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Quantifying muscle fatigue during walking in people with multiple sclerosis

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ABSTRACT

Background: This study aimed to examine muscle fatigue in lower leg muscles in of people with multiple sclerosis and healthy controls, and whether muscle fatigue coincided with potential changes in gait.
Methods: In this case-control study, people with multiple sclerosis (n = 8; 3male; mean age (SD) = 49.7 (9.6) yr) and age-matched healthy controls (n = 10; 4male; mean age (SD) = 47.4 (8.7) yr) walked on a treadmill for 12-min at self-paced speed. Muscle fatigue was indirectly quantified by a decrease in median frequency and increase in root mean square of surface electromyographic recordings of lower leg muscles. Walking speed, ankle push-off power and net ankle work were calculated from marker positions and force plate data using inverse dynamic calculations.
Results: People with multiple sclerosis showed larger decreases in median frequency of soleus (most affected leg: $p = 0.003$; least affected leg: $p = 0.009$) and larger increases in root mean square of soleus (most and least affected leg: $p = 0.037$), gastrocnemius medialis (most affected leg: $p = 0.003$; least affected leg: $p = 0.005$) and lateralis (most and least affected leg: $p < 0.001$) compared to controls. Walking speed ($p = 0.001$), ankle push-off power (most affected leg: $p = 0.018$; least affected leg: $p = 0.001$) and net work around the ankle (most affected leg: $p = 0.046$; least affected leg: $p = 0.001$) were lower in people with multiple sclerosis compared to controls, but increased in both groups.
Interpretation: The results yield preliminary evidence that soleus muscles of people with multiple sclerosis fatigue during prolonged walking. Changes in electromyography of gastrocnemius muscles could however be related to muscle fatigue, changes in gait or a combination.

1. Introduction

Multiple sclerosis (MS) is described as a progressive neurodegenerative disorder of the central nervous system, caused by axonal degeneration and demyelination (Trapp and Nave, 2008). MS can have a substantial impact on physical functioning, activity and participation (Beckerman et al., 2013). In clinical practice, people with MS (PwMS) have reported that problems with walking serve as a major contributor to their disability (Swingler and Compston, 1992; Weinshenker et al., 1989). In addition, approximately 75% of PwMS have been shown to experience clinically significant walking disturbances (Hobart et al., 2001; Swingler and Compston, 1992), including patients with only mild symptoms in relatively early disease stages. The increased recognition of the importance of limited gait performance in PwMS has led to a substantial growth in the literature on this topic, showing limited walking speed, cadence, stride length, etc. (Comber et al., 2018; Goldman et al., 2008; Phan-Ba et al., 2011; Sosnoff et al., 2011; Sosnoff et al., 2012).

The working mechanisms behind limited gait performance in PwMS are complex and multiple impairments have been suggested to contribute to this (Motl and Learmonth, 2014). Recent studies increasingly point to a reduced ankle push-off power as an important contributor to

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limited gait performance (Davies et al., 2017; Huisinga et al., 2013; Kempen et al., 2016). Neurologically induced impairments of ankle dorsi- and plantar flexor muscles, such as muscle weakness, spasticity and altered muscle recruitment have been suggested to contribute to reduced ankle push-off power and foot clearance (Heine et al., 2019; Huisinga et al., 2013; Leone et al., 2016; Thickbroom et al., 2008). In addition, Davies et al. (2017) showed that ankle plantar flexion force was related to mobility of PwMS. Furthermore, reduced mechanical work generated around the ankle joint has been observed in PwMS (Davies et al., 2016). These findings indicate that neurological impairments of ankle dorsi- and plantar flexor muscles contribute to diminished (instant) gait performance in PwMS.

Besides limited gait performance, research has shown that PwMS often experience a decline in gait performance during prolonged walking, known as walking-related motor fatigue (Leone et al., 2016). The functional impact of motor fatigue has been mainly addressed by investigating whether PwMS slowed down during prolonged walking tests (Phan-Ba et al., 2012; Schwid et al., 1999). In addition, Wagner et al. (2014) showed that weakness of plantar flexor muscles was negatively associated with distances of prolonged walking during a 6-minute walk test (Wagner et al., 2014). Furthermore, previous research showed that ankle dorsiflexor muscles are also susceptible to muscle fatigue (Thickbroom et al., 2008), which could result in reduced foot clearance (Benedetti et al., 1999; Martin et al., 2006). The higher proportion of maximum force that PwMS have to generate due to muscle weakness may potentially lead to muscle fatigue during prolonged walking (Wagner et al., 2014). Limited research has however been performed on changes in walking performance *during* prolonged walking in PwMS (Heine et al., 2019; Severijns et al., 2017) and it is not clear yet whether muscles of PwMS fatigue during prolonged walking. Therefore, this study examined muscle fatigue-related changes in surface electromyography (EMG) of lower leg muscles in PwMS and healthy controls, and whether these changes coincide with potential changes in walking speed, ankle push-off power and ankle work. We hypothesized that more muscle fatigue-related changes occur in lower leg muscles of PwMS than of healthy controls. In case muscle fatigue occurs, associated changes are expected in walking performance, such as a decrease in walking speed, ankle push-off power and work around the ankle.

