POLITECNICO DI TORINO
Repository ISTITUZIONALE

Force control during submaximal isometric contractions is associated with walking performance in persons with multiple sclerosis

Original
Force control during submaximal isometric contractions is associated with walking performance in persons with multiple sclerosis / Davis, L. A.; Alenazy, M. S.; Almuklass, A. M.; Feeney, D. F.; Vieira, T.; Botter, A.; Enoka, R. M.. - In: JOURNAL OF NEUROPHYSIOLOGY. - ISSN 0022-3077. - STAMPA. - 123:6(2020), pp. 2191-2200. [10.1152/jn.00085.2020]

Availability:
This version is available at: 11583/2838385 since: 2020-12-01T10:32:30Z

Publisher:
American Physiological Society

Published
DOI:10.1152/jn.00085.2020

Terms of use:

This article is made available under terms and conditions as specified in the corresponding bibliographic description in the repository

Publisher copyright

(Article begins on next page)

12 October 2024

Submitted to: *Journal of Neurophysiology*

Resubmitted: March 23, 2020

Force control during submaximal isometric contractions is associated with walking performance in persons with multiple sclerosis

Leah A. Davis, Mohammed S. Alenazy, Awad M. Almuklass, Daniel F. Feeney, Taian Vieira, Alberto Botter, Roger M. Enoka

Department of Integrative Physiology

University of Colorado Boulder, CO, USA

Leah Davis: leah.davis@colorado.edu (Corresponding Author)
Department of Integrative Physiology
University of Colorado Boulder
Campus Box 354
Boulder, CO 80309, USA
303-492-4975

Mohammed Alenazy: moal4255@colorado.edu
Department of Integrative Physiology
University of Colorado Boulder
Boulder, CO 80309, USA
College of Medicine
Majmaah University
Majmaah, Saudi Arabia

Awad Almuklass: awad.almuklass@colorado.com
College of Medicine
King Saud bin Abdulaziz University for Health Sciences
Riyadh, Saudi Arabia
King Abdullah International Medical Research Center (KAIMRC)
Riyadh, Saudi Arabia
Department of Integrative Physiology
University of Colorado
Boulder, CO, USA

Daniel Feeney: daniel.feeney@colorado.edu
Boa Technologies
Boulder, CO, USA

Taian Vieira: taian.vieira@polito.it
PolitoBIOMed Lab
Politecnico di Torino
Turin, Italy
Department of Electronics and Telecommunications
Politecnico di Torino
Turin, Italy

Alberto Botter: alberto.botter@polito.it
PolitoBIOMed Lab
Politecnico di Torino
Turin, Italy
Department of Electronics and Telecommunications
Politecnico di Torino
Turin, Italy

Roger Enoka: enoka@colorado.edu
Department of Integrative Physiology
University of Colorado Boulder
Boulder, CO 80309, USA

Abstract

Individuals with multiple sclerosis (MS) experience progressive declines in movement capabilities, especially walking performance. The purpose of our study was to compare the amount of variance in walking performance that could be explained by the functional capabilities of lower leg muscles in persons with MS and a sex- and age-matched control group. Participants performed two walking tests (6-min walk and 25-ft walk), strength tests for the plantar flexor and dorsiflexor muscles, and steady submaximal (10% and 20% maximum) isometric contractions. High-density electromyography (EMG) was recorded during the steady contractions and the signals were decomposed to identify the discharge times of concurrently active motor units. There were significant differences between the two groups in the force fluctuations during the steady contractions (force steadiness), the strength of the plantar flexor and dorsiflexor muscles, and the discharge characteristics during the steady contractions. Performance on the two walking tests by the MS group was moderately associated with force steadiness of the plantar flexor and dorsiflexor muscles; worse force steadiness was associated with poorer walking performance. In contrast, the performance of the control group was associated with muscle strength (25-ft test) and force steadiness of the dorsiflexors and variance in common input of motor units to the plantar flexors (6-min test). These findings indicate that a reduction in the ability to maintain a steady force during submaximal isometric contractions is moderately associated with walking performance of persons with MS.

New & Noteworthy. *The variance in walking endurance and walking speed was associated with force control of the lower leg muscles during submaximal isometric contractions in individuals with MS. In contrast, the fast walking speed of a sex- and age-matched control group was associated with the strength of lower leg muscles. These findings indicate that moderate*

declines in the walking performance of persons with MS are more associated with impairments in force control rather than decreases in muscle strength.

Keywords. Multiple sclerosis, walking, force steadiness, common drive, motor units, high-density EMG

Introduction

Multiple sclerosis (MS) is a demyelinating neurological disorder that compromises function within the central and peripheral nervous systems. The damage caused by the disease invariably leads to increases in self-reported levels of fatigue, worse walking and balance, and decreased quality of life. When walking at a preferred speed, for example, individuals with MS take shorter, wider, and more variable strides and spend a greater percentage of the gait cycle in the double-support phase (Benedetti et al. 1999; Comber et al. 2017; Galea et al. 2017; Gutierrez et al. 2005; Sosnoff et al. 2012). These declines in gait kinematics are associated with a greater energetic cost of walking for persons with MS (Motl et al. 2012; Sebastião et ak, 2018), which may contribute to the elevated levels of fatigue they report (Hadjimichael et al. 2008; Kluger et al. 2012; Loy et al. 2017; Zijdewind et al. 2016).

The mobility-limiting symptoms experienced by persons with MS arise in part from the progressive decline in sensorimotor function (Cabib et al. 2015; Newsome et al. 2011; Zackowski et al. 2015). The disease compromises functional connectivity within the central nervous system (Fling et al. 2015, Fritzer et al. 2017; Schlaeger et al. 2015), including the activation signal sent from the spinal cord to muscle (DeLuca et al. 2013; Kearney et al. 2015; Petrova et al. 2018). These changes result in a decrease in the maximal capacity to activate muscle (Andreasen et al. 2009; Ng et al. 2004), a reduction in the number of functioning motor units (Vogt et al. 2009), and a lesser range of rate coding for single motor units (Rice et al. 1992). Consistent with these observations, we have found that the normalized amplitude of the force fluctuations and the mean interspike interval of motor unit action potentials in plantar flexor muscles during steady submaximal contractions can explain moderate, but significant,

amounts of the variance in performance of individuals with MS on tests of maximal walking speed and walking endurance (Almuklass et al. 2018).

