FATIGABILITY AND MOTOR PERFORMANCE IN SPECIAL AND CLINICAL POPULATIONS

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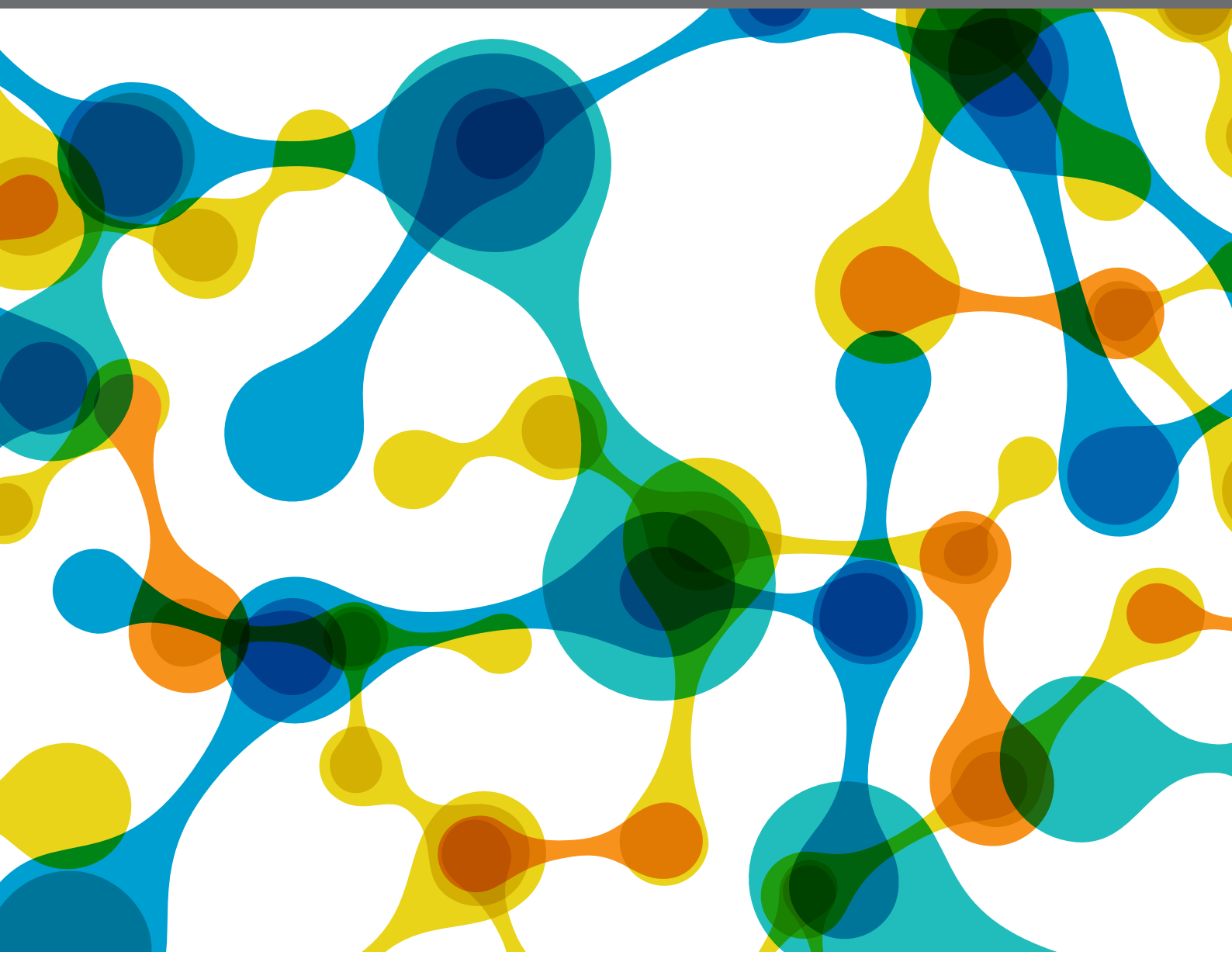

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FATIGABILITY AND MOTOR PERFORMANCE IN SPECIAL AND CLINICAL POPULATIONS

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EDITORIAL
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Editorial: Fatigability and Motor Performance in Special and Clinical Populations

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Keywords: fatigue, cognition, motor performance, elderly, women, clinical populations

Editorial on the Research Topic

Fatigability and Motor Performance in Special and Clinical Populations

Clinical and special populations often report higher levels of fatigue than typically presenting age-matched persons. Despite the high incidence of fatigue, the responsible mechanisms are still poorly understood. This is, partly, a consequence of confusing terminology. Enoka et al. (Kluger et al., 2013; Enoka and Duchateau, 2016), therefore, provided a conceptual framework that defined fatigue as a disabling symptom with attributes of performance fatigability and perceived fatigability. Performance fatigability is defined as the decline in an objective measure of performance (typically motor performance) over time. Perceived fatigability reflects the sensations which accompany regulation of the integrity of the performer and depends on the psychological state and the physiological capacity of the body to maintain homeostasis. Perceived fatigability is measured as a self-reported rating and can be evaluated as a state or trait both during motor performance or at rest.

Performance and perceived fatigability are both relevant to clinical populations and can limit physical and cognitive function. Typically, performance and perceived fatigability are studied as separate attributes in healthy and clinical populations. Consequently, there is minimal understanding of how these attributes of fatigue integrate to affect motor performance and well-being, particularly in clinical populations.

Past research has typically concentrated on the mechanisms that limit performance fatigability during single limb isometric or dynamic contractions, often in healthy young males, with little distinction between males and females, or consideration of race or ethnicity. In populations such as females, old adults, and clinical populations (e.g., people with multiple sclerosis, stroke, cancer, obesity, diabetes, amyotrophic lateral sclerosis, Parkinson's disease, and spinal cord injury to name a few), there is limited knowledge on performance fatigability, the involved mechanisms that limit performance, how fatigability assessed in the laboratory predicts functional tasks in the real world, and the interactions with perceived fatigability. This Research Topic highlights several studies and reviews on: (1) the debilitating effects of perceived fatigability in several clinical populations, and associations with performance fatigability, and (2), the mechanisms of performance fatigability, and the effects on function in various populations, including older adults, females after child birth, stroke survivors, people who are obese, and those with mild traumatic brain injury (MTBI), chronic respiratory disease (CRD) rheumatic arthritis heart failure and multiple sclerosis (MS). Below we highlight the common themes and what can be learned from these collective studies.

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PERCEIVED AND PERFORMANCE FATIGABILITY IN CLINICAL AND SPECIAL POPULATIONS

Many clinical populations report greater levels of perceived fatigability than age-matched controls [multiple sclerosis: (Gould et al.) mild traumatic brain injury: (Prak et al.) and also as highlighted in mini-reviews about people with rheumatoid arthritis (Marrelli et al.) chronic respiratory diseases (Gruet)]. However, despite the prevalence of perceived fatigability in some clinical populations, only a few manuscripts addressed the effects of perceived fatigability on performance fatigability or functional outcomes (Gruet). The mini-reviews emphasize the underreporting in the literature related to fatigue in people individuals with heart failure (Keller-Ross et al.), rheumatoid arthritis (Marrelli et al.), and chronic respiratory disease (Gruet). Thus, there is a need for studies on the interaction of perceptions of fatigue experienced in clinical populations, performance fatigability, and functional tasks.

Studies addressing whether performance fatigability differs between clinical populations and age-matched controls is more numerous than perceived fatigability, although the outcome appears to be dependent on the characteristics of the population, the involved muscle group, the requirements of the fatiguing task and the variable used to quantify fatigability. Several reviews provide examples of greater performance fatigability in populations with heart failure (Keller-Ross et al.) and rheumatoid arthritis (Marrelli et al.) than controls. In contrast, several original data studies report that performance fatigability is similar between clinical populations and controls including stroke survivors (Murphy et al.), and people with MTBI: (Prak et al.); and MS: (Gould et al.). The decline in isometric voluntary force of a single muscle groups (either the knee extensor muscles or finger abductors) was between 25 and 40% but not different between the clinical and control group. Similarly, other studies highlight in this Research Topic found no difference between other populations including young and older adults for a small muscle of the hand (Sars et al.) and between the knee extensor muscles of obese and non-obese older participants (Duan et al.). It is too simplistic however, to conclude that there is no difference in performance fatigability between a select clinical population and controls, or between young and old adults because fatigability is task dependent. The aging literature for example, shows that older adults are less fatigable than young adults for upper and lower limb muscles during an isometric-contraction fatiguing task but more fatigable when performing fast velocity contractions (Hunter et al., 2016). Similarly, based on contraction type, individuals with stroke were more fatigable than age-matched controls (Hyngstrom et al., 2012). Clearly, more studies are needed to determine performance fatigability with different task requirements that are functionally relevant.