2. Methods

2.1. Participants

This case-control study was part of an exercise intervention study (Heine et al., 2019), in which a convenience sample of ten PwMS was recruited from the Amsterdam University Medical Centers, Location VUmc, Department of Rehabilitation Medicine and MS Center Amsterdam, the Netherlands. PwMS were included if they were aged between 18 and 70 years, diagnosed with definite MS, able to walk continuously for 12 min without walking aid, and reported to experience a current decline in walking performance during prolonged walking. PwMS were excluded if they had serious comorbidity, an MS-relapse < 3 months prior to testing, other medical conditions affecting gait or if they were pregnant. For the full inclusion description, see Heine et al. (2019). Disease severity was determined using the Expanded Disability Status Scale by a certified rehabilitation physician (EDSS (Kurtzke, 1983)). Healthy age- and gender-matched adults with no motor impairments were recruited as controls (healthy controls). The study protocol was approved by the Medical Ethics Committee of the VU University Medical Center, Amsterdam, the Netherlands (METc 2015.343) and written consent of each participant was obtained prior to testing.

2.2. 12 minute walking test

All participants were instructed to walk for 12 min at their self-selected comfortable walking speed on a split-belt instrumented treadmill (Gait Real-time Analysis Interactive Lab; (GRAIL); Motekforce Link, Amsterdam, the Netherlands). Prior to the walking test, participants had a familiarization period of 2 min to get comfortable with the split-belt treadmill. A minimum of 10 min rest was accommodated after the familiarization period. Surface electromyography (EMG) of the lower leg muscles *M. tibialis anterior* (TA), *M. gastrocnemius medialis* (GM), *M. gastrocnemius lateralis* (GL) and *M. soleus* (SOL) sampled at 1000 Hz were recorded bilaterally using wireless EMG (Cometa, Milan, Italy). Electrode placement and skin preparations were performed according to the Surface Electromyography for the Non-Invasive Assessments of Muscles (SENIAM) guidelines (Hermens et al., 2000).

The speed of the belt was adjusted in real-time based on a speed correction, which was proportional to the difference between participant's position on the belt and the middle of the belt, in order to match the individual walking speed (Sloot et al., 2014). Ground reaction forces were obtained using two force plates (ForceLink BV, the Netherlands) embedded in both treadmill belts (50 cm × 200 cm) at 1000 Hz. Forty-two reflective markers were placed on the lower extremities and trunk according to the BodyMech model to collect 3D motion data, captured at 100 Hz, using a 10-camera optoelectronic system (Vicon Oxford Metrics, Oxford, United Kingdom) (Cappozzo et al., 1995). All participants wore their regular footwear (trainers or other flat shoes). PwMS were asked to report the leg in which they experienced the most and the least MS-related problems. EMG recordings were online synchronized with the marker and force plate recordings.

2.3. Data processing

Muscle fatigue-related changes were obtained from EMG recordings that were off-line processed using Matlab (Matlab, The Mathworks, Inc., version R2010b, Natick, MA, USA). A decrease in median frequency (EMG-mf) and an increase in root mean square (EMG-rms) have widely been determined to occur during muscle fatigue (De Luca, 1984; Kallenberg and Hermens, 2008). Movement artefacts were removed from the EMG recordings by applying a high pass filter of 5 Hz (second-order bidirectional Butterworth). A notch filter (50 Hz and its harmonics 100 Hz, 200 Hz, etc., second-order bidirectional Butterworth,) was applied to remove power line noise. Median frequency (EMG-mf) of the power spectrum was determined using Fast Fourier Transformation for each gait cycle individually. EMG signals were then rectified and low-pass filtered (second-order bidirectional Butterworth at 5 Hz) to obtain smoothed rectified EMG envelopes, from which the EMG-rms was determined for each individual cycle. For TA, EMG-mf and EMG-rms were determined during the swing phase and for GM, GL and SOL during stance phase, based on their main contributions in the gait cycle (Kempen et al., 2016).

Marker and force plate data were low-pass filtered at 6 Hz. Initial contact and toe-off values were based on vertical ground reaction forces and used to identify individual strides. Strides with foot placement on both belts could not be analysed and were excluded from further analysis. Self-paced walking speed was obtained from the belt speed. Marker and force plate data were used to determine stride length, stride time, step width and stance percentage. Net ankle joint power was calculated using in-house Matlab-based biomechanics software, following CAMARC anatomical frame definitions (www.bodymech.nl) (Cappozzo et al., 1995).

Walking speed (m/s) was averaged per minute. Ankle push-off power (in W) was calculated for the least and most affected leg separately for PwMS, and for the right leg only for the healthy controls. The peak in the ankle push-off power during the stance phase was identified, and normalized to bodyweight (W/kg). Work done was calculated as the integral under the power curve for the ankle power (before time-normalising). This was defined as the period in late stance during which ankle power generation occurred. The net work done (positive work done minus negative work done) was taken as the outcome measure.

