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

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ABSTRACT

Objective Fatigue experienced by persons with multiple sclerosis (pwMS) is multidimensional, consisting of different components, such as perceived, physical and cognitive fatigue and performance fatigability. Actually, there is no gold standard to assess performance fatigability in pwMS; therefore, we aimed at determining if 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 the sEMG may be used as indirect indices of performance fatigability. Moreover, we analyzed if a 3-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 biceps brachii, vastus medialis and lateralis. Performance fatigability was determined at entry (t_0) and discharge (t_1) to 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 at t_0 and t_1 significant changes ($p<0.05$) during the high level contraction in the biceps brachii, whereas rather limited in the vastii muscles. Moreover, rehabilitation did not induce any reductions nor in perceived neither in 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, was found.

Significance Our findings suggest that the sEMG parameters are useful to indirectly assess performance fatigability in pwMS during sub-maximal fatiguing contractions, particularly in the biceps brachii.

Keywords:

- multiple sclerosis
- surface electromyography
- fatigability
- pilot study

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). Persons 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 symptom is represented by high levels of fatigue, experienced by 50-80% of the 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 (Hunter, 2018; Zijdewind *et al* 2016). Recently, Kluger *et al*. (2013) suggested to adopt a unified taxonomy to guide the assessment and management of fatigue in neurologic 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 units (MUs) recruitment and decreased maximal voluntary MU firing rate (Zijdewind *et al* 2016; Dorfman *et al* 1989).

Actually, 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): (1) strength-based (directly measuring a strength decline during a specific task), (2) indirect (e.g. the inability to maintain a target force) and (3) neurophysiological outcomes (e.g. the twitch interpolation technique). sEMG was used in a fifth of the studies (out of 48), where the twitch interpolation technique along with amplitude and spectral variables 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* 2015)), 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 been prove 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. the fuzzy approximate entropy (Xie *et al* 2010; Chen *et al* 2018), the percentage of determinism (Felici et al 2001) or the detrended fluctuation analysis (Hernandez and Camic, 2019). In particular, a decrease in the fractal dimension (FD) was associated to fatigability, ageing and disease (Arjunan and Kumar, 2013; Goldberger *et al* 2002; Gonzalez-Izal *et al* 2012). 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 if 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:

(1) to identify whether a 3-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 hypotheses were 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 (Beretta-Piccoli *et al* 2017; Boccia *et al* 2016). Moreover, after rehabilitation significant changes in the sEMG fatigue parameters were expected.