To understand the mechanisms of performance fatigability, several studies obtained additional measurements to discriminate between a loss of force due to reductions in voluntary activation (neural drive) to the muscle and that due to altered contractile function (Gandevia, 2001). Variables known to reflect differences in voluntary activation are often more depressed in clinical and special populations whereas measures of contractile properties can be less affected for isometric fatiguing tasks (Murphy et al.; Sars et al.). Similar measurements in persons with MTBI (Prak et al.) however, only showed minor differences in voluntary drive and contractile function compared with controls. It is possible that while performance fatigability may not differ between groups, the mechanisms for failure of force during a fatiguing task can differ between populations and provide insight for strategies to address potential functional deficits and testing in different clinical populations. The mini-review by Gruet for example, presents several arguments to evaluate tests used to quantify performance fatigability in clinical populations.

FATIGABILITY AND FUNCTIONAL OUTCOMES

One goal of studying perceived and performance fatigability, and muscle function in general is to determine how it affects functional performance in vulnerable populations in real-life situations. For example, older adults who performed prolonged walking as a fatiguing exercise exhibited greater declines and greater variability in the minimal toe clearance during walking than young adults (Watanabe), possibly exposing them to greater risk of falling. Furthermore, for fatiguing exercise of upper limb muscles, lower force steadiness was associated with (1) intellectual capacity in people with MS (Gould et al.), and (2) executive function in older adults who performed a dual motor and cognitive task (Pereira et al.). The mechanistic link between cognitive function and motor tasks with fatiguing exercise in these populations deserves greater exploration.

Lastly, fatiguing trunk flexor exercise lessened localized sensitivity to pain and decreased pain perception in postpartum women indicating that trunk exercises may be useful for acute pain relief for clinical populations that are characterized by pain and/or weakness in the abdominal region muscles (Deering et al.). Thus, fatigability maybe an important and under-quantified marker of overall function in clinical and special populations.

CONCLUSION

The collective publications in this Research Topic, highlight the need and tremendous opportunity for high impact studies addressing fatigue and its relevance to functional performance in a variety of clinical and special populations. Such studies will provide a foundation for determining optimal rehabilitation strategies involving training/exercise protocols, drugs or other novel interventions to treat fatigue in clinical populations and whether there are differences between the sexes and with aging.

AUTHOR CONTRIBUTIONS

IZ, AH, and SH contributed to writing this editorial. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Age- and Sex-Related Differences in Motor Performance During Sustained Maximal Voluntary Contraction of the First Dorsal Interosseous

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Age and sex affect the neuromuscular system including performance fatigability. Data on performance fatigability and underlying mechanisms in hand muscles are scarce. Therefore, we determined the effects of age and sex on force decline, and the mechanisms contributing to force decline, during a sustained isometric maximal voluntary contraction (MVC) with the index finger abductor (first dorsal interosseous, FDI). Subjects (n = 51, age range: 19–77 years, 25 females) performed brief and a 2-min sustained MVC with the right FDI. Abduction force and root mean squared electromyographic activity (rms-EMG) were recorded in both hands. Double-pulse stimulation was applied to the ulnar nerve during (superimposed twitch) and after (doublet-force) the brief and sustained MVCs. Compared to females, males were stronger (134%, $p < 0.001$) and exhibited a greater decline in voluntary (difference: 8%, $p = 0.010$) and evoked (doublet) force (difference: 12%, $p = 0.010$) during and after the sustained MVC. Age did not affect MVC, force decline and superimposed twitch. The ratio between the doublet- and MVC-force was greater in females (0.33, $p = 0.007$) and in older (0.38, $p = 0.06$) individuals than in males (0.30) and younger (0.30) individuals; after the sustained MVC this ratio increased with age and the increase was larger for females compared to males ($p = 0.04$). The inadvertent contralateral, left force and rms-EMG activity increased over time (2.7–13.6% MVC and 5.4–17.7% MVC, respectively). Males had higher contralateral forces than females ($p = 0.012$) and contralateral force was higher at the start of the contralateral contraction in older compared with young subjects (difference: 29%, $p = 0.008$). In conclusion, our results suggest that the observed sex-differences in performance fatigability were mainly due to differences in peripheral muscle properties. Yet the reduced amount of contralateral activity and the larger difference in evoked versus voluntary force in female subjects indicate that sex-differences in voluntary activation should not be overlooked. These data obtained in neurological healthy adults provides a framework and help the interpretation and referencing of neurophysiological measures in patients suffering from neuromuscular diseases, who often present with symptoms of performance fatigability.

Keywords: aging, sex differences, twitches, doublets, performance fatigability, contralateral activity, voluntary activation, FDI

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INTRODUCTION

Performance fatigability is the decline in an objective measure of performance over a discrete period of time (Enoka and Duchateau, 2016). In the present study, we quantified performance fatigability by the decline in force during a sustained contraction. The details of the motor task, the muscles performing the task and subject characteristics are just a few of the variables that affect performance fatigability (Enoka and Stuart, 1992; Bigland-Ritchie et al., 1995; Allman and Rice, 2002; Hunter, 2016, 2017). Under most experimental conditions, performance fatigability is lower in women and older adults compared with younger men during isometric contractions at a similar percentage of maximal voluntary contraction (MVC) force (Hunter, 2014). Because sex- and age-effects are attenuated during high force isometric contractions (Hunter, 2014), most studies have examined performance fatigability using submaximal contractions of large muscles, including elbow flexors and knee extensors to detect age- and sex-differences (Hunter et al., 2004a; Mcphee et al., 2014; Solianik et al., 2017).

In contrast to large muscles, the small muscles of the hand are well suited for clinical studies focusing on (chronic) disease-related changes in neuromuscular function (Sheean et al., 1997; Thomas, 1997; de Ruiter et al., 2001; Thickbroom et al., 2006; Steens et al., 2012; Murray et al., 2014; Prak et al., 2015; Santarnecchi et al., 2015; Arnold et al., 2017). Previously we examined force decline during sustained maximal contractions with the index finger abductor muscle (the first dorsal interosseous, FDI). However, our sample sizes were small, the age ranges narrow, and the sex of the subjects inconsistently distributed for a systematic determination of the effects of age and sex on individual variation in voluntary and evoked forces and muscle activation. Because data concerning the effects of sex and age on these variables in hand muscles are scarce we decided to examine the effects of sustained MVCs on performance fatigability in the FDI of young and older individuals.

During an MVC, the contralateral homologous muscle typically becomes inadvertently active (Zijdewind and Kernell, 2001; Shinohara et al., 2003; Martin and Rattey, 2007; Post et al., 2008; Hortobagyi et al., 2011; Heetkamp et al., 2014). The magnitude of this activity, however, tends be higher in older and middle-aged compared with younger adults (Shinohara et al., 2003; Heetkamp et al., 2014). Although contralateral activity occurs in various tasks (Shinohara et al., 2003; Martin and Rattey, 2007; Post et al., 2008; Jiang et al., 2012; Watanabe et al., 2017) it is unclear if sex affects contralateral force and activation, parameters that are associated with effort and could be used as outcome variables to further characterize the nature and mechanism of performance fatigability.

The aim of this exploratory study was to determine the effects of age and sex on force decline during MVC, i.e., a measure of performance fatigability and on the mechanisms, using peripheral nerve stimulation, contributing to this force decline. The second aim was to determine the effects of age and sex on the magnitude of unintended force and activation produced in the contralateral, homologous FDI.

MATERIALS AND METHODS

Self-reported neurologically healthy subjects (age: 19–77, mean 48.84 ± 17.16 years, n = 51; 25 females) were included in the study. Some of these subjects were included as control subjects for earlier experiments (Steens et al., 2012; Prak et al., 2015). The University Medical Ethical Committee approved the protocol and the informed consent according to the guidelines of the Declaration of Helsinki (2013), which each subject signed prior to the start of the experiment.

All subjects completed the Fatigue Severity Scale (FSS), the Hospital Anxiety Depression Scale (HADS) and the Oldfield handedness questionnaires to assess perceived fatigue, mood and handedness, respectively (Oldfield, 1971; Zigmond and Snaith, 1983; Krupp et al., 1989).

Experimental Setup

Subjects were seated in a chair with both arms resting on a table adjustable for height with the elbow flexed at approximately 135°. Subjects were asked to place the forearms in a position midway between pronation and supination, so that abduction of the index finger occurred in a vertical direction, but their arm and the hand were not affixed to the table and remained free to move (see **Figure 1A**). A computer monitor was placed approximately 1 m in front of the subject providing visual feedback of the target force throughout the experiment.

Index finger abduction force was measured with custom-made force transducers (van Duinen et al., 2007, **Figure 1A**). The subjects held one transducer in each hand with the index fingers extended. The transducer was positioned such that a bar equipped with strain gages was parallel to the index finger; a C-shaped wedge placed over the proximal interphalangeal joint of the index finger connecting the force transducer to the index finger. To maintain the hand position in relation to the force transducer throughout the experiment, the thumb was taped to digit 3–5 and the index finger was taped to the C-shaped wedge on the transducer. The force signal was amplified and sampled for off-line analysis (CED 1401plus interface, Cambridge Electronic Design, United Kingdom; sampling frequency 500 Hz). During the experimental tasks, subjects could move each arm freely while holding the force transducer. However, the position of the hand in relation to the force transducer was constant.