For each minute of the 12-minute walk test, data were included when there were at least six valid gait cycles. A valid cycle was defined as a cycle where the foot was fully within the boundary of one force plate during the stance phase – i.e. no crossing between the two force plates.

2.4. Statistical analysis

Differences in participants' characteristics between PwMS and healthy controls were identified using a Mann-Whitney *U* test or chi square tests (χ^2). EMG-mf, EMG-rms, ankle push-off power and ankle work averaged over the first minute were observed to be normally distributed. Therefore, the rate of change in EMG-mf, EMG-rms, walking speed as function of time (in minutes) and ankle push-off power and net work around the ankle as function of gait cycle were analysed using mixed linear models analysis. Separate models were constructed for each variable and each muscle separately. EMG-mf, EMG-rms, walking speed, power or work was set as the dependent variable and group and the time/gait cycle number were set as the independent variables. An interaction term of group * time/gait cycle was added to the model to investigate whether the change in dependent variables (of the least and most affected leg) of PwMS was different from the controls. Significance was set at $p < 0.05$. All analyses were performed using SPSS (version 20).

3. Results

3.1. Participants

EMG recordings of two out of ten PwMS were incorrect because of technical reasons and could not be included. Therefore, eight PwMS and ten healthy controls were included in the final analyses. Four PwMS were diagnosed with primary progressive MS, two were diagnosed with secondary progressive MS and two were diagnosed with relapsing-remitting MS. On average, PwMS walked significantly slower than HCs ($p < 0.001$; Table 1). No differences in participants' characteristics were found between groups (Table 1).

3.2. EMG parameters

Results of the mixed models analysis to investigate changes in EMG-mf and EMG-rms are presented in Fig. 1 and Table 2. For EMG-mf and EMG-rms of SOL, the interaction terms for group * gait cycle were significant for both the least and most affected leg of PwMS, indicating more signs of muscle fatigue. Regarding SOL, EMG-mf increased in controls and decreased in PwMS, and the increase in EMG-rms was larger in PwMS. While EMG-rms of both GM and GL decreased in controls (not significant in GM), it increased significantly in both the least and most affected leg of PwMS, resulting in a significant interaction effect. No significant changes in EMG-mf and EMG-rms were observed in TA in both controls and PwMS. The variation in regression coefficients of EMG-mf and EMG-rms was larger in both the least and most affected leg of PwMS, as presented by the 95% CI (Fig. 1 and Table 2).

Table 1
Descriptives of PwMS and control group. Data expressed as mean (SD).*

Parameter	PwMS (n = 8)	Control (n = 10)	p
Gender (male/female)	3/5	4/6	
Age; mean (SD) (yr:mo)	49:9 (9:5)	47:5 (8:8)	0.631
Height (m)	1.8 (0.1)	1.8 (0.1)	0.853
Weight (kg)	82.4 (21.3)	75.0 (13.0)	0.436
Walking speed ($m \cdot s^{-1}$)	1.0 (0.3)	1.5 (0.1)	< 0.001*
EDSS median [range]	2.75 [1.0–6.0]	n/a	

Abbreviations: PwMS, people with multiple sclerosis; EDSS, Expanded Disability Status Scale.
* $p < 0.05$

3.3. Walking speed, power, work and changes over time

Ankle push-off power and net work could not be calculated for certain gait cycles, specifically where participants stepped with both feet on one force plate. The average number of gait cycles taken into account was 350 (SD 18) for PwMS (23% missing), and 296 (SD 20) for controls (20% missing).

Significant group effects were found in walking speed ($p = 0.001$), ankle push-off power (most affected leg: $p = 0.001$; least affected leg: $p = 0.018$) and net work around the ankle (most affected leg: $p = 0.001$; least affected leg: $p = 0.046$), showing that ankle push-off power and net work were lower both the least and most affected leg of PwMS compared to controls (Table 3: intercept). Mixed models analyses showed that walking speed, ankle push-off power and net work around the ankle increased with time, similarly in PwMS and controls (Figs. 2 & 3; Table 3).

4. Discussion

This study aimed to examine muscle fatigue-related changes in PwMS and age- and gender matched healthy controls during prolonged walking over 12 min. In addition, changes in walking speed, ankle push-off power and work were examined to capture any potential associated changes in walking performance. PwMS showed a larger decrease in EMG-mf of SOL and increase in EMG-rms of SOL, GM and GL compared to healthy controls during 12 min walking, which indicates more muscle fatigue-related changes in PwMS compared to healthy controls. These findings are consistent with expectations that muscle fatigue occurs during prolonged walking in PwMS, more than in controls, which could be related to MS.

The presence of muscle fatigue in PwMS during walking is consistent with results of previous research, in which various other methods were used to compare muscle fatigue between PwMS and controls (Severijns et al., 2017), such as electrical stimulation (Lenman et al., 1989; Sharma et al., 1995; Steens et al., 2012), ambulatory fatigue indexes (Burschka et al., 2012; Schwid et al., 1999), and fatigue indexes in concentric or isometric contractions (Kalron et al., 2011; Latash et al., 1996; Schwid et al., 1999; Skurvydas et al., 2011; Thickbroom et al., 2008). The findings of the current study confirm that muscle fatigue of calf muscles also occurs *during* prolonged walking in PwMS, which could be one of the contributors of walking-related motor fatigue often reported in PwMS. Furthermore, muscle fatigue could contribute to increased self-reported fatigue that PwMS experience during daily life (Compston and Coles, 2008).