METHODS

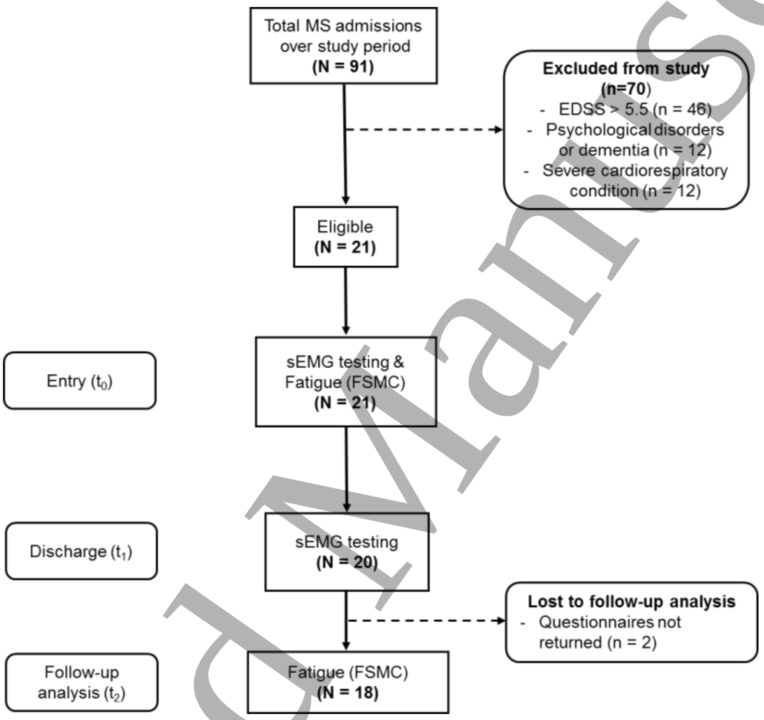

Figure 1. Flowchart of experimental design and patients included. EDSS expanded disability status scale; N, total number of participants; sEMG, surface electromyography; FSMC, fatigue scale of motor and cognitive functions.

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, 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 assessments.

Twenty-one participants fulfilled the main study criteria and of 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.

Table 1: Patient characteristics.

Characteristics	
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.

Experimental procedures

Performance fatigability was assessed twice, at entry (t_0) and discharge (t_1) to a 3-week rehabilitation program in 21 pwMS. Evaluation of perceived fatigability was collected twice under resting conditions: at t_0, and at t_2, 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 minutes) and one low intensity physiotherapeutic session (30 minutes). Progressive resistance training focused more on lower limb muscles and consisted in six exercise sequences held equal for all the participants, four for the lower limb and three for the upper limb. Occupational therapy focused on activities of daily living functions (30 minutes). Neuropsychological training was performed daily for 30 minutes. The experimental design and patients included are shown in figure 1.

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). PwMS were asked to report if fatigue had an impact in general, on twenty different daily functioning situations (not relevant and appropriate to a rehabilitation context). According to the cutoff values of ≥43, ≥53, ≥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.

2. Performance fatigability

The protocol showed to induce fatigability in the knee extensor and elbow flexor muscles in healthy subjects, and was described in detail elsewhere (Beretta-Piccoli *et al* 2015; Beretta-Piccoli *et al* 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 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 degree of impairments (Schwid *et al* 1999), and that upper limb disability is, on average, developing later in the disease progression (Kister *et al* 2013), the vastii muscles were chosen as more affected, whereas the BB as less affected by MS.

A) Vastus lateralis and medialis

Participants were seated on a 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, 8x8 grid, 10 mm interelectrode distance; model ELSCH064NM3; OT-Bioelettronica) was cut in two identical portions along the midline to obtain two arrays of 32 electrodes, that were applied along the direction of the muscle fibers, away from the innervation zone, according to (Barbero *et al* 2012) (figure 2A). The ground electrode was placed on the contralateral ankle.

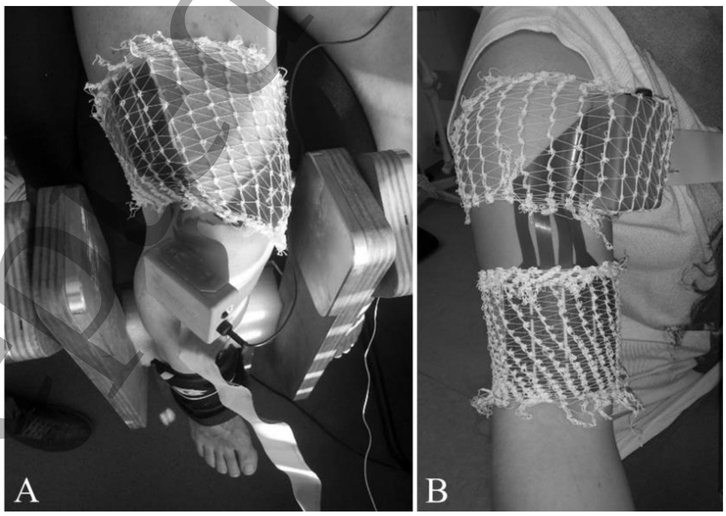

Figure 2 sEMG signals were recorded from vastus lateralis and medialis (A) as well as biceps brachii (B) during isometric contractions of the right leg, respectively arm. EMG was recorded using bi-dimensional arrays of 64 electrodes. The array was cut in two parts for vastus medialis and lateralis.

