|------------------|
| ARV (%/s)      | 0.14 (0.83)      | 0.95 (1.31)      | 2.896            | 0.39 (0.50)      | 1.00 (2.67)      | −1.895           | 0.0043           |
| MNF (%/s)      | −0.08 (0.12)     | −0.71 (0.44)     | −3.920           | 0.00009          | −0.06 (0.10)     | −0.69 (0.51)     | −3.920           | 0.00009          |
| CV (%/s)       | −0.04 (0.06)     | −0.69 (0.45)     | −3.361           | 0.001            | −0.05 (0.19)     | −0.64 (0.42)     | −3.516           | 0.0004           |
| FD (%/s)       | −0.02 (0.02)     | −0.14 (0.09)     | −3.920           | 0.00008          | −0.02 (0.03)     | −0.14 (0.12)     | −3.621           | 0.00003          |

| Vastii muscles | $t_0$ (baseline) | $t_1$ (discharge) | $t_0$ (baseline) | $t_1$ (discharge) |
|----------------|------------------|------------------|------------------|------------------|
| ARV (%/s)      | 0.44 (0.51)      | 0.46 (0.74)      | −0.373           | NS               | 0.74 (0.89)      | 0.32 (0.68)      | −0.859           | NS               |
| MNF (%/s)      | −0.06 (0.12)     | −0.13 (0.17)     | −3.061           | 0.002            | −0.05 (0.14)     | −0.12 (0.14)     | −3.248           | 0.001            |
| CV (%/s)       | −0.004 (0.09)    | −0.041 (0.15)    | −1.590           | NS               | −0.005 (0.11)    | −0.10 (0.14)     | −3.114           | 0.002            |
| FD (%/s)       | −0.003 (0.03)    | −0.02 (0.02)     | −1.867           | NS               | −0.01 (0.03)     | −0.02 (0.03)     | −1.605           | NS               |

Normalized slope (with respect to the initial value) of ARV, mean frequency of the power spectrum (MNF), muscle fiber CV and FD, calculated during isometric contractions at 20% and 60% of MVC. Values are indicated as median (interquartile range). NS: not significant.

Conversely, during the 60% MVC contraction in the BB evident signs of muscle fatigue were measured (i.e. decrease of MNF, CV and FD, and increase in ARV slopes) (Gonzalez-Izal et al 2012). In addition, the MNF and CV slopes (at $t_1$) showed significant differences between the two contraction levels also in the VV (table 3).

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In contrast, the decline in MVC torque has generally been used as index of performance fatigability, although one could question that this procedure may not be representative of fatigability after activities in daily living, where mainly sub-maximal contractions are performed. However, in the study of Severijns et al (2016) isometric
Hand grips were performed and performance fatigability was also assessed as the change over time of amplitude and spectral parameters during maximal contractions performed in between sub-maximal exercises. Surprisingly, pwMS did not show more performance fatigability compared to controls, contrary to what was determined during MVCs (Severijns et al 2017).

Performance fatigability after rehabilitation

PwMS underwent the usual three-week rehabilitation program, which did not elicit any reduction in performance fatigability (figure 4(B)). Moreover, the rehabilitation program did not change the FSMC score, MVC torque or endurance time. Therefore, although during the 20% MVC contraction the ARV and CV normalized slopes showed significant increases at \( t_1 \) in the BB and in the VV respectively, these changes are clinically meaningless (table 2). Previous studies have reported conflicting results regarding fatigability after a short rehabilitation period in pwMS (e.g. Gehlsen et al 1984, Surakka et al 2004, Hameau et al 2018). Moreover, as stated above, since most studies used different protocols, and fatigability is task and muscle dependent (Bigland-Ritchie et al 1995, Enoka and Duchateau 2008), it is difficult to make comparisons (Severijns et al 2017).

At least two hypotheses can be made for these results: (i) the selected progressive resistance training was unable to improve strength, which was suggested to also increase neural drive (Fimland et al 2010) and, thus, reduce performance fatigability indirectly; (ii) since the sEMG outcomes at \( t_0 \) in the VV were reduced, and rehabilitation did not improve MVC torque, any changes in the MNF and CV normalized slopes at \( t_1 \) would have been negligible.