Although changes in both EMG-mf and EMG-rms confirmed the presence of muscle fatigue in SOL muscles, this muscle fatigue was not accompanied by concurrent changes in outcomes of walking performance. On the contrary, walking speed, ankle push-off power and work increased over the course of 12-min walking, in both PwMS and healthy controls. Especially EMG-rms is directly related to ankle work and walking speed, while a decrease in EMG-mf has been identified as a more robust measure for muscle fatigue (Dimitrova and Dimitrov, 2003). Because of these changes in walking performance, it is not clear yet whether muscle fatigue of the SOL muscle was due to the increase in walking speed, whether it generally occurs during walking in PwMS in daily life, or both. In addition, changes in GM and GL were limited to an increase in EMG-rms, and hence could also be related to the changes in walking performance, rather than to fatigue. Nevertheless, although changes in walking performance were similar in both groups, fatigue-related changes in EMG only occurred in PwMS, which could suggest that muscle fatigue was related to MS. In addition, the increase in EMG-rms in GM of the least affected leg of PwMS was accompanied by a decrease in EMG-mf, which could also indicate the presence of muscle

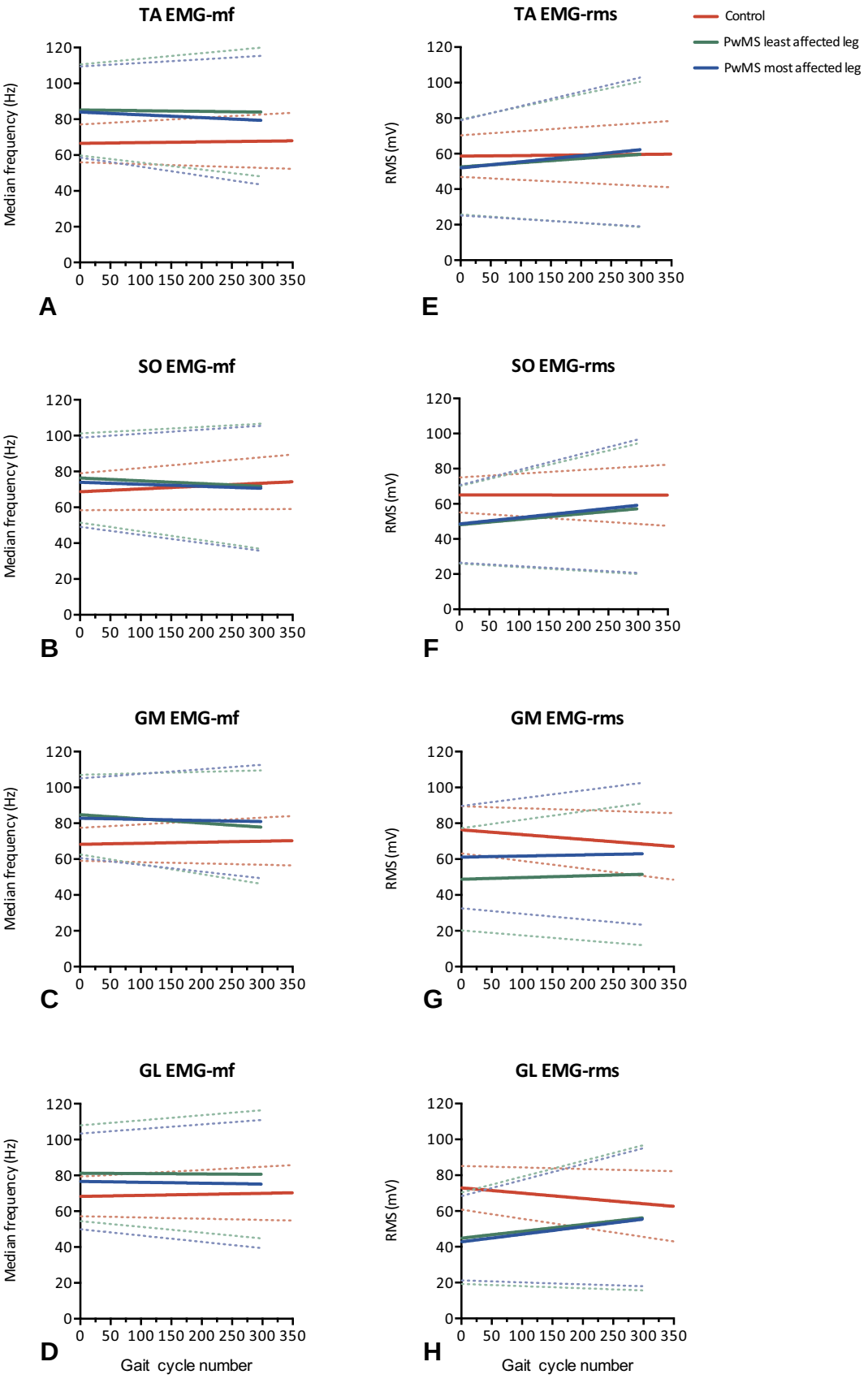

Fig. 1. Results of mixed models analyses representing the changes in EMG-mf and EMG-rms of TA (A and E), SOL (B and F), GM (C and G) and GL (D and H) for controls (red line), least affected leg of PwMS (green line) and most affected leg of PwMS (blue line). Tick lines represent the average changes for each group, while dotted lines represent 95% confidence intervals. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Mixed linear model to identify the change in EMG-mf and EMG-rms per gait cycle in age- and gender matched healthy controls, the least affected leg and most affected leg of PwMS.

Variable	EMG-mf (Hz)			EMG-rms (mV)		
Muscle: TA	**β**	**95% CI**	**p value**	**B**	**95% CI**	**p value**
Intercept	66.536	55.993 to 77.078	< 0.001	58.627	46.906 to 70.349	< 0.001
Group (controls = ref)						
PwMS least affected leg	***18.624***	***3.715 to 33.533***	***0.020***	-6.092	-21.160 to 8.977	0.417
PwMS most affected leg	***17.468***	***2.559 to 32.377***	***0.024***	-6.622	-21.700 to 8.457	0.378
Gait cycle	$0.400 \cdot 10^{-2}$	$-1.067 \cdot 10^{-2}$ to $1.087 \cdot 10^{-2}$	0.574	$0.317 \cdot 10^{-2}$	$-1.675 \cdot 10^{-2}$ to $2.310 \cdot 10^{-2}$	0.744
Gait cycle * group (controls = ref)						
Gait cycle * PwMS least affected leg	$0.788 \cdot 10^{-2}$	$-2.852 \cdot 10^{-2}$ to $1.277 \cdot 10^{-2}$	0.433	$2.052 \cdot 10^{-2}$	$-0.707 \cdot 10^{-2}$ to $4.812 \cdot 10^{-2}$	0.137
Gait cycle * PwMS most affected leg	$-1.950 \cdot 10^{-2}$	$-4.015 \cdot 10^{-2}$ to $0.114 \cdot 10^{-2}$	0.063	$2.420 \cdot 10^{-2}$	$-0.336 \cdot 10^{-3}$ to $5.170 \cdot 10^{-2}$	0.082
Muscle: SOL	**β**	**95% CI**	**p value**	**B**	**95% CI**	**p value**
Intercept	68.685	58.361 to 79.009	< 0.001	65.079	55.103 to 75.055	< 0.001
Group (controls = ref)						
PwMS least affected leg	7.670	-6.928 to 22.269	0.284	***-16.991***	***-29.137 to -4.844***	***0.007***