To assure the repeatability of the measurements among t_0 and t_1, at t_0 the position of the arrays with respect to anatomical references was reported on a transparent sheet. The base of patella and iliac crest were identified and the line between the two anatomical landmarks was marked on the skin. The re-positioning error was estimated to be less than 2 mm.

B) 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 electromyographic 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 BB along a line from the cubital fossa to the acromion (figure 2B). The ground electrode was placed on the contralateral wrist.

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 2,000 to 5,000 (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 4 and 7 (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 in the 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 among 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 off-line 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.

$$MNF = \frac{\int_{f1}^{f2} f \cdot PS(f) \cdot df}{\int_{f1}^{f2} PS(f) \cdot df}$$

where PS(f) is the sEMG power spectrum calculated using Fourier transform, and f1 and f2 determine the bandwidth of the surface electromyography (f1 = lowest frequency and f2 = 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 side 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 squared procedure) is the FD (Mesin et al 2009). Therefore, the following expression defines the FD of the sEMG signal:

$$FD = \log N / \log (1/L)$$

with N the number of boxes required to cover the signal, L the box side, 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, non-parametric Wilcoxon signed-rank test was run to determine if 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 VL were analyzed together and averaged with data from 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 if 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 $\alpha=0.05$. Results are reported as median and interquartile range.

RESULTS

21 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.