Relation between performance and perceived fatigability

No significant correlation was found between the FSMC score and the normalized slope of the considered sEMG parameters during the 60% MVC before and after rehabilitation.

Recent studies performed during sub-maximal contractions presented contradictory results: the studies (Dodd et al 2011, Wolkorte et al 2015a, Severijns et al 2016), performed in lower limb, forearm and finger muscles respectively, did not identify a significant correlation between performance and perceived fatigability, similar to the results of the present study. However, Wolkorte et al (2015b) found a significant association between fatigability during sub-maximal finger abductions and perceived fatigability; their result may be explained by the fact that fatigability was assessed as strength decline in pwMS, after correcting for their MVCs.

The findings of this pilot study must be interpreted in the context of a number of potential limitations. First, a control group of participants without MS was not included, which limits the interpretation of the results. A second limitation is generalizability, as the sample size was small and mainly focused on relapsing-remitting phenotypes. In addition, we studied performance fatigability of leg muscles that are more prone to showing signs
of deconditioning related to diminished muscle usage and muscle weakness. Thus, the results of the VV should be treated with caution, since deconditioning may contribute to an increased perception of fatigability of the participants.

Conclusions

In summary, this pilot study showed that ARV, MNF, CV and FD may be used to detect fatigability in pwMS during a performance task. Notably, the results revealed a paradoxical reduced performance fatigability in the VV, probably due to the impaired MU recruitment (a physiological condition required for a valid analysis of fatigability using sEMG) in the lower limb muscles in pwMS, or to an inappropriate intensity for the sub-maximal contraction. Given the central role of lower limbs in the disability of pwMS, future studies should identify other solutions/approaches to detect changes in the sEMG signal during a fatiguing task involving lower limb muscles.

Conflict of interest

The authors declare that there is no conflict of interest.

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References

Arjunan S P and Kumar D K 2013 Age-associated changes in muscle activity during isometric contraction Muscle Nerve 47 545–9
Bansi J, Bloch W, Gamper U, Riedel S and Kesselring J 2013 Endurance training in MS: short-term immune responses and their relation to cardiorespiratory fitness, health-related quality of life, and fatigue J. Neurol. 260 2993–3001
Barbero M, Rainoldi A and Merletti R 2012 Atlas of Muscle Innervation Zones (New York: Springer)
Beretta-Piccoli M, Cescon C, Barbero M and D’Antona G 2019 Reliability of surface electromyography in estimating muscle fiber conduction velocity: a systematic review J. Electromyogr. Kinesiol. 48 53–68
Beretta-Piccoli M, D’Antona G, Barbero M, Fisher B, Diel-Cornwright CM, Clijisen R and Cescon C 2015 Evaluation of central and peripheral fatigue in the quadriceps using fractal dimension and conduction velocity in young females PLoS One 10 e0123921
Beretta-Piccoli M, D’Antona G, Zampella C, Barbero M, Clijisen R and Cescon C 2017 Test–retest reliability of muscle fiber conduction velocity and fractal dimension of surface EMG during isometric contractions Physiol. Meas. 38 616–30
Bigland-Ritchie B, Rice C L, Garland S I and Walsh M I 1995 Task–dependent factors in fatigue of human voluntary contractions Adv. Exp. Med. Biol. 384 361–80
Physiol. Rev. Gandevia S C 2001 Spinal and supraspinal factors in human muscle fatigue

Felici F, Rosponi A, Sbriccoli P, Filligoi G C, Fattorini L and Marchetti M 2001 Linear and non-linear analysis of surface electromyograms in

Farina D, Zagari D, Gazzoni M and Merletti R 2004 Reproducibility of muscle-fiber conduction velocity estimates using multichannel

J. Physiol. Dodd K J, Taylor N F, Shields N, Prasad D, McDonald E and Gillon A 2011 Progressive resistance training did not improve walking but can

Chen Y, Hu H, Ma C, Zhan Y, Chen N, Li L and Song R 2018 Stroke-related changes in the complexity of muscle activation during obstacle
crossing using Fuzzy approximate entropy analysis Frontiers Neurol. 9 131

Dideriksen J L, Enoka R M and Farina D 2011 Neuromuscular adjustments that constrain submaximal EMG amplitude at task failure of