Technological advances in electromyography (EMG) now make it possible to evaluate more thoroughly the influence of the impairments in muscle activation on the capacity of an individual to control muscle force (Farina et al. 2016). In particular, multi-channel electrode systems enable the decoding of the neural drive to muscle by identifying the discharge times of several concurrently active motor units from surface EMG recordings (Farina et al. 2010). In a seminal study, for example, Negro et al. (2009) demonstrated that the first principal component of the smoothed discharge rates of ≥4 motor units in a hand muscle was strongly correlated (72 ± 13%) with the fluctuations in abductor force applied by the little finger during steady submaximal contractions. They found a similar association (58 ± 14%) for motor units in tibialis anterior when the dorsiflexors performed a steady, isometric contraction at 10% maximal voluntary contraction (MVC) force. Subsequently, Thompson et al. (2018) demonstrated with an *in vivo* cat model that the cumulative spike trains of ≥9 motor units were strongly correlated with both the total force (99.2 ± 0.2%) and the higher frequency force fluctuations (83.5 ± 1.3%) evoked in the soleus muscle.

The normalized amplitude of the force fluctuations (coefficient of variation for force) during steady submaximal contractions provides a measure of force steadiness (Galganski et al. 1993). Force steadiness is a sensitive marker of fine motor control as it varies with the target force for the steady contraction (Galganski et al. 1993; Laidlaw et al. 2000; Tracy and Enoka, 2002), the test muscle (Grunte et al. 2010; Tracy et al. 2007), the difficulty of the task (Almuklass et al. 2016; Holmes et al. 2015), the level of physiological arousal (Christou et al. 2004; Pereira et al. 2015; Rice et al. 2015), the age of the performer (Castronovo et al. 2018; Hamilton et al. 2017;

Marmon et al. 2011), and the neurological health of the individual (Bilodeau et al. 2000; Carville et al. 2007; Gould et al. 2018). Critically, force steadiness has consistently emerges as a statistically significant explanatory variable for the variance in performance on a number of dynamic tasks, such as walking (Almuklass et al. 2018, Mani et al. 2018), manual dexterity (Almuklass et al. 2016, Feeney et al. 2018; Hamilton et al. 2017; Marmon et al. 2011), risk of falls in older adults (Carville et al. 2007), and postural sway (Davis et al. 2020).

The purpose of our study was to compare the amount of variance in walking performance that could be explained by the functional capabilities of lower leg muscles in persons with MS and an age- and sex-matched control group. Walking performance was quantified as fast walking speed (25-ft test) and walking endurance (6-min test), whereas muscle function was characterized with measures of muscle strength, force steadiness during submaximal isometric contractions, and the discharge characteristics of single motor units during the steady contractions. Due to the explanatory power of force steadiness for the performance of older adults on tests of motor function, we hypothesized that significant amounts of the variance in walking performance for individuals with MS would be explained by differences in force steadiness, whereas we expected measurements of muscle strength to be the dominant explanatory variable for the control group.

METHODS

Subjects

Data from 18 participants with relapsing-remitting MS who participated in a previous study (52 ± 8 yrs, 7 men, 3.6 ± 0.96 PDDS; Almuklass et al., 2017, Almuklass et al., 2018) were compared with 18 sex- and age-matched (± 5 yrs) control subjects (52 ± 9 yrs) who reported no neurological diseases. The control subjects were explicitly recruited for our current report. The MS participants provided written informed consent (IRB#: 13-0720) for the previous study. For

the current study, a waiver-of-consent document was approved in accordance with the exception to the regulations of the Office of Human Research Protections in that there was no more than minimal risk of harm to subjects and it involved no procedures for which written consent is normally required outside the research context. The MS subjects were sent an approved e-mail message that requested permission to use their data by replying either 'yes, I consent for you to use my data' or 'no, I do not consent for you to use my data.' The control group provided written informed consent to participate in a protocol (IRB#: 16-0396) that was approved by the Institutional Review Board at the University of Colorado.

The MS participants completed a baseline evaluation over a 2-day period that included measurements of muscle strength, force steadiness, walking endurance, and fast walking speed (Almuklass et al., 2017). They then performed a 6-wk intervention in which neuromuscular electrical stimulation was applied to their plantar flexor and dorsiflexor muscles 3x/wk for a total of 18 treatment sessions. The current report includes only those data that were obtained from the MS participants during the baseline evaluation. These baseline data were compared with those for the control group that was collected using the same protocol performed by the MS group, but within a single session.

Strength and force steadiness.

Both groups performed measurements of muscle strength and force steadiness with the dorsiflexor and plantar flexor muscles. Participants lay in a supine position with the hip and knee joints at neutral angles and the ankle at 90°. A strap was placed around the widest section of the forefoot and connected to a strain-gauge transducer (MLP-300, Transducer Techniques, Temecula, CA). The force signal was sampled at 1 kHz (Power 1401, Cambridge Electronic Design, Cambridge, UK) and displayed on a monitor that was placed ~1 m in front of the

participants. They performed maximal voluntary contractions (MVC) with the ankle-spanning dorsiflexor and plantar flexor muscles; the task was to increase muscle force gradually (~30% MVC/s) up to maximum and then sustain it for ~ 3 s. They were verbally encouraged to provide a maximal effort during each MVC. They performed 2-5 MVCs until the peak forces in 2 trials were within 10% of each other, the greater of which was taken as the MVC force. The moment arm for the muscle torque calculation was measured as the distance from the lateral malleolus to the center of the strap around the forefoot.

Participants then performed submaximal isometric contractions for ~30 s while matching target forces of 10% or 20% MVC force (Figure 1. A and B). The submaximal contractions were performed with the dominant leg (Waterloo footedness questionnaire) by the control group and in the self-reported leg with fewer symptoms (less-affected leg) by the MS group. The task was to increase the force from an initial resting value up to the target force displayed on a monitor (visual angle ~0.25°) and then to maintain a steady contraction for ~30 s. Participants were not asked to achieve a specific a rate of increase in force, but typically reached the target force ≥2 s (~5 – 10% MVC/s). Participants performed two trials at each target force for both muscle groups.