EMG Recordings

Electromyographic (EMG) activity was recorded bilaterally from the main index finger abductor, the FDI. After cleaning the skin with alcohol, two 2 mm surface electrodes (Ag-AgCl) with conducting gel were placed over the belly of the FDI and close to the second metacarpophalangeal joint (**Figure 1A**). A strap electrode was placed around the wrist of the right hand and served as a reference. The EMG signals were amplified (200x) and filtered (band pass filter: 10–1000 Hz) with a custom made amplifier, and sampled (at 2 kHz) using Spike2 (version 7.12b for Windows).

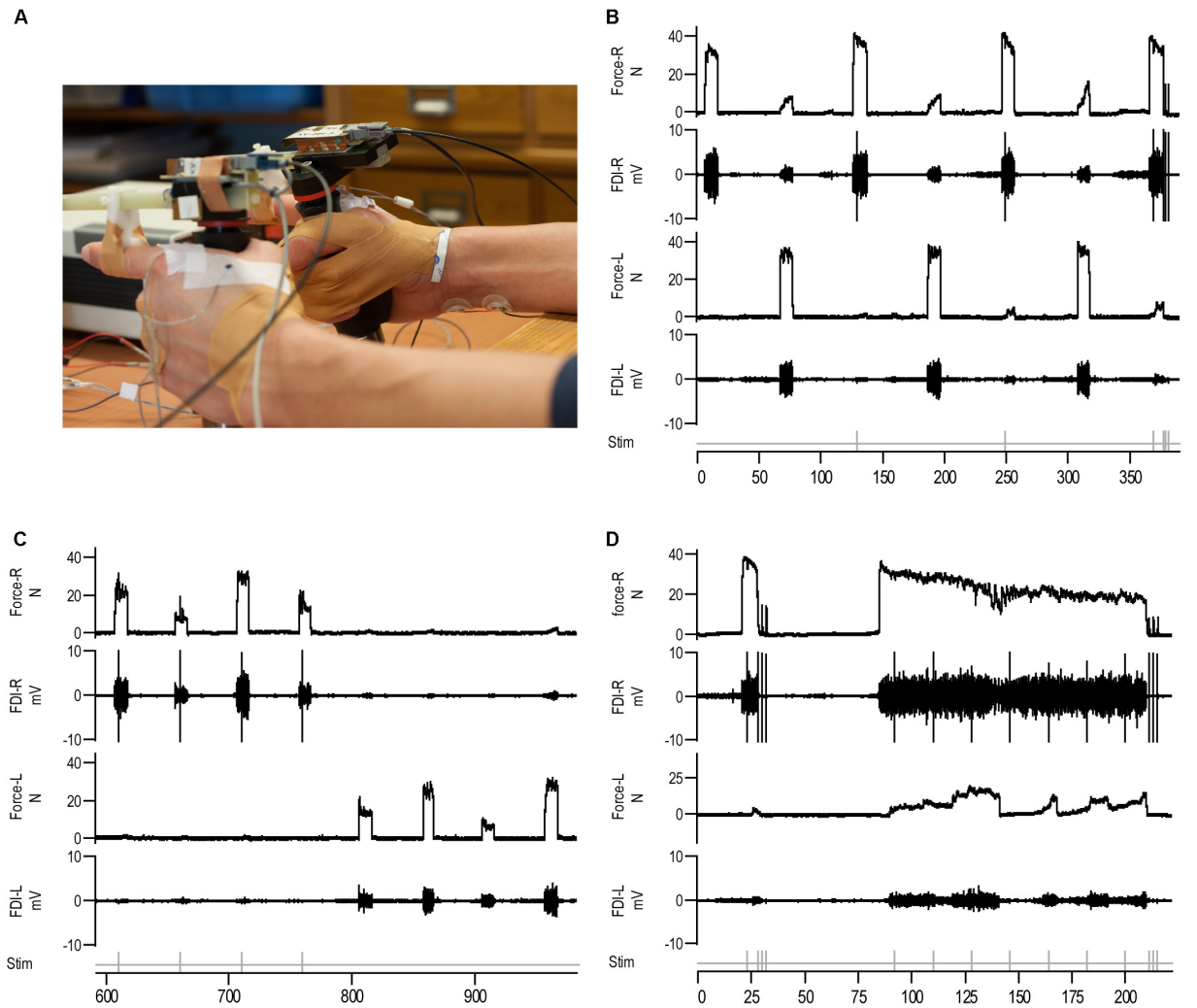

FIGURE 1 | Illustration of the force transducer and an overview of the motor tasks as illustrated by data of an individual subject (female, 64 years old). **(A)** Photo of the hands holding the force transducers. EMG electrodes were taped to the muscle belly of the FDI and close to the second metacarpal joint. Stimulation electrodes were placed on the ulnar nerve of the right forearm, one electrode at and a second electrode approximately two centimeters proximal from the wrist. **(B)** An example of four right and three left maximal voluntary contractions (MVCs) at baseline. Subjects alternated between the right and left hand. Electrical stimulation (stim) was applied to the ulnar nerve during the MVCs with the right hand and at rest (during the first stimulus the subject was not at rest yet). **(C)** Submaximal contractions with the left and right FDI at four different levels (10, 30, 50, and 70% MVC). During each contraction with the right FDI, electrical stimulation was applied to the ulnar nerve. **(D)** Brief MVC with electrical stimulation of the ulnar nerve, followed by two to three stimuli at rest. After 60 s rest, subjects performed a sustained MVC for 124 s. During this sustained contraction seven stimuli were applied to the ulnar nerve (18 s interval). Following the sustained contraction three doublet-forces were evoked at rest.

Nerve Stimulation

Two electrodes were placed over the right ulnar nerve, one electrode at the wrist and a second electrode approximately two centimeters proximal to the wrist (**Figure 1A**) for electrical stimulation (DS7, Digitimer, United Kingdom) of the ulnar nerve. The ulnar nerve was stimulated with electric current (stimulus duration: 200 μs) starting from 5 mA with increasing steps of 5 mA to obtain a maximal EMG-response from the right FDI (Mmax). The constant-current stimulator could use a source voltage variable from 100 to 400 Volt to produce the necessary output current. Throughout the experiment the ulnar nerve was stimulated at ≥130% of the intensity needed to obtain Mmax (mean 39 mA, range: 25–67 mA).

To assess contractile properties and voluntary activation of the right FDI double-pulse stimulation (10 ms interstimulus interval) was given to the right ulnar nerve at rest and during voluntary contractions (superimposed twitch technique). The force evoked by the double-pulse stimulation at rest is referred to as doublet-force.

Motor Tasks

Throughout the experiment subjects were encouraged to produce a maximal effort during the MVCs, no explicit instructions were

given to the subject regarding the contralateral hand. During the first task, subjects were asked to produce seven MVCs, starting with the right FDI (4 MVCs) and alternating between hands (10 s duration, followed by 50 s rest, **Figure 1B**). During at least two right-hand MVCs, superimposed doublets (SITs) were evoked. After the last MVC two to three potentiated doublets at rest were evoked (some subjects maintained the contraction a little too long resulting in only two doublets being evoked at rest).

To evaluate differences in voluntary activation with a different method the second task consisted of three sets of submaximal efforts at 10, 30, 50, and 70% MVC in pseudo-random order, alternating sets between the left and right hand (**Figure 1C**). To determine the relationship between voluntary force and SITs (De Serres and Enoka, 1998), electrical stimulation was applied to the right ulnar nerve during at least two sets of submaximal contractions (minimal eight contractions).

The final task consisted of a brief MVC (6 s) followed by a 124 s sustained MVC (**Figure 1D**). Throughout the contraction, subjects were continuously encouraged to give their maximal effort. During the brief MVC, a SIT was evoked followed by three doublets at rest (pre-sustained doublets). In total, seven SITs were evoked during the sustained contraction (stimulus interval 18 s), followed by two or three doublets at rest immediately after the sustained contraction (post-sustained doublets, **Figure 1D**).

Outcome Measures

During MVCs, peak force was measured and highest force of all MVCs was used as reference MVC. The EMG signals were root mean squared (rms) over 500 ms and the highest value was used as a reference for the EMG values. For the electrically evoked doublets the amplitude, contraction time (CT) and half relaxation time (HRT) were measured. The amplitude of the largest doublet at rest was used as a reference, for the CT and HRT we took average values as a reference.