Goldberger A L, Amaral L A, Hausdorff J M, Ivanov P, Peng C K and Stanley H E 2002 Fractal dynamics in physiology: alterations with

effects of an aquatic fitness program on the muscular strength and endurance of patients with multiple sclerosis Phys. Ther. 64 653–7

Gitter J A and Czerniecki M J 1995 Fractal analysis of the electromyographic interference pattern J. Neurosci. Methods 58 103–8

Goldberger A L, Amaral L A, Hausdorff J M, Ivanov P, Peng C K and Stanley H E 2002 Fractal dynamics in physiology: alterations with
disease and aging Proc. Natl. Acad. Sci. USA 99 2466–72

Gonzalez-Izal M, Malanda A, Corostenga E and Izquierdo M 2012 Electromyographic models to assess muscle fatigue J. Electromyogr.

Koch-Henriksen N and Sorensen P S 2010 The changing demographic pattern of multiple sclerosis epidemiology Lancet Neurol. 9 520–32

Koom P Y and Tesch P 1979 EMG frequency spectrum, muscle structure, and fatigue during dynamic contractions in man Eur. J. Appl.

Korkmaz N C, Kirdi N, Temucin C M, Armutlu K, Yakut Y and Karabudak R 2011 Improvement of muscle strength and fatigue with high

Koch-Henriksen N and Sorensen P S 2010 The changing demographic pattern of multiple sclerosis epidemiology Lancet Neurol. 9 520–32

Koom P Y and Tesch P 1979 EMG frequency spectrum, muscle structure, and fatigue during dynamic contractions in man Eur. J. Appl.

Kuster I, Chamot E, Salter A R, Cutter G R, Bacon T E and Herbert J 2013 Disability in multiple sclerosis: a reference for patients and

Kluger B M, Krupp L B and Enoka R M 2013 Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy Neurology

Koch-Henriksen N and Sorensen P S 2010 The changing demographic pattern of multiple sclerosis epidemiology Lancet Neurol. 9 520–32

Koom P Y and Tesch P 1979 EMG frequency spectrum, muscle structure, and fatigue during dynamic contractions in man Eur. J. Appl.

Korkmaz N C, Kirdi N, Temucin C M, Armutlu K, Yakut Y and Karabudak R 2011 Improvement of muscle strength and fatigue with high

voltage pulsed galvanic stimulation in multiple sclerosis patients Clin. Physiol. Funct. Imaging 19 292–38

Kister I, Knauth M and De Luca C J 1990 Myoelectric manifestations of fatigue in voluntary and electrically elicited contractions J. Appl.

Cochrane-Janzen N and Sorensen P S 2010 The changing demographic pattern of multiple sclerosis epidemiology Lancet Neurol. 9 520–32

Koom P Y and Tesch P 1979 EMG frequency spectrum, muscle structure, and fatigue during dynamic contractions in man Eur. J. Appl.

Korkmaz N C, Kirdi N, Temucin C M, Armutlu K, Yakut Y and Karabudak R 2011 Improvement of muscle strength and fatigue with high

voltage pulsed galvanic stimulation in multiple sclerosis patients— a non-randomized controlled trial J. Pak. Med. Assoc. 61 736–43

Lataf M, Kalugina E, Nichols J, Orpett C, Stefoski D and Davis F 1996 Myogenic and central neurogenic factors in fatigue in multiple

Lublin F D and Reingold S C 1996 Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple

sclerosis society (USA) advisory committee on clinical trials of new agents in multiple sclerosis Neurology 46 907–11

Merletti R, Knauth M and De Luca C J 1990 Myoelectric manifestations of fatigue in voluntary and electrically elicited contractions J. Appl.

Merletti R, Knauth M and De Luca C J 1990 Myoelectric manifestations of fatigue in voluntary and electrically elicited contractions J. Appl.

Physiology 80 1018–14

Knauth M, Krupp L B and Enoka R M 2013 Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy Neurology

Koch-Henriksen N and Sorensen P S 2010 The changing demographic pattern of multiple sclerosis epidemiology Lancet Neurol. 9 520–32

Koom P Y and Tesch P 1979 EMG frequency spectrum, muscle structure, and fatigue during dynamic contractions in man Eur. J. Appl.