The force signals were amplified (Coulbourn Instruments, Allentown, PA) and then recorded on a computer with Spike2 data acquisition software (Version 6.17, Cambridge Electronic Design, Cambridge, UK). The force signals were subsequently low-pass filtered with a cut-off frequency of 20 Hz and the fluctuations in force during the steady contractions (force steadiness) were quantified as the coefficient of variation for force (Galganski et al., 1993).

High-density surface EMG.

Three high-density surface electrodes (4x8 detection points, 10 mm interelectrode distance) were placed longitudinally over the tibialis anterior, medial gastrocnemius, and lateral portion of the soleus muscles during the steady isometric contractions (Figure 1.A; plantar flexors or dorsiflexors x two target forces x two trials at each target force). A custom MATLAB script was used to decompose motor unit activity from the EMG signals (Figure 1, C and D; Holobar & Zazula, 2007).

[Figure 1]

The interspike intervals (ISI) for each motor unit were calculated as the difference between consecutive discharge times. Due to limitations in decomposition algorithms, the signals likely contained both motor unit signals as well as non-physiological waveforms. To control for aberrant waveforms, the decomposed signal was deemed not to be a motor unit when all four of the following criteria were met: 1) 25 < ISI > 400 ms; 2) 8% < coefficient of variation for ISI > 55%; 3) if the skewness of the ISI histogram was between -0.5 and 0.5; and 4) if the coefficient of variation for ISI was <10% *and* the skewness of the ISI histogram was <1 (Almuklass et al., 2018).

When the discharge times of ≥5 motor units were identified for a given trial, the data were entered into a state-space model (Feeney et al., 2017, Macke et al., 2011) to estimate the variance in the common synaptic input to the motor neuron pools during the steady contractions. Briefly, the unobserved common input at a given time, x(t), is related to a linear approximation of the common input (A) at the previous time point, the influence of the intended target force on discharge rate (b*f*(t)), and the effects of synaptic noise on signal transmission as represented as a Gaussian noise vector (E(t)). The target force is represented by *f*(t), which is influenced by a vector representing discharge rate saturation in low threshold motor units (b)

$$\boldsymbol{x}(t) = \boldsymbol{A}x(t-1) + \boldsymbol{b}f(t) + \boldsymbol{E}(t)$$

The common synaptic input varies over the contraction and is modeled with Poisson linear dynamics.

$$x_i \sim N(x_o, Q_o)$$

$$x_t | x_{t1} \sim N(Ax_{t1}, bf_t, Q)$$

The term Q represents the variance in the state-space trajectory, which corresponds to the fluctuations in the common input signal. Q is assumed to remain constant during each steady contraction.

Motor unit discharge times were sorted into 10-ms bins and arranged into a binary matrix where the occurrence of an action potential was represented by 1. The matrix was entered into an open source Expectation-Maximization algorithm (Macke et al., 2011; Buesing et al., 2012) to estimate the parameters of the state-space model. The Q values were subsequently low-pass filtered to account for the response characteristics of muscle. The unfiltered Q values were interpreted as the variance in the common synaptic input received by the motor neuron pool, whereas the filtered Q values estimated the variance in the activation signal received by the muscles.

Walking tests.

Each participant performed two walking tests: 25-ft walk (fast walking speed) and the 6-min walk (walking endurance). Fast walking speed was represented as the average of two 25-ft tests. Participants stood ~1 m before the start line and a timer was started as soon as one foot stepped over the line and stopped when one foot stepped over the end line. The 6-min test required participants to walk around an indoor track for 6 minutes and the distance covered was

measured. The instruction for both tests was to walk as quickly but as safely as possible. Due to the influence of fatigue on the performance of persons with MS, they performed the two walking tests on one day and the tests of muscle function on another day. The control subjects performed all the tests on the same day.

Questionnaires.

The disability status of the MS participants was quantified with three questionnaires: patient determined disease steps (PDDS), MS walking scale-12 (MSWS-12), and modified fatigue impact score (MFIS). Only the PDDS scores are reported here.

Data Analysis.

Descriptive statistics for both pairwise and group values were calculated and are reported as mean ± standard deviation. Pairwise differences across groups were calculated as the absolute difference between paired subjects for each variable. When the 95% confidence interval of the differences included 0, the difference was deemed not to be statistically significant. Conversely, the absence of 0 in the 95% confidence interval corresponded to a statistically significant pairwise difference. Group differences were examined with linear regression analysis for each variable ($P < 0.05$). Muscle strength was compared between 1) the less-affected leg from the MS group to the dominant leg from the control group, and 2) the more-affected leg of the MS group and the non-dominant leg of the control group. Due to the variable numbers of motor units across subjects, we could only examine group differences for both the filtered and unfiltered Q values.

Pearson-product correlations were used to compare performance on the walking tests (25-ft test and 6-min test) with muscle strength, force steadiness, and the variability in common input (Q) for each group of participants. Significantly correlated variables were entered in a backward

linear regression analysis to identify the measures of muscle function that were most strongly associated with the variability in walking performance for each group.

All statistical procedures were performed in R (Version 3.5.1) with an α level of $P<0.05$ (with Bonferroni correction for multiple comparisons) for statistical significance.

RESULTS

The results comprise an assessment of the associations between walking performance and measures of muscle function and motor unit activity in lower leg muscles of persons with MS and an age- and sex-matched control group.

Strength, force steadiness, and walking.

Table 1 contains the pairwise and group differences for the measurements of force steadiness and muscle strength. In contrast to the control group, force steadiness (coefficient of variation for force) for both the plantar flexors and dorsiflexors was not less at the greater target force (20% MVC) than the lower target force (10% MVC) for the MS group. However, force steadiness for the dorsiflexors of both groups was greater at the two target forces than that for the plantar flexors. Nonetheless, there were no significant differences between groups in force steadiness of the plantar flexors at either target force (10% or 20% MVC) and in the force steadiness for the dorsiflexors at 10% MVC. At the greater target force (20% MVC) for the dorsiflexors, however, the MS participants exhibited significantly worse force steadiness (greater force fluctuations) than the control group.

[Table 1]

There were no statistically significant differences in MVC torque between legs for the plantar flexor muscles of each group of participants and for the dorsiflexor muscles in the control group.

In contrast, dorsiflexor MVC torque for the more-affected leg was significantly less for the less-affected leg in the MS group. Further, the MS group was consistently weaker than the control group for both the plantar flexor and dorsiflexor muscles of each leg.