The SITs were used to quantify voluntary activation using the following equation:

$$VA\,(\%) = 100 \times \left[1 - \frac{SIT}{largest\ doublet\ at\ rest}\right]$$

During the submaximal contractions, the force at the time of the stimulation was determined and expressed as percentage of MVC. The SITs were expressed as percentage of the reference doublet.

During the sustained MVC, mean force, standard deviation (SD) of the force and rms-EMG obtained in the right (target side) and left hand were calculated over 2 s windows. To quantify force variability the SD was divided by the average force. The average of the first and last 6 s of the sustained contraction were used to index initial and end rms-EMG and force values. We also calculated a doublet/MVC ratio for (1) the doublet before the sustained MVC divided by the initial sustained MVC force, and (2) the doublet after the sustained MVC and the end sustained force values.

The twitches evoked during the sustained contraction were corrected for fatigue-related changes in the muscle with the following equation, before VA was calculated (Schillings et al., 2003).

$$Corrected\ twitch(T) = \frac{SIT\ (at\ t)}{presustained\ doublet - \left(\frac{t}{1245}\right) * (presustained - postsustained\ doublet)} * 100$$

Statistical Analysis

Primary outcomes were analyzed using SPSS (IBM SPSS Statistics, version 24). For outcome measures and residuals, normality assumptions were examined by probability and normality plots. If assumptions were violated, data were transformed.

Force and rms-EMG values obtained during the MVCs, and the initial and end force and rms-EMG values during the sustained contraction, were analyzed with univariate analysis of variance (ANOVAs) with sex as between subject factor and age as covariate. A repeated measures ANOVA (rm-ANOVA) was used to evaluate changes in doublets and doublet/MVC ratio with time (at baseline, prior to, and after the sustained MVC) as within subjects factor, sex as between subject factor and age as a covariate, including the interaction effect between sex and age.

SITs during submaximal contractions were analyzed using multilevel analysis (MLwiN for Windows, version 3.00, Centre for Multilevel Modelling, University of Bristol), with force (% MVC) as repeated measure at level 1 nested within subject at level 2 hierarchy. First, the model was fit using voluntary force (% MVC) as explanatory variable. Subsequently, intercept and slope were allowed to vary at both level 1 and level 2. Next, the fixed factors age, sex and their interaction terms were added. After each inclusion, the models were evaluated and only models with the smallest log-likelihood values survived.

To characterize changes over time within and between subjects we used pre-planned multilevel analysis for force, rms-EMG and SITs evoked during the sustained contraction with time as a first level variable nested within subject (level 2). These models were used to assess the effects of time, age, and sex on the outcome variable. First, the model was fitted with time and polynomials of time as fixed factors. Subsequently, intercepts were allowed to vary across subjects, followed by a model that allowed random slopes. Additionally, age, sex, and their interaction with time were included in the model. Only models with the lowest log-likelihood values survived.

In addition, Spearman correlations coefficients were calculated to determine the relation between perceived fatigue and mood with the percentage of force decline, age and sex, during the sustained MVC.

Statistical significance was set at α of 0.05. In the text mean and SD values are given unless stated otherwise. For multilevel model comparisons, difference in log likelihood values (LLH) are presented.

RESULTS

Baseline Measurements

All subjects performed the task as instructed. In one male subject the force of the left hand was not obtained due to a technical

problem with the force transducer and in another female subject random noise affected the EMG recording of the left FDI. The affected parameters of these two sets of data were removed from the analyses.

Table 1 shows the subject characteristics. According to Oldfield Handedness Questionnaire (Oldfield, 1971)), one male subject was left handed (mean laterally index: 87 ± 27). All subjects presented an FSS score < 4.5, indicative of no perceived fatigue (Bakshi et al., 2000, **Table 1**) and HADS score < 8, suggesting no signs of depression (Spinhoven et al., 1997). These questionnaires revealed no age nor sex effect (sex: FSS: Spearman's $\rho = 0.124$, $p = 0.386$; H_DS: Spearman's $\rho = -0.125$, $p = 0.381$; HA_S: Spearman's $\rho = 0.076$, $p = 0.597$; age: FSS: Spearman's $\rho = -0.165$, $p = 0.248$; H_DS: Spearman's $\rho = 0.126$, $p = 0.379$; HA_S: Spearman's $\rho = 0.062$, $p = 0.667$).

Brief Maximal Contractions

Both right-hand voluntary force (MVC: males: 43.0 ± 11.2 N vs. females: 32.0 ± 6.6 N, $p < 0.001$) and evoked force (doublet: males 12.7 ± 4.2 N; females 10.7 ± 2.9 N, $p = 0.049$) were higher in males than females. Larger MVCs were obtained in subjects with greater VA (mean: 94.1 ± 5.6%, $r = 0.34$, $p = 0.016$) but the VA did not differ between sexes ($p = 0.83$). The contraction time of the doublet did not differ [males: 93 ± 16 ms; females: 99 ± 13 ms; $F_{(1,47)} = 1.873$, $p = 0.177$], whereas half relaxation time (HRT) did differ between males (85 ± 12 ms) and females [96 ± 14 ms; $F_{(1,47)} = 9.180$, $p = 0.004$].

We found no main effect of age for MVC [$F_{(1,49)} = 0.074$, $p = 0.787$], voluntary activation [$F_{(1,49)} = 2.012$, $p = 0.162$], contraction time [$F_{(1,49)} = 0.017$, $p = 0.90$] or HRT [$F_{(1,49)} = 0.013$, $p = 0.91$].

The ratio between the evoked doublet and the voluntary MVC was lower in males (0.30 ± 0.08) than in females [0.33 ± 0.06; $F_{(1,47)} = 7.991$, $p = 0.007$, **Figure 2**]. Additionally, this ratio showed a trend for an effect of age [$F_{(1,47)} = 3.716$, $p = 0.06$] and an interaction effect of sex * age [$F_{(1,47)} = 5.316$, $p = 0.026$; **Figure 2A**]. The interaction effect was mainly due to an increase in the doublet/MVC ratio in older males (0.022 increase per year).

The MVCs of the left hand also differed between male (51.6 ± 11.7 N) and female subjects (39.8 ± 9.7 N; $p < 0.001$). The MVCs obtained in the left and right hand were correlated ($r = 0.75$, $p < 0.001$), however, only the MVC of the left hand differed with age ($r = -0.30$, $p = 0.017$). Sex and age together explained 36% of the variability in MVC ($p < 0.005$).

While producing MVCs, the contralateral hand also showed an index finger abduction force (in left hand: median: 5.3% of MVC, range: 0.66–30.43%; in right hand: median 4.1% of MVC, range: 0.37–37.49%; $Z = -1.3$, $p = 0.19$). The associated force in the left hand was positively associated with age (Spearman's $\rho = 0.47$, $p = 0.001$) but did not differ by sex.

Submaximal Contractions

To examine voluntary activation with a different method we evoked SITs during submaximal right hand index finger abductions. Multilevel analysis showed that the model improved ($p < 0.001$) after allowing random intercept and slopes for each individual. This model was further improved by including sex

TABLE 1 | Primary outcomes of study population, separately for different age groups and sex (mean ± SD).