Korkmaz N C, Kirdi N, Temucin C M, Armutlu K, Yakut Y and Karabudak R 2011 Improvement of muscle strength and fatigue with high

voltage pulsed galvanic stimulation in multiple sclerosis patients— a non-randomized controlled trial J. Pak. Med. Assoc. 61 736–43

Lublin F D and Reingold S C 1996 Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple

sclerosis society (USA) advisory committee on clinical trials of new agents in multiple sclerosis Neurology 46 907–11

Merletti R, Knauth M and De Luca C J 1990 Myoelectric manifestations of fatigue in voluntary and electrically elicited contractions J. Appl.

Merletti R, Knauth M and De Luca C J 1990 Myoelectric manifestations of fatigue in voluntary and electrically elicited contractions J. Appl.

Physiology 80 1018–14

Mesin L, Cascon C, Gazzoni M, Merletti R and Rainoldi A 2009 A bi-dimensional index for the selective assessment of myoelectric

manifestations of peripheral and central muscle fatigue J. Electromyogr. Kinesiol. 19 851–63

Penner I K and Paul F 2017 Fatigue as a symptom or comorbidity of neurologic diseases Nat. Rev. Neurol. 13 662–75

Penner I K, Rasciutti C, Stocklin M, Opwis K, Kappos L and Calabrese P 2009 The fatigue scale for motor and cognitive functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue Mult. Scler. 15 1509–17

Polman C H et al 2005 Diagnostic criteria for multiple sclerosis: 2005 revisions to the ‘McDonald Criteria’ Ann. Neurol. 58 840–6

Schwind R, Thornton C A, Pandya S, Manzur K L, Sianjak M, Petrie M D, McDermott M P and Goodman A D 1999 Quantitative assessment

of motor fatigue and strength in MS Neurology 53 743–50

Scott S M, Hughes A R, Galloway S D and Hunter A M 2011 Surface EMG characteristics of people with multiple sclerosis during static

cissions of the knee extensors Clin. Physiol. Funct. Imaging 31 11–7

Severijns D, Lammers M, Theolen R and Feyes P 2016 Motor fatigue characterized by low-intensity hand grip exercises in persons with multiple

sclerosis Mult. Scler. Relat. Disord. 10 7–13

Severijns D, Octavia J R, Kerklofs L, Comix K, Lamers I and Feyes P 2015 Investigation of fatigabilityduring repetitive robot-mediated arm

training in people with multiple sclerosis PLoS One 10 e0135729

Severijns D, Zijdewind I, Dalgas U, Lamers I, Lismont C and Feyes P 2017 The assessment of motor fatigability in persons with multiple

sclerosis: a systematic review Neurorehabil. Neural Repair 31 413–31

Sjogaard G, Savad G and Juel C 1988 Muscle blood flow during isometric activity and its relation to muscle fatigue Eur. J. Appl. Physiol.

Occup. Physiol. 57 327–35

Surakka J, Römberg, Å, Ruttainen J, Aunola S, Virtanen A, Karppi S-L and Mänttäka K 2004 Effects of aerobic and strength exercise on

motor fatigue in men and women with multiple sclerosis: a randomized controlled trial Clin. Rehabil. 18 737–46

10
Thickbroom G W, Sacco P, Kermode A G, Archer S A, Byrnes M L, Guilfoyle A and Mastaglia F L 2006 Central motor drive and perception of effort during fatigue in multiple sclerosis J. Neurol. 253 1048–53
Wolkorte R, Heersema D J and Zijdewind I 2015a Muscle fatigability during a sustained index finger abduction and depression scores are associated with perceived fatigue in patients with relapsing-remitting multiple sclerosis Neurorehabil. Neural Repair 29 796–802
Wolkorte R, Heersema D J and Zijdewind I 2015b Reduced dual-task performance in MS patients is further decreased by muscle fatigue Neurorehabil. Neural Repair 29 424–35
Xie H B, Guo J Y and Zheng Y P 2010 Fuzzy approximate entropy analysis of chaotic and natural complex systems: detecting muscle fatigue using electromyography signals Ann. Biomed. Eng. 38 1483–96
Zijdewind I, Prak R F and Wolkorte R 2016 Fatigue and fatigability in persons with multiple sclerosis Exerc. Sport Sci. Rev. 44 123–8