The difference in time to complete the 25-ft walk test between the MS and control groups was not statistically significant despite substantially different group means. This was due to the large standard deviation for the MS group (Table 2). In contrast, the control group walked further during the 6-min walk test at each recorded timepoint (1 min, 2 min, 4 min, and 6 min) than the MS group. Furthermore, the absolute difference in distance walked between participants matched across groups increased progressively during the 6-min test (Table 2).

[Table 2]

Motor units.

Motor unit data were recorded for the tibialis anterior, medial gastrocnemius, and soleus muscles during the submaximal contractions at the two target forces. Our analysis required ≥5 identified motor units in each trial in order to calculate Q (Feeney et al., 2017). As the 19 participants in each group performed 2 trials for every condition, there was the possibility of recording usable data from 38 trials for each muscle group at each target force. However, the number of viable trials was less than 38 for both the MS and control groups, respectively: tibialis anterior (10% MVC: 24 and 32 trials; 20% MVC: 30 and 36 trials), soleus (10% MVC: 13 and 20 trials; 20% MVC: 18 and 25 trials), and medial gastrocnemius (10% MVC: 6 and 20 trials; 20% MVC: 14 and 21 trials). Thus, it was more difficult to identify a sufficient number of motor units in the MS participants than the control group and in the plantar flexor muscles than the dorsiflexor muscle. Due to the shared contribution of medial gastrocnemius and soleus to the net plantar

flexor torque, the discharge times of motor units recorded from the medial gastrocnemius and soleus were pooled and the variance in the common input (Q) was calculated for the pooled data.

When performing a steady isometric contraction at 10% MVC force with the dorsiflexor muscles, the mean and coefficient of variation for interspike interval for motor units in tibialis anterior were greater and the unfiltered Q value was lower for the MS group than the control group (Table 3). At the higher target force (20% MVC), only the coefficient of variation for interspike interval of motor units in tibialis anterior was greater for the MS group than the control group (Table 3).

There were fewer group differences in motor unit activity during the steady contractions performed with the plantar flexor muscles. The most consistent difference between the groups was the lower unfiltered Q values (medial gastrocnemius + soleus) for the MS group compared with the control group at both target forces (10% & 20% MVC; Table 5). Also, the mean interspike interval for motor units in medial gastrocnemius was greater at the 20% target force for the MS group than the control group. Notably, there was only one statistically significant difference for either group of participants in the mean and coefficient of variation for interspike intervals across target forces (Table 4). Mean interspike interval for motor units in the tibialis anterior of the control group were significantly lower at 20% MVC than at 10% MVC.

[Table 3, 4, & 5]

The filtered Q values for tibialis anterior were correlated with force steadiness in the dorsiflexor muscles of the MS group. When the target forces (10 and 20% MVC) were pooled, the correlation coefficient was 0.32 ($P = 0.04$) for the MS group and 0.23 ($P = 0.06$) for the control group. The association between the filtered Q values from the tibialis anterior and force steadiness of the dorsiflexors when the MS group maintained a steady contraction at 10% MVC

was not statistically significant when the data were not collapsed across target forces (r = 0.37, *P* = 0.10). The filtered Q values from tibialis anterior and force steadiness for the dorsiflexors at 20% MVC were significantly correlated (r = 0.45, *P* = 0.008) in the control group. There were no significant correlations between the filtered Q values and force steadiness of the plantar flexors.

Walking correlations and regression analyses.

To assess the relative explanatory power of the outcome variables on the two tests of walking performance, we first identified the variables that showed statistically significant correlations with each walking test and then compared the relative influence of these correlations by developing regression models that retained the most influential variables. Table 6 shows that there were a greater number of significant Pearson-product correlations between muscle function (force steadiness, strength, and motor unit discharge characteristics) and walking performance for the MS group than for the control group. The distance walked in 6 min by the MS group was correlated with three of the four measures of force steadiness, with the filtered Q values for the motor units in the plantar flexors, and with the strength of the dorsiflexors in the more-affected leg. The distance walked in 6 min by the control group was correlated with force steadiness for the dorsiflexors at the lower target force and the filtered Q value for the plantar flexors.

The time it took the MS group to walk 25 ft was correlated with the same set of outcome variables as for the 6-min walk, except not with the strength of the dorsiflexors in the more affected leg. The time it took the control group to walk 25 ft was correlated with one measure of force steadiness (plantar flexors at 10% MVC) and the strength of plantar flexors and dorsiflexors of the left and right legs.

355 Four regression models were developed (2 groups x 2 tests of walking performance); each model
356 involved up to three variables with the strongest correlations to walking performance. The
357 regression model for the 6-min distance of the MS group explained 54% of the variance with two
358 predictor variables (Figure 2A): force steadiness of the plantar flexors at 20% MVC force (partial
359 r = -0.52) and force steadiness for the dorsiflexors at 10% MVC (partial r = -0.36). The
360 regression model for the 6-min distance of the control group explained 36% of the variance with
361 two predictor variables (Figure 2B): force steadiness of the dorsiflexors at 20% MVC force;
362 partial r = -0.54) and the filtered Q values for the plantar flexors (partial r = -0.19).

363 The regression model for the time it took the MS group to walk 25 ft explained 34% of the
364 variance with two predictor variables (Figure 2C): force steadiness of the plantar flexors at 20%
365 MVC force (partial r = -0.47) and force steadiness for the dorsiflexors at 10% MVC (partial r =
366 0.48). The regression model for the time it took the control group to walk 25 ft explained 56%
367 of the variance with two predictor variables (Figure 2D): MVC torque for the plantar flexors of
368 the non-dominant leg (partial r = -0.49) and MVC torque for the dorsiflexors of the dominant leg
369 (partial r = -0.39).

370 [Table 6 & Figure 2]

371 **DISCUSSION**

372 The main finding of our study was that moderate amounts of the variance in two tests of walking
373 performance for persons with MS and control participants were explained by measurements
374 derived from submaximal, isometric contractions with the plantar flexor and dorsiflexor muscles.
375 The exception to this general conclusion was that the explanatory variables for the fast walking
376 speed (25-ft test) performed by the control group were two measurements of muscle strength.
377 We hypothesized that significant amounts of the variance in walking performance would be

explained by differences in force steadiness for individuals with MS, whereas we expected muscle strength to be the dominant explanatory variable for the control group.