Variables	<30		30–40		40–50		50–60		60–70		70–80	
Age												
Sex	**M (*n* = 3)**	**F (*n* = 5)**	**M (*n* = 5)**	**F (*n* = 5)**	**M (*n* = 4)**	**F (*n* = 5)**	**M (*n* = 4)**	**F (*n* = 3)**	**M (*n* = 5)**	**F (*n* = 3)**	**M (*n* = 5)**	**F (*n* = 4)**
Left MVC (N)	53.4 (13.3)	44.7 (7.6)	57.9 (12.3)	49.4 (12.0)	51.0 (12.8)	36.9 (6.3)	46.0 (7.8)	32.1 (5.8)	54.2 (13.4)	39.42 (2.75)	45.3 (11.2)	31.6 (6.8)
Right MVC (N)	46.0 (8.5)	31.83 (7.2)	43.4 (9.8)	34.1 (8.8)	41.2 (16.3)	30.7 (6.0)	35.6 (3.9)	28.7 (4.3)	47.7 (10.9)	37.0 (9.2)	42.4 (17.4)	30.3 (3.2)
Doublet-force (N)	11.9 (4.7)	10.69 (2.12)	12.1 (2.1)	10.9 (3.2)	10.1 (6.4)	10.2 (2.6)	9.1 (1.7)	10.0 (3.4)	15.8 (2.2)	13.4 (4.9)	15.8 (3.8)	9.6 (2.1)
Doublet/MVC	0.25 (0.06)	0.34 (0.04)	0.29 (0.07)	0.32 (0.03)	0.23 (0.05)	0.34 (0.12)	0.26 (0.06)	0.34 (0.07)	0.34 (0.06)	0.35 (0.05)	0.40 (0.10)	0.32 (0.05)
Voluntary activation (VA)	96.6 (3.4)	96.2 (2.4)	92.7 (10.7)	95.6 (2.2)	96.1 (2.2)	91.5 (5.1)	97.1 (3.6)	92.4 (9.4)	95.3 (2.5)	93.4 (6.7)	89.6 (9.3)	93.6 (2.8)
Contraction time (CT)	90.8 (14.8)	102.6 (16.1)	92.3 (26.7)	99.5 (14.1)	90.3 (17.4)	100.5 (14.2)	106.0 (12.3)	97.8 (10.3)	90.4 (4.5)	94.2 (8.9)	90.8 (14.3)	95.3 (10.9)
Half relaxation time (HRT)	84.2 (10.9)	95.6 (13.0)	78.9 (9.6)	101.5 (7.3)	95.7 (14.7)	91.2 (6.4)	84.0 (11.3)	90.0 (11.3)	85.9 (12.9)	105.4 (30.9)	84.9 (10.4)	93.7 (13.2)
Superimposed twitch (SIT)	3.5 (3.4)	3.8 (2.4)	7.3 (10.7)	4.4 (2.2)	3.9 (2.2)	8.5 (5.2)	2.9 (3.6)	7.6 (9.4)	4.7 (2.5)	6.6 (6.7)	12.2 (9.6)	6.4 (6.7)
FSS	2.6 (1.4–4.0)		2.5 (1.8–3.4)		2.8 (1.1–3.9)		1.9 (1.3–3.2)		2.6 (1.1–3.6)		2.3 (1.7–3.7)	
H_DS	0.0 (0.0–3.0)		0.0 (0.0–2.0)		1.0 (0.0–2.0)		1.0 (0.0–2.0)		1.0 (0.0–4.0)		0.0 (0.0–4.0)	
HA_S	4.5 (0.0–7.0)		4.0 (1.0–6.0)		2.0 (0.0–6.0)		3.0 (0.0–7.0)		5.0 (3.0–7.0)		4.0 (0.0–7.0)	
Handedness	95 (80–100)		100 (58–100)		100 (67–100)		100 (68–100)		84.5 (−60–100)		90 (80–100)	

Age in years; Sex divided in male (M) and female (F); MVC, (brief) maximal voluntary contraction; FDI, first dorsal interosseous; MVCs are in N; doublets are referred to as potentiated doublet-forces at rest; Voluntary activation (VA) in percentage; Doublet contraction time (CT) in ms; Doublet half relaxation time (HRT) in ms; Superimposed doublet-force (SIT) as % of doublet-force at rest; FSS, Fatigue Severity Scale; H_DS, subdivision depression of the Hospital Anxiety Depression Scale; HA_S, subdivision anxiety of the Hospital Anxiety Depression Scale (FSS, H_DS and HA_S scores in median and range); Handedness expressed as Oldfield (Oldfield, 1971) laterally index in percentage (median and range).

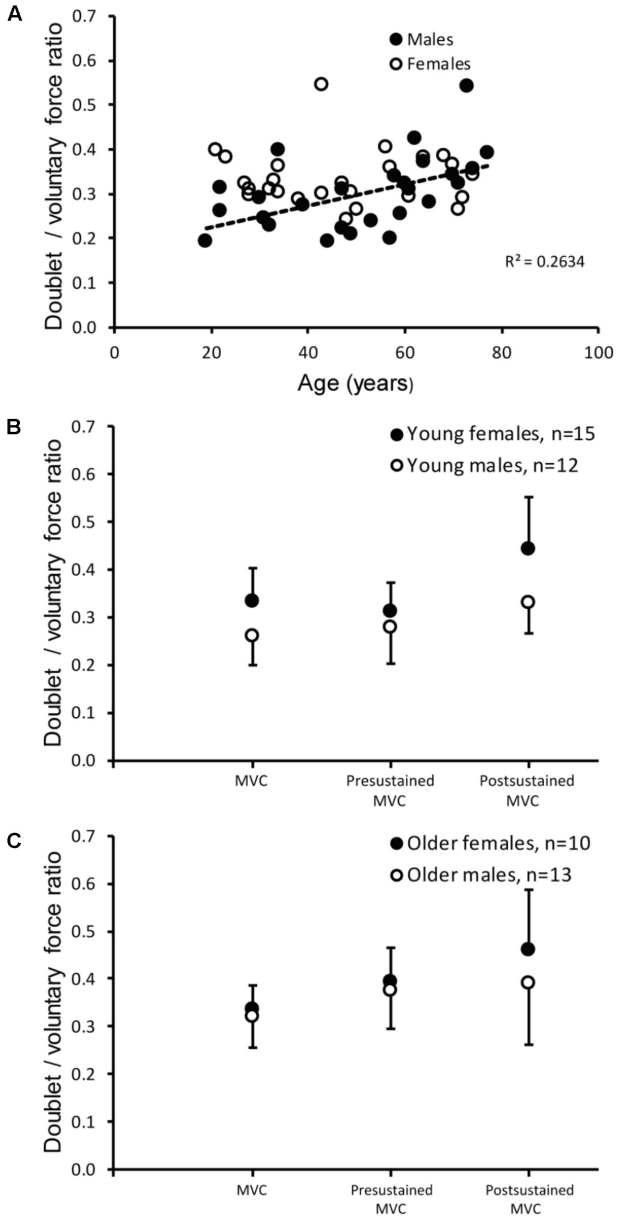

FIGURE 2 | Mean and standard deviation of the doublet/voluntary force ratios. **(A)** Association between age and the ratio between the doublet at baseline and the MVC during brief MVC for male (closed symbols) and female subjects (open symbols). Data showed a significant effect of sex, and an interaction effect of sex * age. **(B,C)** The doublet at baseline/MVC, doublet prior to the sustained MVC/mean force during first 6 s of sustained MVC (Presustained MVC), doublet after the sustained MVC/mean force during last 6 s of sustained MVC (Postsustained MVC). Data **(B)** is illustrated for young males (<50 years old, open symbols) and females (closed symbols) and **(C)** for older males (≥50 years old, open symbols) and females (closed symbols).

as explanatory variable (ΔLLH = 5.93, $p = 0.007$; sex: $Z = 2.96$; $p = 0.003$). The sex * force interaction did not improve the model further, demonstrating that the difference in SIT did not depend on the force levels (**Figure 3**). Adding age as a fixed variable did not further improve the model ($p > 0.05$).

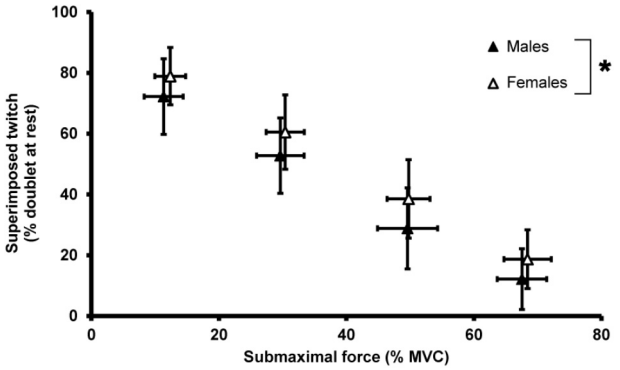

FIGURE 3 | Mean and standard deviation of the doublet-force for males and females during different force levels of submaximal contractions. Submaximal contractions were performed at circa 10, 30, 50, and 70% of subjects' MVC. Doublet-forces were normalized as percentage of maximal doublet-force at rest during baseline measurements. Closed symbols represent male subjects, open symbols represent female subjects. The asterisk identifies a significant difference between males and females.

Sustained Maximal Voluntary Contraction

For all parameters, the multilevel analysis revealed that the model with the best fit included time, and the 2nd and 3rd order polynomial of time, pointing to non-linear changes over time (**Figures 4**, **5**). The models improved further by allowing intercepts and slopes to vary randomly for each subject, illustrating the large variability between subjects. Throughout the results section, this model will be referred to as the basic model.

Right Index Finger Abduction Force

The brief MVC prior to the sustained MVC declined to 33.2 N [±9.6; 88% of initial MVC; $F_{(1,47)} = 5.044$, $p = 0.029$]. However, neither sex nor age affected this decline [sex: $F_{(1,47)} = 2.653$, $p = 0.110$; age: $F_{(1,47)} = 0.414$, $p = 0.523$].

Index finger abduction force declined further during the sustained MVC over time ($p < 0.001$). Mean force averaged over the first 6 s of the sustained contraction (79.1% MVC ± 7.97) was not different between males (78.1% MVC ± 7.04) and females (80.0% MVC ± 8.86; **Figure 4A**). However, at the end of the sustained contraction, the abduction force declined to 30.8% of MVC (±9.4%) in male and to 38.7% of MVC (±9.2%) in female participants [$F_{(1,48)} = 7.1$, $p = 0.010$].