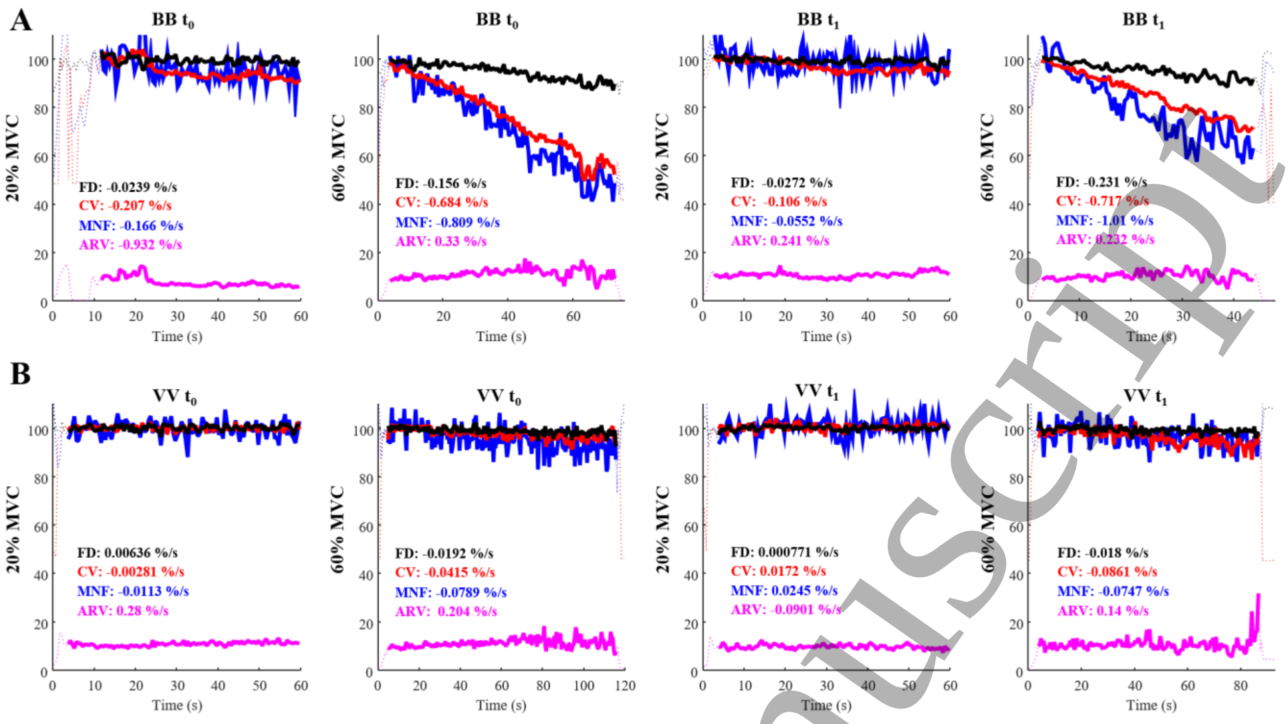

Figure 3 Time course of fractal dimension (FD), muscle fiber conduction velocity (CV), mean frequency of the power spectrum (MNF) and average rectified value (ARV) for a representative participant at t_0 and t_1. Surface EMG signals were detected from the biceps brachii (A) and vastus medialis and lateralis (B) using bi-dimensional arrays during isometric contractions at 20% and 60% MVC. Data are normalized with respect to their initial values. ARV values were divided by a factor 10 due to graphical reasons.

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, 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). On the contrary, in the VV, only MNF and CV normalized slope showed a significant decrease at 60% MVC, respectively at t_0 and t_1, and at t_1 only ($p<0.005$) (figure 4A).

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, $r_s = 0.46$, $p = 0.06$).

Table 2: Results of the sEMG variables.

Biceps brachii		***t_0* (baseline)**				***t_1* (discharge)**			
		20% MVC	**60% MVC**	*Z*	*p-value*	**20% MVC**	**60% MVC**	*Z*	*p-value*
ARV	(%/s)	0.14 (0.83)	0.95 (1.31)	-2.896	0.004	0.39 (0.50)	1.00 (2.67)	-1.895	0.050
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)**			
		20% MVC	**60% MVC**	*Z*	*p-value*	**20% MVC**	**60% MVC**	*Z*	*p-value*
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 average rectified value (ARV), mean frequency of the power spectrum (MNF), muscle fiber conduction velocity (CV) and fractal dimension (FD), calculated during isometric contractions at 20% and 60% of maximal voluntary contraction (MVC). Values are indicated as median (interquartile range). NS: not significant.

Effects of rehabilitation on performance fatigability

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

Table 3: Descriptive outcome measures at different time points.

	time point	*delta*	*p-value*

		t_0 *(baseline)*	t_1 *(discharge)*	t_2 *(follow-up)*		
Perceived fatigue	FSMC_C	30.3 ± 9.0		30.0 ± 11.8	-0.3	0.46
	FSMC_M	39.4 ± 8.4		35.9 ± 11.9	-3.5	0.21
	FSMC_S	70 ± 15.9		65.9 ± 9.0	-4.1	0.23
MVC (kg)	BB	22.9 ± 9.9	23.6 ± 10.5		+0.7	0.47
	VV	35.9 ± 19.0	36.9 ± 20.4		+1	0.60
RPE (Borg)	BB	11.1 ± 2.4	11.4 ± 2.1		+0.3	0.48
	VV	11.8 ± 2.8	12.2 ± 2.2		+0.4	0.77
ET (s)	BB	35.1 ± 17.5	39.1 ± 20.7		+4	0.41
	VV	50.7 ± 19.5	48.4 ± 19.1		-2.3	0.58

FSMC: fatigue scale for motor and cognitive functions; _C: cognitive subscale; _M: motor subscale; _S: sum score of scales; MVC: maximal voluntary contraction; BB: biceps brachii; VV: vastus medialis and lateralis; RPE: rate of perceived exertion at 20% MVC; ET: endurance time at 60% MVC. Data are expressed as mean ± SD.

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_2 (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.