Walking, strength, and force steadiness.

We found that greater coefficients of variation in force (worse force steadiness) corresponded to a shorter distance walked in 6 min in both groups of participants and to a longer time to walk 25 ft in the MS participants. These associations were stronger for the MS group than the control group. The functional significance of force steadiness is that it represents an individual's accuracy in producing and maintaining a force trajectory (Christou et al. 2003). Within the last 5 years, our lab has found that force steadiness, a measurement derived from submaximal isometric contractions, consistently emerges as a significant explanatory variable in regression models to explain the variance in performance of a dynamic task (Almuklass et al. 2016, Almuklass et al. 2018, Davis et al. 2020, Feeney et al. 2018, Mani et al. 2018).

Although the direction of the correlations (positive or negative) has differed across studies, the correlation coefficients and partial-r values have consistently comprised moderate-to-strong values. Of particular note, when both force-steadiness values and muscle strength (MVC torques) have both been entered into the regression models, force steadiness frequently has the greater explanatory power for the variance in the outcome variables (Almuklass et al. 2016; Hamilton et al. 2017; Justice et al. 2014; Mani et al. 2018; Marmon et al. 2011). Taken together with previous research, these results suggest that an individual's ability to sustain a constant force during a steady isometric contraction at a submaximal target force is more often functionally relevant than maximum muscle strength for most activities of daily living. The stronger correlations between walking performance and force steadiness for the MS group than the control group suggests that the negative impact of the disease on the ability to sustain steady

submaximal contractions has functional consequences. Moreover, the underlying mechanisms presumably involve the variance in the common input received by the activated motor neurons (Feeney et al. 2017; Negro et al. 2009; Thompson et al. 2018).

The only case in which muscle strength emerged as a significant explanatory variable was for the 25-ft test performed by the control group. Stronger lower leg muscles were associated with faster times to walk 25-ft (faster). As the goal of this test is to walk as quickly as possible for a relatively short distance, the same relative muscle strength produces greater absolute forces and faster gait cycles (Bohanan, 1997; Broekmans et al. 2012; Clark et al. 2013). Although muscle strength did not emerge as an explanatory variable for the MS participants, dorsiflexor MVC torque for the more-affected leg was negatively correlated with their walking endurance.

Motor units.

Previously, Almuklass et al. (2018) found that the walking performance of individuals with MS (n = 27) was associated with the mean interspike intervals of single motor units in medial gastrocnemius and soleus muscles during steady contractions (10% MVC force) averaged across 2 to 3 time points. The current study comprised the data obtained from a subset of these participants (n = 18) in only one of the experimental sessions. In this reduced data set, we did not find any significant associations between either the mean or the coefficient of variation for interspike interval with performance on the two walking tests.

Instead of estimating the cumulative influence of motor unit activity by collapsing data across experimental sessions (Almuklass et al. 2018), we derived Q values from the discharge times of many motor units during steady submaximal contractions to infer the activity of the motor unit pool. We found that lower filtered Q values for the plantar flexors of individuals with MS

423 corresponded to a longer time to complete the 25-ft test and a shorter distance walked in 6 min.
424 In contrast, the filtered Q value for the plantar flexors of the control group was negatively
425 associated with walking endurance, but not with fast-walking speed. These findings suggest that
426 greater variance in the common input to motor neurons, once it had been low-pass filtered by the
427 muscle, was associated with better walking endurance and faster walking speed in individuals
428 with MS, but with worse walking endurance in healthy adults. Although we hypothesized that
429 variance in the common input would be associated with better walking performance, we
430 expected the association to be for the dorsiflexors and not the plantar flexors.

431 The current study appears to be the first to examine the common input to the motor unit pool in
432 individuals with MS. The moderate correlations between the variance in the common
433 modulation of motor units within the tibialis anterior and force steadiness of the dorsiflexors are
434 consistent with previous work reported from our lab on the wrist extensor muscles (Feeney et al.
435 2018). In that study, they found that the unfiltered Q values derived from the discharge times of
436 motor units during a steady contraction at 20% MVC force were significantly correlated with
437 force steadiness for both young ($r^2 = 0.31$) and older ($r^2 = 0.39$) adults. However, only the
438 correlation for the older adults had a functional influence on the time it took older adults to
439 complete a pegboard test of manual dexterity. Perhaps these findings suggest that the functional
440 significance of the variance in common input is most evident in individuals with a reduced
441 integrity of the sensorimotor system.

442 A key issue that needs to be addressed in this field is the discrepancy in the magnitude of the
443 correlation between the variance in common input and force steadiness (fluctuations in force) for
444 the classic studies (Negro et al. 2009; Thompson et al. 2018) and our work (Feeney et al. 2018;
445 current study). One likely confounding factor is the number of muscles that contribute to the

446 applied force. Negro et al. (2009) studied the sole contributor to the abduction force exerted by
447 the little finger (abductor digiti minimi), whereas Thompson et al. (2018) examined the isolated
448 soleus muscle in a decerebrate cat preparation. In these two studies, 72% and 84%, respectively,
449 of the force fluctuations during steady contractions were explained by the estimated variance on
450 the common input signal of the activated motor units. In contrast, the current study assessed the
451 association between the net force and motor units in just a few of the involved muscles. For
452 example, there are nine muscles that can contribute to the net plantar flexor force with each
453 muscle varying in architecture and lines of action. Although some evidence suggests that the
454 motor neuron pools of synergist muscles share most of their synaptic input (Laine et al. 2015),
455 the generalizability of this conclusion needs to be examined in a broader array of synergistic
456 muscles. Even among the dorsiflexor muscles where tibialis anterior contributes approximately
457 60% to the applied force (Andreassen & Arendt-Nielsen, 1987), the Q value calculated from the
458 discharge times of those motor units was only moderately associated with the force fluctuations
459 (current study and Negro et al., 2009). Moreover, it is the fluctuations in the net force rather than
460 the activity of a few selected motor units that is more strongly associated with motor
461 performance.