Multilevel modeling confirmed this observation; adding sex and the interaction of sex * time improved the basic model significantly [ΔLLH = 4.41, $p = 0.015$; sex * time: $Z = 2.27$, $p = 0.023$]. We further evaluated whether differences in MVC could explain the effect of sex by including the right hand MVC and the interaction term of MVC * time into the basic model. Adding these variables did improve the basic model but the comparison between this model and the model including sex demonstrated that the latter model was superior (ΔLLH = 6.72, $p = 0.01$). In contrast, no improvement was observed after adding age or the interaction of age * time into the basic model ($p = 0.496$; $p = 0.461$, respectively; **Figure 5A**).

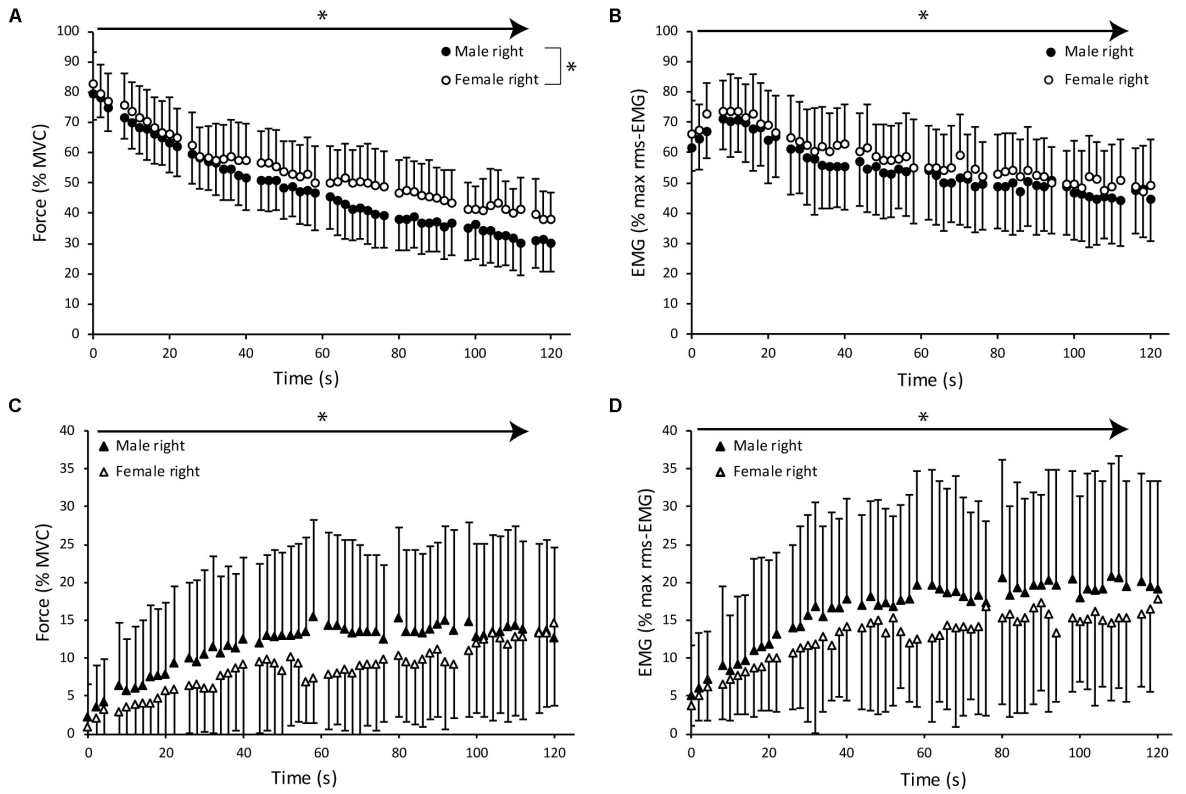

FIGURE 4 | Mean and standard deviation of index finger abduction force and root mean squared EMG (rms-EMG) of the first dorsal interosseous (FDI) averaged over 2 s windows during the sustained MVC for males and females. Abduction force expressed as percentage of maximal force and rms-EMG activity expressed as percentage of maximal rms-EMG during brief MVCs at baseline. Values obtained at the times of peripheral nerve stimulation were excluded (every 18 s). **(A)** Index finger abduction force obtained in the right hand for male (closed symbols) and female subjects (open symbols). **(B)** Mean rms-EMG activity of the right FDI for male and female subjects during sustained MVC. **(C)** Averaged index finger abduction force obtained from the left non-target hand. **(D)** Mean rms-EMG activity of the left, contralateral non-target FDI for male and female subjects separately. The arrows with asterisks identify significant changes over time. Additionally, the significant interaction effect of time * sex is identified with a bracket and asterisk.

The rms-EMG of the Right FDI

The maximal rms-EMG during the brief MVC prior to the sustained contraction equaled 96.3% (23.5 SD) of the initial MVC. Mean 2-s rms-EMG values increased in the first 6 s from 66.3% (±8.0%) to 72.2% (±9.5%) of the initial rms-EMG and started to decline after 15 s to 47.3% (±13.0%) at the end of the sustained MVC ($p < 0.001$). The EMG activity at the end of the contraction did not differ between the sexes [$F_{(1,48)} = 0.36$, $p = 0.549$, **Figure 4B**] nor with age [$F_{(1,48)} = 1.45$, $p = 0.234$, **Figure 5B**]. The multilevel analysis also showed no main or interaction effect of sex on the EMG activity (ΔLLH = 1.31, $p = 0.315$). However, after inclusion of age and the interaction term of age * time the model explained EMG variation significantly better (ΔLLH = 8.26, $p = 0.0014$; age * time: $Z = 3.64$, $p < 0.001$). That is, older adults showed a smaller increase in EMG in the first minute of the sustained contraction than younger adults (**Figure 5B**) and a smaller decline in the second half of the sustained MVC.

Variability of Force

Force variability increased in both males and females from the start to the end of the sustained contraction (0.04–0.10, $p < 0.001$). Neither for the first 6 s nor for the last 6 s of the sustained contraction, did the force variability differ between males and females ($p = 0.194$; $p = 0.743$, respectively). The multilevel analysis also showed no effects of sex, age or the interaction terms of sex with time on EMG activity (although a trend was observed for age * time; ΔLLH = 4.93, $p = 0.079$; $Z = -2.059$; $p = 0.039$).

Associated Activity During the Sustained Maximal Voluntary Contraction

During right index finger abduction, force in the contralateral non-target hand progressively increased from 2.6% (±3.7%) to 13.6% of MVC (±10.8%, $p < 0.001$, **Figure 4C**).

Adding sex to the basic model explained more of the variance (ΔLLH = 4.89, $p = 0.032$; sex: $Z = -2.50$; $p = 0.012$). Age showed a tendency to improve the model (ΔLLH = 3.40, $p = 0.065$; age: $Z = 1.952$, $p = 0.051$, **Figure 5C**) without significant interaction terms. As can be observed in **Figure 4C**, the analysis implies that, overall, mean contralateral activity is larger in males (11.89 ± 9.12% MVC) than in females (8.6 ± 6.01% MVC).