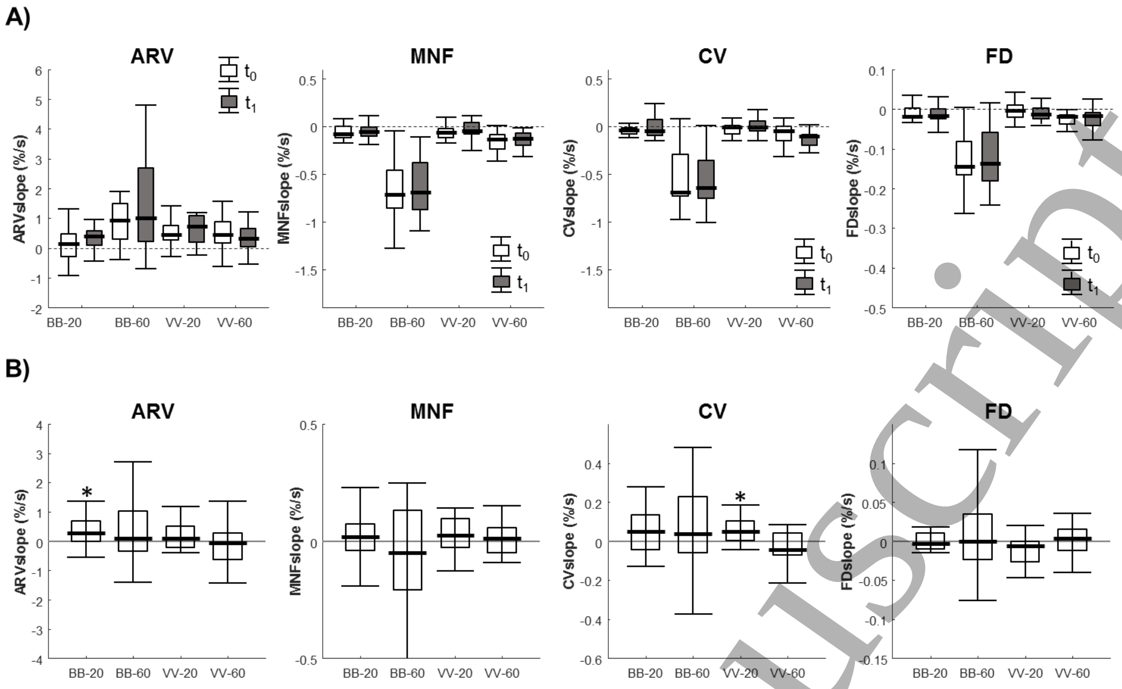

Figure 4. Box-and-whisker plots of the slopes (normalized with respect to their initial values) of average rectified value (ARV), mean frequency of the power spectrum (MNF), conduction velocity (CV) and fractal dimension (FD) during the 20% and 60% MVC of biceps brachii (BB) and vastus medialis and lateralis (VV). Results of the t_0 and t_1 measurements are represented either through white and grey box-and-whiskers, respectively (A) and as the difference between t_1 and t_0 for the considered sEMG parameters values (B). Asterisk denotes statistical significance ($p < 0.05$).

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) both in the BB and in the VV. Surprisingly, during the 60% MVC in the VV, ARV and FD normalized slopes were not different compared to those at 20% MVC. Since upper limb disability is on average developing later in MS progression compared to the lower limb (Schwid *et al* 1999), and the included pwMS had an average EDSS 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 a study investigated sub-maximal isometric contractions of lower limb muscles in pwMS (average EDSS 3.7), though 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, 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 of specific operator expertise to estimate CV or the use of multichannel electrodes (Beretta-Piccoli *et al* 2019).