462 The variance in the common input in the current study was quantified using a state-space model,
463 which Feeney et al. (2017) used to model the variance of the common input signal to motor
464 neurons. This parameter differs from the cumulative spike train (CST) estimate, which explains
465 a large part of the fluctuations in the motor output from the spinal cord during isometric
466 contractions (Negro et al., 2009). To enable a more direct comparison with the estimate of the
467 variance derived from the CST, the Q values were filtered to mimic the low-pass filtering
468 influence of muscle on the variance in the common synaptic input to motor neurons (Farina et

469 al., 2014). Consistent with the classic finding of a significant association between CST values
470 and force fluctuations (Negro et al., 2009; Thompson et al., 2018), we found that it was the
471 filtered Q values that were significantly correlated for three of the four walking-test results
472 (Table 6). Moreover, the filtered Q values for the plantar flexors emerged as one of the two
473 significant explanatory variables for the distance walked in 6 min by the control group.
474 Although the unfiltered Q values for the motor units in the plantar flexors during the two steady
475 contractions (10% and 20% MVC) were greater for the control group, this difference did not
476 explain the variance in performance on the walking tests for either group of participants. Taken
477 together, these findings reveal some of the differences between the CST and state-space model
478 measures of variance in common input. It appears that the state-space model may approximate
479 the common input to the motor neurons, whereas the CST more accurately represents the
480 common output of the motor pool.

481 **Conclusion**

482 The time it took individuals with MS to walk 25 ft and the distance they could walk in 6 min
483 were most strongly associated with the fluctuations in force during steady, submaximal
484 contractions (force steadiness) with the plantar flexors and the dorsiflexors. In contrast, the 25-ft
485 time for the control group was associated with the strength (MVC torque) of the plantar flexors,
486 whereas their 6-min distance was explained by force steadiness for the dorsiflexors and the
487 variance in common input to the plantar flexors during the steady contractions. These findings
488 indicate that the ability to maintain a constant force during a submaximal, isometric contraction
489 has a greater influence than the strength of lower leg muscles on the walking performance of
490 persons with MS.

491

Grants

The Eunice Kennedy Shriver National Institute of Child Health and Human Development provided support for the preliminary study in the MS group (R03 HD-079508). The current study was not funded.

Disclosures

The authors have no conflicts of interest, financial or otherwise, to report.

Author contributions

L.A.D., A.M.A. and R.M.E. conceived and designed research; L.A.D., A.M.A., and M.S.A. performed experiments; L.A.D, A.M.A, M.S.A, D.F.F, T.V., A.B., R.M.E interpreted results of experiments; L.A.D, M.S.A, and R.M.E. prepared figures; L.A.D. and R.M.E. drafted manuscript; L.A.D, A.M.A, M.S.A, D.F.F, T.V., A.B., R.M.E edited and revised manuscript; L.A.D, A.M.A, M.S.A, D.F.F, T.V., A.B., R.M.E approved final version of manuscript.

References

Almuklass AM, Davis LA, Hamilton LD, Vieira TM, Botter A, Enoka RM. Motor unit discharge characteristics and walking performance of individuals with multiple sclerosis. *J Neurophysiol* 119: 1273-1282, 2018.

Almuklass AM, Davis LA, Hamilton LD, Hebert JR, Alvarez E, Enoka RM. Pulse width does not influence the gains achieved with neuromuscular electrical stimulation in people with multiple sclerosis: double-blind, randomized trial. *Neurorehabil Neural Repair* 32: 84-93, 2018.

Almuklass AM, Price RC, Gould JR, Enoka RM. Force steadiness as a predictor of time to complete a pegboard test of dexterity in young men and women. *J Appl Physiol* 120: 1410 – 1417, 2016.

Andreasen AK, Jakobsen J, Petersen T, Andersen H. Fatigued patients with multiple sclerosis have impaired central muscle activation. *Mult Scler* 15: 818-827, 2009.

Andreassen B, Arendt-Nielsen L. Muscle fibre conduction velocity in motor units of the human anterior tibial muscle: a new size principle parameter. *J Physiol* 391: 561-571, 1987.

Baert I, Freeman J, Smedal T, Dalgas U, Romberg A, Kalron A, Conyers H, Elorriaga I, Gebara B, Gumse J, Heric A, Jensen E, Jones K, Knuts K, Maertens de Noordhout B, Martic A, Normann B, Eijnde BO, Rasova K, Santoyo Medina C, Truyens V, Wens I, Feys P. Responsiveness and clinically meaningful improvement, according to disability level of five walking measures after rehabilitation in multiple sclerosis: a European multicenter study. *Neurorehabil Neural Repair* 28: 621–631, 2014.

Benedetti MG, Piperno R, Simoncini L, Bonato P, Tonini A. Gait abnormalities in minimally impaired multiple sclerosis patients. *J Mult Scler* 5: 363-368, 1999.

Bilodeau M, Keen DA, Sweeney PJ, Shields RW, Enoka RM. Strength training can improve steadiness in persons with essential tremor. *Muscle Nerve* 23: 771-778, 2000.

Binder MD, Powers RK, Heckman CJ. Nonlinear input-output functions of motoneurons. *Physiology* 35: 31-39, 2020.

Bohannon RW. Comfortable and maximum walking speed of adults aged 20-79 years: reference values and determinants. *Age Ageing* 26: 15-19, 1997.

Broekmans T, Gijbels D, Eijnde BO, Alders G, Lamers I, Roelants M, Feys P. The relationship between upper leg muscle strength and walking capacity in persons with multiple sclerosis. *Mult Scler J* 19: 112-119, 2012.

Cabib C, Llufriu S, Casanova-Molla J, Saiz A, Valls-Sollé J. Defective sensorimotor integration in preparation for reaction time tasks in patients with multiple sclerosis. *J Neurophysiol* 113: 1462-1469, 2015.

Carville SF, Perry MC, Rutherford OM, Smith ICH, Newham DJ. Steadiness of quadriceps contractions in young and older adults with and without a history of falling. *Eur J Appl Physiol* 100: 527-533, 2007.

Castronovo AM, Mrachacz-Kersting N, Stevenson AJT, Holobar A, Enoka RM, Farina D. Decrease in force steadiness with aging is associated with increased power of the common but independent input to motor neurons. *J Neurophysiol* 120; 1616-1624, 2018.

Christou EA, Jakobi JM, Critchlow A, Fleshner M, Enoka RM. The 1- to 2-Hz oscillations in muscle force are exacerbated by stress, especially in older adults. *J Appl Physiol* 97: 225-235, 2004.