PwMS most affected leg	5.294	-9.304 to 19.893	0.456	***-16.487***	***-28.641 to -4.334***	***0.009***
Gait cycle	$\boldsymbol{0.159 \cdot 10^{-2}}$	$\boldsymbol{0.195 \cdot 10^{-2}}$ ***to*** $\boldsymbol{2.994 \cdot 10^{-2}}$	***0.028***	$-0.051 \cdot 10^{-2}$	$-2.185 \cdot 10^{-2}$ to $2.082 \cdot 10^{-2}$	0.961
Gait cycle * group (controls = ref)						
Gait cycle * PwMS least affected leg	$\boldsymbol{-3.146 \cdot 10^{-2}}$	$\boldsymbol{-5.109 \cdot 10^{-2}}$ ***to*** $\boldsymbol{-1.182 \cdot 10^{-2}}$	***0.003***	$\boldsymbol{3.101 \cdot 10^{-2}}$	$\boldsymbol{2.035 \cdot 10^{-2}}$ ***to*** $\boldsymbol{5.998 \cdot 10^{-2}}$	***0.037***
Gait cycle * PwMS most affected leg	$\boldsymbol{-2.722 \cdot 10^{-2}}$	$\boldsymbol{-4.686 \cdot 10^{-2}}$ ***to*** $\boldsymbol{-0.759 \cdot 10^{-3}}$	***0.009***	$\boldsymbol{3.098 \cdot 10^{-2}}$	$\boldsymbol{2.043 \cdot 10^{-2}}$ ***to*** $\boldsymbol{5.998 \cdot 10^{-2}}$	***0.037***
Muscle: GM	**β**	**95% CI**	**p value**	**β**	**95% CI**	**p value**
Intercept	68.286	59.068 to 77.504	< 0.001	76.355	63.181 to 89.530	< 0.001
Group (controls = ref)						
PwMS least affected leg	***16.518***	***3.483 to 29.553***	***0.016***	***-27.581***	***-42.978 to -12.184***	***0.001***
PwMS most affected leg	***14.561***	***1.526 to 27.596***	***0.031***	-15.232	-30.639 to 0.176	0.053
Gait cycle	$0.574 \cdot 10^{-2}$	$-0.740 \cdot 10^{-2}$ to $1.894 \cdot 10^{-2}$	0.371	$\boldsymbol{-2.652 \cdot 10^{-2}}$	$\boldsymbol{-4.207 \cdot 10^{-2}}$ ***to*** $\boldsymbol{-1.096 \cdot 10^{-2}}$	***0.002***
Gait cycle * group (controls = ref)						
Gait cycle * PwMS least affected leg	$\boldsymbol{-2.901 \cdot 10^{-2}}$	$\boldsymbol{-4.754 \cdot 10^{-2}}$ ***to*** $\boldsymbol{-1.057 \cdot 10^{-2}}$	***0.004***	$\boldsymbol{3.591 \cdot 10^{-2}}$	$\boldsymbol{1.428 \cdot 10^{-2}}$ ***to*** $\boldsymbol{5.754 \cdot 10^{-2}}$	***0.003***
Gait cycle * PwMS most affected leg	$-1.203 \cdot 10^{-2}$	$-3.051 \cdot 10^{-2}$ to $0.646 \cdot 10^{-2}$	0.189	$\boldsymbol{3.278 \cdot 10^{-2}}$	$\boldsymbol{1.118 \cdot 10^{-2}}$ ***to*** $\boldsymbol{5.438 \cdot 10^{-2}}$	***0.005***
Muscle: GL	**B**	**95% CI**	**p value**	**β**	**95% CI**	**p value**
Intercept	68.288	57.213 to 79.363	< 0.001	72.934	60.716 to 85.153	< 0.001
Group (controls = ref)						
PwMS least affected leg	12.923	-2.739 to 28.584	0.100	***-28.094***	***-41.455 to -14.733***	< ***0.001***
PwMS most affected leg	8.384	-7.278 to 24.045	0.276	***-28.009***	***-41.468 to -14.731***	< ***0.001***
Gait cycle	$0.574 \cdot 10^{-2}$	$-0.686 \cdot 10^{-2}$ to $1.835 \cdot 10^{-2}$	0.353	$\boldsymbol{-2.956 \cdot 10^{-2}}$	$\boldsymbol{-5.072 \cdot 10^{-2}}$ ***to*** $\boldsymbol{-0.841 \cdot 10^{-2}}$	***0.009***
Gait cycle * group (controls = ref)						
Gait cycle * PwMS least affected leg	$-0.771 \cdot 10^{-2}$	$-2.541 \cdot 10^{-2}$ to $0.998 \cdot 10^{-2}$	0.373	$\boldsymbol{6.763 \cdot 10^{-2}}$	$\boldsymbol{3.872 \cdot 10^{-2}}$ ***to*** $\boldsymbol{9.655 \cdot 10^{-2}}$	< ***0.001***
Gait cycle * PwMS most affected leg	$-1.070 \cdot 10^{-2}$	$-2.840 \cdot 10^{-2}$ to $0.699 \cdot 10^{-2}$	0.221	$\boldsymbol{6.769 \cdot 10^{-2}}$	$\boldsymbol{3.880 \cdot 10^{-2}}$ ***to*** $\boldsymbol{9.658 \cdot 10^{-2}}$	< ***0.001***