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

On the contrary, in general, the decline in MVC torque was used as index of performance fatigability, although one could question that this procedure may not be representative for the 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 assessed also 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 a usual 3-week rehabilitation program which did not elicit any reduction in performance fatigability (figure 4B). Moreover, the rehabilitation program did not change the FSMC score, MVC torque and the endurance time. Therefore, although during the 20% MVC contraction 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: (1) 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. (2) Since the sEMG outcomes at t_0 in the VV were reduced, and rehabilitation did not improve MVC torque, any changes in 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; Severijns *et al* 2016; Wolkorte *et al* 2015a) 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 had mainly focused relapsing-remitting phenotypes. In addition, we studied performance fatigability of leg muscles that are more prone to show 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 MUs 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 for lower limbs in the disability of pwMS, future studies should identify other solution/approach to detect changes in the sEMG signal during a fatiguing task involving lower limbs muscles.

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

CONFLICT OF INTEREST

The Authors declare that there is no conflict of interest.

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REFERENCES

Arjunan SP, Kumar DK 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, Dieli-Conwright C M, Clijsen 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, Clijsen R and Cescon C 2017 Test-retest reliability of muscle fiber conduction velocity and fractal dimension of surface EMG during isometric contractions *Physiological measurement* **38** 616-30

Bigland-Ritchie B, Rice C L, Garland SJ, Walsh M L 1995 Task-dependent factors in fatigue of human voluntary contractions *Adv Exp Med Biol* **384** 361-380

Boccia G, Dardanello D, Beretta-Piccoli M, Cescon C, Coratella G, Rinaldo N, Barbero M, Lanza M, Schena F and Rainoldi A 2016 Muscle fiber conduction velocity and fractal dimension of EMG during fatiguing contraction of young and elderly active men *Physiological measurement* **37** 162-74

Borg G A 1982 Psychophysical bases of perceived exertion *Medicine and science in sports and exercise* **14** 377-81

Chen Y, Hu H, Ma C, Zhan Y, Chen N, Li L, Song R 2018 Stroke-Related Changes in the Complexity of Muscle Activation during Obstacle Crossing Using Fuzzy Approximate Entropy Analysis. *Front Neurol* **9**:131

Dideriksen J L, Enoka R M and Farina D 2011 Neuromuscular adjustments that constrain submaximal EMG amplitude at task failure of sustained isometric contractions *Journal of applied physiology* **111** 485-94

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 improve muscle performance, quality of life and fatigue in adults with multiple sclerosis: a randomized controlled trial *Mult Scler* **17** 1362-74

Dorfman L J, Howard J E and McGill K C 1989 Motor unit firing rates and firing rate variability in the detection of neuromuscular disorders *Electroencephalogr Clin Neurophysiol* **73** 215-24

Enoka R M and Duchateau J 2008 Muscle fatigue: what, why and how it influences muscle function *J Physiol* **586** 11-23

Farina D and Merletti R 2003 A novel approach for estimating muscle fiber conduction velocity by spatial and temporal filtering of surface EMG signals *IEEE transactions on bio-medical engineering* **50** 1340-51

Farina D, Zagari D, Gazzoni M and Merletti R 2004 Reproducibility of muscle-fiber conduction velocity estimates using multichannel surface EMG techniques *Muscle Nerve* **29** 282-91

Felici F, Rosponi A, Sbriccoli P, Filligoi GC, Fattorini L, Marchetti M 2001 Linear and non-linear analysis of surface electromyograms in weightlifters *Eur J Appl Physiol* **84** 337-42

Fimland M S, Helgerud J, Gruber M, Leivseth G and Hoff J 2010 Enhanced neural drive after maximal strength training in multiple sclerosis patients *Eur J Appl Physiol* **110** 435-443

Gandevia S C 2001 Spinal and supraspinal factors in human muscle fatigue *Physiol Rev* **81** 1725-89

Gehlsen G M, Grigsby S A and Winant D M 1984 Effects of an aquatic fitness program on the muscular strength and endurance of patients with multiple sclerosis *Phys Ther* **64** 653–657

Gitter J A and Czerniecki M J 1995 Fractal analysis of the electromyographic interference pattern *Journal of neuroscience 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 *Proceedings of the National Academy of Sciences of the United States of America* **99 Suppl 1** 2466-72