Christou EA, Shinohara M, Enoka RM. Fluctuations in acceleration during voluntary contractions lead to greater impairment of movement accuracy in old adults. *J Appl Physiol* 95: 373-384, 2003.

Clark DJ, Manini TM, Fielding RA, Patten C. Neuromuscular determinants of maximum walking speed in well-functioning older adults. *Exp Gerontol* 48: 358-363, 2013.

Comber L, Galvin R, Coote S. Gait deficits in people with multiple sclerosis: a systematic review and meta-analysis. *Gait Posture* 51: 25-35, 2017.

Davis LA, Allen SP, Hamilton LD, Grabowski AM, Enoka RM. Differences in postural sway among healthy adults are associated with the ability to perform steady contractions with leg muscles. *Exp Brain Res* 238: 487-497, 2020.

DeLuca GC, Alterman R, Martin JL Mittal A, Blundell S, Bird S, Beale H, Hong LS, Esiri MM. Casting light on multiple sclerosis heterogeneity: the role of HLA-DRB-1 on spinal cord pathology. *Brain* 136: 1025-1034, 2013.

Duchateau J, Enoka RM. Human motor unit recordings: origins and insight into the integrated motor system. *Brain Res* 1409: 42-61, 2011.

Evangelou N, Esiri MM, Smith S, Palace J, Matthews PM. Quantitative pathological evidence for axonal loss in normal appearing white matter in multiple sclerosis. *Annal Neurol* 47: 391-395, 2000.

Farina D, Holobar A, Merletti R, Enoka RM. Decoding the neural drive to muscles from the surface electromyogram. *Clin Neurophysiol* 121: 1616-1623, 2010.

Farina D, Negro F, Dideriksen JL. The effective neural drive to muscles is the common synaptic input to motor neurons. *J Physiol* 592: 3427-3441, 2014.

Farina D, Negro F, Muceli S, Enoka RM. Principles of motor unit physiology evolve with advances in technology. *Physiology* 31: 83-94, 2016.

Feeney DF, Mani D, Enoka RM. Variability in common synaptic input to motor neurons modulates both force steadiness and pegboard time in young and older adults. *J Physiol* 596: 3793 – 3806, 2018.

Feeney DF, Meyer FG, Noone N, Enoka RM. A latent low-dimensional common input drives a pool of motor neurons: a probabilistic latent state-space model. *J Neurophysiol* 118: 2238-2250, 2017.

Fling BW, Dutta GG, Horak FB. Functional connectivity underlying postural motor adaptation in people with multiple sclerosis. *NeuroImage Clinical* 8: 281-289, 2015.

Fritzer NE, Keller J, Calabresi PA, Zackowski KM. Quantitative measures of walking and strength provide insight into brain corticospinal tract pathology in multiple sclerosis. *NeuroImage Clinical* 14: 490-498, 2017.

Fu L, Matthews PM, De Stefano N, Worsley KJ, Narayanan S, Francis GS, Antel JP, Wolfson C, Arnold DL. Imaging axonal damage of normal-appearing white matter in multiple sclerosis. *Brain* 121: 103-113, 1998.

Fuglevand AJ, Winter DA, Enoka RM. Models of recruitment and rate coding organization in motor-unit pools. *J Neurophysiol* 70: 2470-2488, 1993.

Galea MP, Cofré LizM LE, Butzkueven H, Kilpatrick TJ. Gait and balance deterioration over a 12-month period in multiple sclerosis patients with EDSS ≤3.0. *NeuroRehabilitation* 40: 277-284, 2017.

Galganski ME, Fuglevand AJ, Enoka RM. Reduced control of motor output in a human hand muscle of elderly subjects during submaximal contractions. *J Neurophysiol* 69: 2108-2115, 1993.

Goldman MD, Motl RW, Sagnelli J, Pula JH, Sosnoff JJ, Cadavid D. Clinically meaningful performance benchmarks in MS: timed 25-foot walk and the real world. *Neurology* 81: 1856-1863, 2013.

Gould JR, Reineberg AE, Cleland BT, Knoblauch KE, Clinton GK, Banich MT, Corboy JR, Enoka RM. Adjustments in torque steadiness during fatiguing contractions are inversely correlated with IQ in persons with multiple sclerosis. *Front Physiol* 9: 1404, 2018.

Gunte I, Hunter GR, McCurry BD, Bolding MS, Roy JL, McCarthy JP. Age and gender differences in hip extension and flexion torque steadiness. *Gerontology* 56: 533-541, 2010

Gutierrez GM, Chow JW, Tillman MD, McCoy SC, Castellano V, White LJ. Resistance training improves gait kinematics in persons with multiple sclerosis. *Arch Phys Med Rehabil* 86: 1824-1829, 2005.

Hadjimichael O, Vollmer TJ, Oleen-Burkey M. Fatigue characteristics in multiple sclerosis: the North American Research Committee on Multiple Sclerosis (NARCOMS) survey. *Health Qual Life Outcomes* 6: 100, 2008.

Hamilton LD, Thomas E, Almuklass AM, Enoka RM. A framework for identifying adaptations responsible for differences in pegboard times between middle-aged and older adults. *Exp Gerontol* 97: 9-16, 2017.

Holobar A, Zazula D. Multichannel blind source separation using convolution kernel compensation. *IEEE Tran Signal Process* 55: 4487-4496, 2007.

Holmes MR, Gould JR, Peña-González I, Enoka RM. Force steadiness during a co-contraction task can be improved with practice, but only by young adults and not by middle-aged or old adults. *Exp Physiol* 100: 182-192, 2015.

Justice JN, Mani D, Pierpoint LA, Enoka RM. Fatigability of the dorsiflexors and associations among multiple domains of motor function in young and old adults. *Exp Gerontol* 55: 92-101, 2014.

Kearney J, Schneider T, Yiannakas MC, Altmann DR, Wheeler-Kingshott CA, Ciccarelli O, Miller DH. Spinal cord grey matter abnormalities are associated with secondary progression and physical disability in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 86: 608-614, 2015.

Kieseier BC, Pozzilli C. Assessing walking disability in multiple sclerosis. *Mult Scler* 18: 914-924, 2012.

Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. *Neurology* 80: 409-416, 2013.

Laidlaw DH, Bilodeau M, Enoka RM. Steadiness is reduced and motor unit discharge is more variable in old adults. *Muscle Nerve* 23: 600-612, 2000.