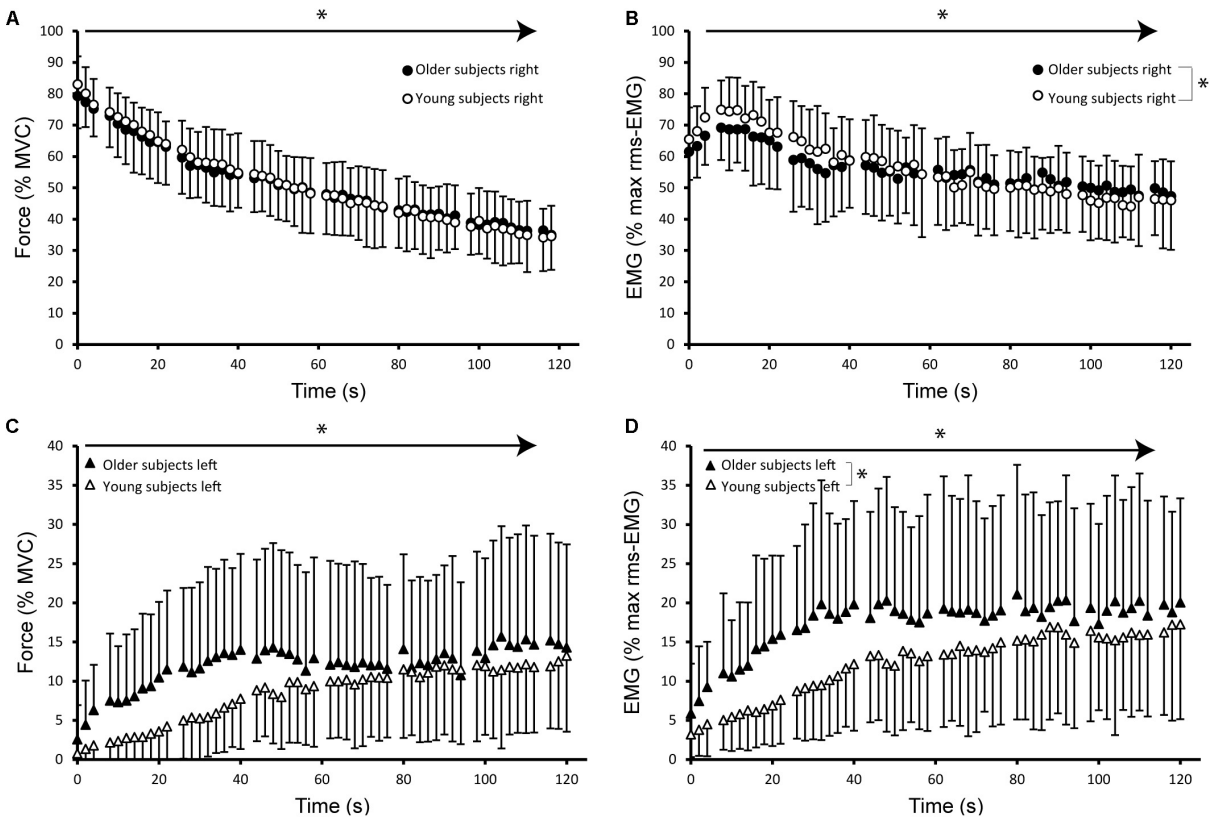

FIGURE 5 | Mean and standard deviation of index finger abduction force and rms-EMG of the FDI averaged over 2 s windows during the sustained MVC for young (<50 years old, $n = 27$, 15 females; open symbols) and older (≥50 years old, $n = 24$, 10 female; closed symbols) subjects. Values obtained at the times of peripheral nerve stimulation were excluded (every 18 s). **(A)** Index finger abduction force obtained in the right hand during sustained MVC. **(B)** Averaged rms-EMG activity of the right FDI. Older subjects showed a smaller potentiation at the start of the sustained contraction, whereas young subjects show a gradual decline in rms-EMG activity of the right FDI. **(C)** Averaged index finger abduction force of the left hand. **(D)** Averaged rms-EMG activity of the left FDI. Older subjects exhibited higher averaged rms-EMG activity compared to young subjects. The arrows with asterisks identify significant changes over time. Additionally, the significant interaction effects of time * age are identified with a bracket and asterisk.

The EMG activity of the left FDI showed no significant effect of sex (**Figure 4D**). Including age in the basic model contributed to a better model with a trend toward significance (ΔLLH = 3.073, $p = 0.080$; age: $Z = 1.968$, $p = 0.049$). Adding the interaction term of age * time further improved the model (ΔLLH = 10.306, $p = 0.006$; age*time: $Z = -2.87$, $p = 0.004$). **Figure 5** shows the larger EMG in the older than the younger subjects during the first minute.

Doublet-Force Before, During and After the Sustained Contraction

Doublet-Force at Rest

Repeated measures ANOVA revealed that the doublet declined from pre- to post-sustained contraction [$F_{(1,64)} = 195.58$; $p < 0.001$]. Moreover, the interaction effect of doublet * sex was significant [$F_{(1,64)} = 9.66$; $p = 0.001$], revealing that the decrease in doublet-force after the sustained MVC was higher in males (60.9 ± 13.4% of initial doublet) than females (49.0 ± 14.3% of initial doublet). The decline in doublet-force was associated with the decline in MVC ($r = 0.48$, $p < 0.001$).

The ratio of doublet and sustained MVC at the start (males: 0.33 ± 0.09, females: 0.34 ± 0.07) was smaller than the ratio at the end of the sustained MVC (males: 0.36 ± 0.11, females: 0.45 ± 0.11; **Figures 2B,C**). Statistical analysis of these ratios revealed main effects of time [$F_{(1,47)} = 10.79$, $p = 0.002$], sex [$F_{(1,47)} = 7.17$, $p = 0.010$], and age [$F_{(1,47)} = 5.26$, $p = 0.026$]. Additionally, an interaction effect of time and sex [$F_{(1,47)} = 4.54$, $p = 0.038$], and a trend toward a significant effect of time and age were found [$F_{(1,47)} = 3.89$, $p = 0.055$]. In other words, the doublet/voluntary force ratio was larger in females and in older subjects and the decline in doublet-force was less than the decline voluntary force in females after the sustained contraction. One subject was excluded from the analysis; the post-sustained ratio (1.41) differed more than 3 SD from the mean.

After the sustained contraction, the HRT of the doublet was increased but males (119.7 ± 26.6% of initial) still had shorter HRTs than females [124.0 ± 26.2% of initial; $F_{(1,49)} = 7.401$, $p = 0.009$]. Age, however, did not contribute to the increase in HRT or CT [HRT: $F_{(1,49)} = 1.46$, $p = 0.233$; although CT showed a trend toward significance CT: $F_{(1,49)} = 3.83$, $p = 0.056$].

Superimposed Twitches (SITs)

The SITs during the sustained contraction were analyzed with multilevel analysis. In total, seven double stimuli were applied with an interval of 18 s. The model that explained the variance in SIT amplitude the best only included time, allowing random intercepts and slopes (**Figure 6**). Sex and age did not contribute to an improved model, which implies that the observed increase in SIT amplitude throughout the sustained MVC did not differ by sex or age.

Additional Analysis

Because our data suggested that changes in peripheral muscle properties were important contributors to the decline in voluntary force, we included doublet-force (% presustained doublet) in a model to explain the variance in voluntary force. This model explained force decline better than the model including sex (ΔLLH = 55.48, $p < 0.001$).

DISCUSSION

The primary finding of this study was that during a sustained maximal contraction of a small hand muscle, force declined more in males than females but without a difference in rms-EMG. This difference was independent of variation in MVC force but did depend on the decline in the electrically evoked doublet after the sustained contraction. Subjects showing a larger decline in the evoked force also showed a larger decline in voluntary force; both forces showed a larger decline in males. Nevertheless, this decline in doublet-force was, however, smaller than the decline in voluntary force, especially in females. Age, on the other hand, did not affect force decline but did affect rms-EMG, showing a smaller increase in the rms-EMG activity at the start of the contraction for older versus younger individuals. Throughout the contraction, the superimposed twitches increased independent of sex and age. Overall, the results suggest that the sex differences were mainly due to differences in peripheral muscle properties. This conclusion was further strengthened by additional analysis showing that changes in electrically evoked doublets explained variation in voluntary force even more accurately than sex differences. Yet the greater decline in voluntary than evoked force, especially in females, combined with less contralateral activity suggests that sex-differences in voluntary activation of the FDI should not be overlooked.

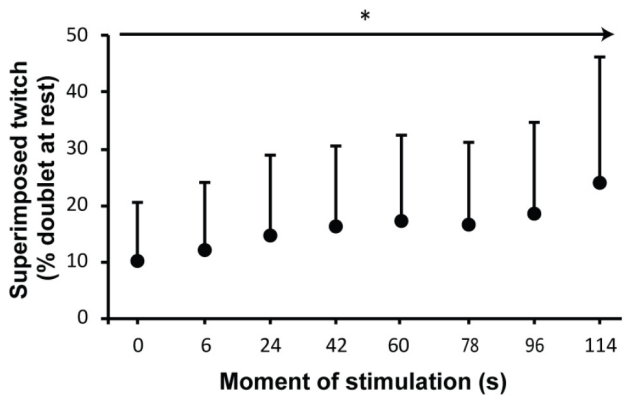

FIGURE 6 | Mean and standard deviation of the superimposed twitches (SITs) as percentage of presustained twitch at rest. The *x*-axis shows times of stimulation; (0) SIT during brief MVC prior to the sustained MVC and times of SITs during sustained MVC (in seconds). The arrow with asterisk identifies a significant change over time.

Sex Differences During the Sustained Contraction

During the sustained MVC with the FDI, force declined less in females than males. This result is expected if one considers data obtained in other (larger) muscle groups during submaximal contractions (West et al., 1995; Russ and Kent-Braun, 2003; Hunter et al., 2004a; Senefeld et al., 2013; Ansdell et al., 2017; Solianik et al., 2017). However, this result is in contrast with data obtained in an intrinsic hand muscle, the adductor pollicis. During intermittent MVCs (Ditor and Hicks, 2000), electrically evoked 30-Hz contractions (Zijdewind and Kernell, 1994) and in older subjects (Cheng et al., 2003), no sex-related differences were observed in this hand muscle. Sex differences in fatigability, however, could be masked in the adductor pollicis because this muscle has a high percentage of type I fibers (80%, Johnson et al., 1973; Round et al., 1984); FDI: 57%, (Johnson et al., 1973). It is suggested that females are more fatigue resistant than males due to a greater proportional area of type I fibers (Kent-Braun et al., 2012; Hunter, 2014) and the observed longer HRTs for females (∼15% longer) in the present data support the suggestion of more type I fibers.