Gonzalez-Izal M, Malanda A, Gorostiaga E and Izquierdo M 2012 Electromyographic models to assess muscle fatigue *J Electromyogr Kinesiol* **22** 501-12

Gould J R, Reineberg A E, Cleland B T, Knoblauch K E, Clinton G K, Banich M T, Corboy J R and Enoka R M 2018 Adjustments in Torque Steadiness During Fatiguing Contractions Are Inversely Correlated With IQ in Persons With Multiple Sclerosis *Frontiers in physiology* **9** 1404

Hameau S, Bensmail D, Roche N and Zory R 2018 Adaptations of fatigue and fatigability after a short intensive, combined rehabilitation program in patients with multiple sclerosis *J Rehabil Med* **50** 59-66

Hernandez LR, Camic CL 2019 Fatigue-Mediated Loss of Complexity is Contraction-Type Dependent in Vastus Lateralis Electromyographic Signals *Sports* **7** pii: E78

Hunter S K 2018 Performance Fatigability: Mechanisms and Task Specificity *Cold Spring Harbor perspectives in medicine* **8**

Jonkers I, Nuyens G, Seghers J, Nuttin M and Spaepen A 2004 Muscular effort in multiple sclerosis patients during powered wheelchair manoeuvres *Clinical biomechanics (Bristol, Avon)* **19** 929-38

Kister 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 clinicians *Neurology* **80** 1018-24

Kluger B M, Krupp L B and Enoka R M 2013 Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy *Neurology* **80** 409-16

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

Komi P V and Tesch P 1979 EMG frequency spectrum, muscle structure, and fatigue during dynamic contractions in man *Eur J Appl Physiol Occup Physiol* **42** 41-50

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 *JPMA. The Journal of the Pakistan Medical Association* **61** 736-43

Latash M, Kalugina E, Nicholas J, Orpett C, Stefoski D and Davis F 1996 Myogenic and central neurogenic factors in fatigue in multiple sclerosis *Mult Scler* **1** 236-41

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, Knaflitz M and De Luca C J 1990 Myoelectric manifestations of fatigue in voluntary and electrically elicited contractions *Journal of applied physiology* **69** 1810-20

Mesin L, Cescon 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 neurological diseases *Nature reviews. Neurology* **13** 662-75

Penner I K, Raselli 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, Reingold S C, Edan G, Filippi M, Hartung H P, Kappos L, Lublin F D, Metz L M, McFarland H F, O'Connor P W, Sandberg-Wollheim M, Thompson A J, Weinshenker B G and Wolinsky J S 2005 Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria" *Ann Neurol* **58** 840-6

Schwid S R, Thornton C A, Pandya S, Manzur K L, Sanjak 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 contractions of the knee extensors *Clin Physiol Funct Imaging* **31** 11-7

Severijns D, Lemmens M, Thoelen R and Feys P 2016 Motor fatigability after low-intensity hand grip exercises in persons with multiple sclerosis *Multiple sclerosis and related disorders* **10** 7-13

Severijns D, Octavia J R, Kerkhofs L, Coninx K, Lamers I and Feys P 2015 Investigation of Fatigability during Repetitive Robot-Mediated Arm Training in People with Multiple Sclerosis *PloS one* **10** e0133729

Severijns D, Zijdewind I, Dalgas U, Lamers I, Lismont C and Feys P 2017 The Assessment of Motor Fatigability in Persons With Multiple Sclerosis: A Systematic Review *Neurorehabil Neural Repair* **31** 413-31

Sjogaard G, Savard 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, Romberg A, Ruutiainen J, Aunola S, Virtanen A, Karppi S-L and Mäentaka 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** 737–746

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 *Annals of biomedical engineering* **38** 1483-96

Zijdewind I, Prak R F and Wolkorte R 2016 Fatigue and Fatigability in Persons With Multiple Sclerosis *Exercise and sport sciences reviews* **44** 123-8