Laine CM, Martinez-Valdes E, Falla D, Mayer F, Farina D. Motor neuron pools of synergistic thigh muscle share most of their synaptic input. *J Neurosci* 35: 12207-12216, 2015.

Liddell EGT, Sherrington C. Recruitment and some other factors of reflex inhibition. *Proc Royal Soc London B* 97: 488-518, 1925.

Loy BD, Taylor RL, Fling BW, Horak FB. Relationship between perceived fatigue and performance fatigability in people with multiple sclerosis: a systematic review and meta-analysis. *J Psychosomatic Res* 100: 1-7, 2017.

Macke JH, Buesing L, Cunningham JP, Byron MY, Shenoy KV, Sahani M. Empirical models of spiking in neural populations. *NIPS* 24: 1350-1358, 2011.

Mani D, Almuklass AM, Hamilton LD, Vieira TM, Botter A, Enoka RM. Motor unit activity, force steadiness, and perceived fatigability are correlated with mobility in older adults. *J Neurophysiol* 120: 1988-1997, 2018.

Marmon AR, Pascoe MA, Schwartz RS, Enoka RM. Associations among strength, steadiness, and hand function across the adult life span. *Med Sci Sports Exerc* 43: 560-567, 2011.

Motl RW, Sandroff BM, Suh Y, Sosnoff JJ. Energy cost of walking and its association with gait parameters, daily activity, and fatigue in persons with mild multiple sclerosis. *Neurorehabil Neural Repair* 26: 1015-1021, 2012.

Negro F, Holobar A, Farina D. Fluctuations in isometric muscle force can be described by one linear projection of low-frequency components of motor unit discharges. *J Physiol* 587: 5925-5938, 2009.

Newsome SD, Wang JI, Kang JY, Calabresi PA, Zackowski KM. Quantitative measure detect sensory and motor impairments in multiple sclerosis. *J Neurol Sci* 305: 103-111, 2011.

Ng AV, Miller RG, Gelinas D, Kent-Braun JA. Functional relationships of central and peripheral muscle alterations in multiple sclerosis. *Muscle Nerve* 29: 843-852, 2004.

Pereira HM, Spears VC, Schindler-Delap B, Yoon T, Nielson KA, Hunter SK. Age and sex differences in steadiness of elbow flexor muscles with imposed cognitive demand. *Eur J Appl Physiol* 115: 1367-1379, 2015.

Petrova PN, Carassiti D, Altmann DR, Baker D, Schmierer K. Axonal loss in the multiple sclerosis spinal cord revisited. *Brain Pathol* 28: 334-348, 2018.

Rice DA, McNair PJ, Lewis GN, Mannion J. Experimental knee pain impairs submaximal force steadiness in isometric, eccentric, and concentric muscle actions. *Arthritis Res Ther* 17: 259, 2015.

Rice CL, Vollmer TL, Bigland-Ritchie B. Neuromuscular responses of patients with multiple sclerosis. *Muscle Nerve* 15: 1123-1132, 1992.

Schlaeger R, Papinutto N, Zhu AH, Lobach IV, Bevan CJ, Bucci M, Castellano A, Gelfand JM, Graves JS, Green AJ, Jordon KM, Keshavan A, Panara V, Stern WA, von Büdingen HC, Waubant E, Goodin DS, Cree BA, Hauser SL, Henry RG. Association between thoracic spinal gray matter atrophy and disability in multiple sclerosis. *JAMA Neurol* 72: 897-904, 2015.

Sebastião E, Bikkaert RE, Hubbard EA, Motl RW. Gait variability and energy cost of overground walking in persons with multiple sclerosis: a cross-sectional study. *Am J Phys Med Rehabil* 97: 646-650, 2018.

Sosnoff JJ, Sandroff BM, Motl RW. Quantifying gait characteristics in persons with multiple sclerosis with minimal disability. *Gait Posture* 36: 154-156, 2012.

Thompson CK, Negro F, Johnson MD, Holmes MR, Miller Mcpherson L, Powers RK, Farina D, Heckman CJ. Robust and accurate decoding of motoneuron behavior and prediction of the resulting force output. *J Physiol* 596: 2643-2659, 2018.

Tracy BL, Enoka RM. Older adults are less steady during submaximal isometric contractions with the knee extensor muscles. *J Appl Physiol* 92: 1004-1012, 2002.

Tracy BL, Mehoudar PD, Ortega JD. The amplitude of force variability is correlated in knee extensor and elbow flexor muscles. *Exp Brain Res* 176: 448-464, 2007.

Vogt J, Paul F, Aktas O, Müller-Wielsch K, Dörr J, Dörr S, Bharathi S, Glumm R, Schmitz C, Steinbusch H, Raine CS, Tsokos M, Nitsch R, Zipp F. Lower motor neuron loss in multiple sclerosis and experimental autoimmune encephalomyelitis. *Ann Neurol* 66: 310-322, 2009.

Zijdewind I, Prak RF, Wolkorte R. Fatigue and fatigability in persons with multiple sclerosis. *Exerc Sport Sci Rev* 44: 123-128, 2016.

Figure Legends

Figure 1. A. The experimental setup for measuring muscle strength and force steadiness for the dorsiflexors (Above) and the plantar flexors (Below) of the right leg. High-density grid electrodes were placed over the tibialis anterior, medial gastrocnemius, and soleus muscles. B. Participant's maintained a steady contraction for 30 s at 10% and 20% MVC force. C. Monopolar signals were recorded during submaximal, isometric contractions. The high-density grid recordings resulted in bipolar electromyographic recordings that were subsequently decomposed into motor unit discharge times. D. The discharge times of 9 motor units during a steady, isometric contraction.

Figure 2. Regression models for fast-walking speed (A, B) and walking endurance (C, D) for the participants in the MS (n = 18; A, C) and control (n = 18; B, D) groups. The explanatory variables for each model were as follows: A, force steadiness of the plantar flexors at 20% MVC force and force steadiness for the dorsiflexors at 10% MVC; B, force steadiness of the dorsiflexors at 20% MVC force and the filtered Q values for the plantar flexors; C, force steadiness of the plantar flexors at 20% MVC force and force steadiness for the dorsiflexors at 10% MVC; D, MVC torque for the plantar flexors of the non-dominant leg and MVC torque for the dorsiflexors of the dominant leg.