Regression models are displayed, including the intercept, the estimated regression coefficient (β), i.e. the change in EMG-mf and EMG-rms per gait cycle per group/leg, and the interaction effect of gait cycle * group/leg. A significant interaction effect indicated that the change in EMG-mf or EMG-rms was significantly different in the least affected leg or most affected leg of PwMS from the control group. Significant values are indicated in bolt and italic (except for intercept).

fatigue. Muscle fatigue of the GM of particularly the least affected leg could be due to a compensation strategy, where the least affected leg may compensate for weakness of the most affected leg. Furthermore, on average EMG-mf seemed to decrease in both GM and GL of PwMS, although non-significant, which could be due to the small sample size. Hence, although underlying mechanisms of walking-induced motor fatigue in PwMS are still largely unknown, our findings give preliminary evidence for a contribution of muscle fatigue in SOL and, to a lesser extent, GM and GL.

The counter-intuitive increase in walking speed found in our study is in contrast to previous studies that showed PwMS slowed down during prolonged walking (Phan-Ba et al., 2012; Schwid et al., 1999). In these studies, however, PwMS were asked to walk at maximum speed during a 6-minute walking test, while in the current study participants walked at self-selected speed. This difference in walking task could explain the difference in outcome. An explanation for the increase in walking speed, ankle push-off power and net work around the ankle observed in current study might be that participants got more familiar while walking on the dual-belt treadmill. Future research with for example fixed walking speed or over ground walking could clarify muscle fatigue-related changes in PwMS during walking.

Muscle fatigue-related changes were predominantly observed in calf muscles of PwMS, particularly in SOL, while no changes in EMG parameters were observed in TA during prolonged walking. Hence, there appears to be a difference in the development of muscle fatigue between dorsiflexor and plantar flexor muscles in PwMS. This could be explained by previous research that showed that plantar flexors in particular are critical for ambulation in persons with stroke and other brain disease (Kim and Eng, 2003; Nadeau et al., 1999; Pradon et al., 2013). In addition, Wagner et al. (2014) showed that plantar flexor strength was a stronger predictor for walking endurance than dorsiflexor strength. However, previous research by Thickbroom et al. (2008) showed that ankle dorsiflexors were also particularly susceptible to muscle fatigue, which could cause impaired swing-phase foot clearance and drop foot (Benedetti et al., 1999; Martin et al., 2006). For this reason, ankle-foot orthoses are often prescribed for PwMS. Based on these clinical experiences and previous research, muscle fatigue in dorsiflexors was expected as well. An explanation for the lack of changes in dorsiflexors could be that the walking trial of 12 min was too short for participants to show muscle fatigue in dorsiflexors. Furthermore, this study focused particularly on muscle fatigue in PwMS who were able to walk continuously for 12 min, whereas PwMS who are more severely affected might show earlier and/or more pronounced signs of muscle fatigue.

Although muscle fatigue-related changes in calf, primarily SOL, muscles were observed, other factors, such as cognitive, behavioural, emotional and psychological, may also contribute to walking-related fatigue in PwMS. A full understanding of the determinants of walking-related fatigue is needed to develop targeted, effective therapies for improving walking in PwMS. These findings may help clinicians to

Table 3
Mixed linear model to identify the change in walking speed in per minute and ankle push-off power and positive work around ankle during push-off phase per gait cycle in control, the least affected leg of PwMS and most affected leg of PwMS.

Variable			
Walking speed (m/s)	**β**	**95% CI**	**p value**
Intercept	1.122	0.993 to 1.252	< 0.001
Group (controls = ref)			
PwMS	***-0.389***	***-0.583 to -0.194***	***0.001***
Minute	***0.034***	***0.023 to 0.045***	***< 0.001***
Minute * group (controls = ref)			
PwMS	-0.0004	-0.016 to 0.015	0.958
Ankle push-off power (W/kg)	**β**	**95% CI**	**p value**
Intercept	3.060	2.483 to 3.368	< 0.001
Group (controls = ref)			
PwMS least affected leg	***-1.014***	***-1.833 to -1.950·10 $^{-1}$***	***0.018***
PwMS most affected leg	***-1.620***	***-2.439 to -8.001·10 $^{-1}$***	***0.001***
Gait cycle	***0.316·10 $^{-2}$***	***0.104·10 $^{-2}$ to 0.527·10 $^{-2}$***	***0.006***
Gait cycle * group (controls = ref)			
Gait cycle * PwMS least affected leg	-0.031·10 $^{-2}$	-0.336·10 $^{-2}$ to 0.273·10 $^{-2}$	0.861
Gait cycle * PwMS most affected leg	0.087·10 $^{-2}$	-0.218·10 $^{-2}$ to 0.392·10 $^{-2}$	0.831
Ankle net work (J/kg)	**β**	**95% CI**	**p value**
Intercept	0.222	0.184 to 0.260	< 0.001
Group (controls = ref)			
PwMS least affected leg	***-5.533·10 $^{-2}$***	***-10.950·10 $^{-2}$ to -0.119·10 $^{-2}$***	***0.046***
PwMS most affected leg	***-10.003·10 $^{-2}$***	***-15.448·10 $^{-2}$ to -4.608·10 $^{-2}$***	***0.001***
Gait cycle	***0.022·10 $^{-2}$***	***0.002·10 $^{-2}$ to 0.042·10 $^{-2}$***	***0.033***
Gait cycle * group (controls = ref)			
Gait cycle * PwMS least affected leg	0.0004·10 $^{-2}$	-0.028·10 $^{-2}$ to 0.029·10 $^{-2}$	0.977
Gait cycle * PwMS most affected leg	0.002·10 $^{-2}$	-0.026·10 $^{-2}$ to 0.031·10 $^{-2}$	0.882

Regression models are displayed, including the intercept, the estimated regression coefficient (β), i.e. the change in walking speed per minute and ankle push-off power and ankle work per gait cycle per group, and the interaction effect of gait cycle * group. A significant interaction effect indicated that the change in walking speed, ankle push-off power or ankle work was significantly different in the least affected leg or most affected leg of PwMS from the control group. Significant values are indicated in bolt and italic (except for intercept).

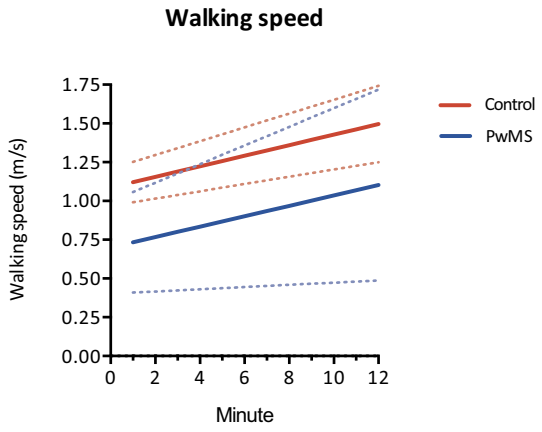

Fig. 2. Results of mixed models analyses representing the changes in walking speed for controls (red line) and PwMS (blue line). Tick lines represent the average changes for each group, while dotted lines represent 95% confidence intervals. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

develop better-tailored interventions, focusing on endurance of the calf muscles to reduce and/or avoid muscle fatigue during walking. Future research is needed to investigate the relationship between muscle weakness and muscle fatigue during walking in PwMS. Specifically endurance training for calf muscles may delay the onset of muscle fatigue in PwMS.

4.1. Limitations

The results of the current study should be interpreted with some limitations in mind. First, a relatively small sample of PwMS was included. Based on this small sample, no distinction between patients with mild to moderate MS severity and severe MS (based on the EDSS) could be made. Despite this, the consistent muscle fatigue observed in soleus muscles in this small sample highlights that awareness of this problem should be raised. In addition, PwMS who reported not to be able to walk continuously for 12 min were excluded from participation (18% of eligible participants). Though, these PwMS might show more pronounced signs of muscle fatigue. Future research should be conducted to confirm current findings in a larger sample of PwMS. Second, PwMS walked slower than healthy controls. Since gait speed affects muscle activity (Neptune et al., 2008), this could have led to differences in changes in EMG in PwMS and controls. Third, the percentage of missing gait cycles to obtain ankle push-off power and net work was relatively high (20–23%). Therefore, mixed models analyses were constructed, since they allow for missing values. Missing values were slightly higher in PwMS. This could be caused by the fact that they did not walk cleanly with one foot on each force plate, which could be attributed to compensation strategies. Research including EMG recordings of a broader scale of lower extremity muscles could provide important information about these potential compensation strategies.

5. Conclusion

From this study, we can cautiously conclude that calf muscles showed more signs of muscle fatigue in PwMS compared to age- and gender matched healthy controls during prolonged walking at self-selected speed. These observations of muscle fatigue were not accompanied by concurrent changes in walking speed, push off and ankle work, which were found to increase in both PwMS and healthy controls. These findings yield preliminary evidence that muscle fatigue of especially SOL muscles contributes to walking-related motor fatigue in MS. If supported by a larger sample, these findings may help to develop better-tailored interventions, focusing on endurance of plantar flexors to reduce muscle fatigue during walking.

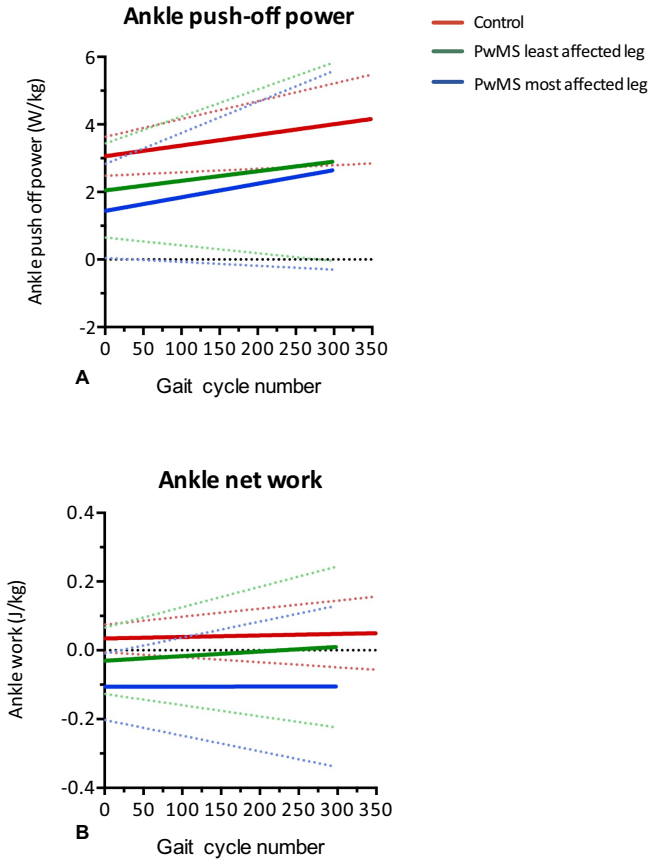

Fig. 3. Results of mixed models analyses representing the changes in (A) ankle push-off power and (B) net work around the ankle for controls (red line), least affected leg of PwMS (green line) and most affected leg of PwMS (blue line). Tick lines represent the average changes for each group, while dotted lines represent 95% confidence intervals. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

CRediT authorship contribution statement

Maaike M. Eken:Conceptualization, Methodology, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Visualization.**Rosie Richards**:Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - review & editing, Visualization.**Heleen Beckerman**:Conceptualization, Methodology, Software, Writing - review & editing, Supervision, Funding acquisition.**Marjolein van der Krogt**:Conceptualization, Methodology, Software, Validation, Writing - review & editing.**Karin Gerrits**:Conceptualization, Methodology, Writing - review & editing.**Marc Rietberg**:Conceptualization, Methodology, Writing - review & editing.**Vincent de Groot**:Conceptualization, Methodology, Writing - review & editing, Supervision, Funding acquisition.**Martin Heine**:Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

None.

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