Beyond differences in muscle fiber type composition, higher absolute strength in males versus females is often suggested as a reason for the smaller force decline in females. Higher contractile forces tend to reduce blood flow, hence oxygen supply to the working muscles, resulting in accumulation of metabolic by-products which can interfere with contractile function (Barnes, 1980). However, the model including sex explained more variance in force decline than the model containing MVC. Additionally, the argument referring to differences in MVC forces between male and females is probably less relevant during maximal than during submaximal contractions because intramuscular pressure restricts blood flow as long as the contraction is maximal independent of its magnitude (Barnes, 1980; Petrofsky and Hendershot, 1984). We also found that the doublet declined more in males than in females (difference: 12%) but without sex-differences in voluntary muscle activation and that the decline in doublet could explain more of the variability in force decline than sex. Together these observations point to sex-related differences in performance fatigability being induced by changes in the muscle (possibly fiber type related) rather than differences in the activation of the muscle. Yet, the larger doublet during the submaximal contractions and the relatively large decline in voluntary force (61%) relative to the decline in doublet-force (49%) in females could point to possible sex differences in voluntary muscle activation (Russ and Kent-Braun, 2003; Martin and Rattey, 2007) which we were unable to

capture with the superimposed twitch technique during MVCs (see Methodological Considerations). Earlier experiments also showed conflicting results concerning superimposed twitches evoked during MVCs and submaximal contractions in elbow flexor muscles (De Serres and Enoka, 1998).

Age Differences During Sustained Maximal Contraction

In experiments with electrically evoked contractions in hand muscles, force decline in older compared to younger participants resulted in conflicting results. Force decline was found to be less (adductor pollicis: Narici et al., 1991) or more (adductor pollicis: Lennmarken et al., 1985). Whereas experiments using voluntary contractions produced either no difference (thenar muscles: Bemben et al., 1996) or reduced force decline (Chan et al., 2000; Ditor and Hicks, 2000) in older compared with younger participants, we found no effects of age on force decline, but observed small differences in the EMG response with age. At the beginning of the contraction, a larger increase in EMG was seen in young subjects. This increase in EMG could be due to an increase in motor unit firing rate and or to potentiation of the muscle fiber action potential (Zijdewind and Kernell, 1994; Zijdewind et al., 1999). An increase in motor unit firing rate could suggest that subjects did not contract maximally at the start of the sustained contraction despite continuous encouragement. However, the lack of age differences in voluntary force and voluntary activation suggests that the possible submaximal activation did not differ with age. The EMG potentiation is most likely a consequence of slowing of the muscle fiber action potential and hyperpolarization of the muscle fiber membrane (Hicks and McComas, 1989; Hicks et al., 1989) because of increased activation of the sodium-potassium pump. Whether this difference in potentiation reflects an age-related change in the activation of this pump during activity remains unclear. The smaller decline at the end of the sustained contraction accompanies the slightly smaller decline in force in older subjects.

The increase in the ratio between the doublet and MVC with age (∼2% per year) was unexpected. Similar to the larger ratio in females compared with males, it could reflect reduced activation during MVCs (Bilodeau et al., 2001; however, Chan et al., 2000; Solianik et al., 2017) but also age- and sex-related changes in the muscle stiffness could play a role (Eby et al., 2015). Increased muscle stiffness, as observed in older and female individuals (Eby et al., 2015), enhances the translation of contractile shortening into force production during short-lasting contractions.

An important difference between the present and previous experiments is that we searched for age-related changes with age as a continuous variable whereas most authors compared (two) groups of younger and older individuals. MVC force is relatively stable until over age 60 (Narici et al., 1991), although the decline in MVC force tend to be greater and earlier in males than females (Ditroilo et al., 2010; Abe et al., 2016). In our experimental group only a few individuals were 70 or more years of age (n = 9). In addition, the older adults in the current study were still physically active (most subjects cycled to our lab), experienced an overall wellbeing as illustrated by low scores on the FSS and HADS questionnaires, which could cause a bias toward the fit and healthy population of older adults.

Contralateral Activity During the Sustained Maximal Voluntary Contraction

The unintentional activity in the contralateral FDI was higher in older compared with younger adults during both brief and at the start of the sustained contractions (Shinohara et al., 2003; Heetkamp et al., 2014). The time course of the contralateral force in older adults, i.e., more contralateral activity in older subject at the start of the contraction but a larger increase in young subjects agrees with previous data (Shinohara et al., 2003; Heetkamp et al., 2014). The amount of unintended contralateral activity increases with effort (Zijdewind and Kernell, 2001; Shinohara et al., 2003). The plateau phase at the end of the sustained contraction was not accompanied by a steeper increase in the superimposed twitches in the older subjects suggesting that the amount of effort was similar in young and older participants. It is suggested that the contralateral activity is the consequence of a reduced ability to suppress unwanted activity, possibly due to an age-related degeneration of the corpus callosum (Bashir et al., 2014). Another possible explanation is that older adults require additional and more widespread recruitment of brain areas, in order to compensate for neuromuscular changes with aging (Mattay et al., 2002; Naccarato et al., 2006).

No other study reported sex-differences in contralateral activity, but sex hormones can affect interhemispheric inhibition (Weis and Hausmann, 2010). Unfortunately, we did not collect data on the hormonal cycle of our female subjects. In addition to variation in sex hormones, effort could also affect contralateral activity. Although, few other experiments showed reduced activation in females (Martin and Rattey, 2007) most experiments did not observe differences between the males and females (Cheng et al., 2003; Hunter et al., 2006). Still, as discussed in earlier paragraphs, the submaximal data and the ratio between the doublet and voluntary force suggest that a difference in effort could play a role in the observed sex difference in force decline in the FDI.

Methodological Considerations: Choice of Muscle and Contraction Intensity

Contrary to most (preclinical) studies, the present study examined sex- and age-differences during brief and sustained index finger abduction. The FDI contributes most to the index finger abduction and synergists minimally confound force output (An et al., 1983). A disadvantage is that stimulation of the ulnar nerve activates not only the FDI but also its antagonist (the second palmar interosseous, SPI; (An et al., 1983; Zijdewind and Kernell, 1994) which could result in an underestimation of the superimposed twitch and thus an overestimation of the voluntary activation. We reduced the contribution of the SPI by holding the force transducer in the hand (i.e., with fingers 3–5 flexed) with an extended index finger and the thumb adducted and taped to fingers 3–5 (**Figure 1A**). This position favors the length-tension

relation of the FDI and reduces the contribution of the SPI. The relatively small contribution of the SPI at baseline is further illustrated by the large doublet/MVC ratio (0.32 ± 0.07). The relative contribution of the SPI increases during the sustained contraction but we feel that this would not affect males versus females or young versus older subjects differently. Furthermore, pilot data (n = 5) showed that the twitches evoked by ulnar stimulation and motor point stimulation resulted in similar estimates of index finger abduction force (see Discussion, Prak et al., 2015). The ratio between the maximal forces estimated on basis of the ulnar nerve stimulation and motor point stimulation equaled 0.95 (range 0.86–1.01) suggesting a relatively small contribution of the SPI. The intraclass correlation coefficient (absolute agreement) was 0.96 ($p < 0.001$).

We chose to use a sustained high intensity contraction, whereas most preclinical studies which focus on sex- and age differences used submaximal and/or intermittent contractions. For clinical populations (e.g., multiple sclerosis, spinal cord injury, mild traumatic brain injury), sustained maximal contractions are easier to standardize because they are less affected by problems with motor control (Severijns et al., 2017).

Implications and Conclusion

The age- and sex-related effects on performance fatigability associated with a sustained maximal contraction we report here demonstrate the strength of including (male and female) subjects over a broad age range and provides a strong motivation for further longitudinal studies. Additionally, the observation that variables show (significant and non-significant) sex-specific changes with age stress the importance of population characteristics on basic muscle properties. Furthermore, this data is relevant to clinical populations. Such reference data are currently lacking but needed for a clearer distinction between changes in fatigability as the result of neuromuscular dysfunctions caused by disease and the (physiological) effects due to age and sex. The use of maximal, rather than submaximal, contractions in patients is related to the difficulty of standardizing the tasks. Heterogeneity between patients and clinical conditions in the levels of motor control and skills can confound performance fatigability produced in submaximal paradigms (Severijns et al., 2017). Yet studies in healthy adults often examine the effects of age and sex on performance fatigability caused by submaximal and intermittent contractions in large muscles (Enoka and Stuart, 1992; Allman and Rice, 2002; Hunter, 2016, 2017).

An implication of studying sex differences in individuals with a broad age range is that the interaction effects of age and sex can be ascertained. Also in this study (significant and non-significant) results showed that sex differences are more prominent in young compared to older individuals (Ditor and Hicks, 2000; Cheng et al., 2003; Hunter et al., 2004b).

In conclusion, we found that age- and sex-differences produced by sustained high intensity voluntary forces with a hand muscle are most likely caused by changes within the muscle. The age- and sex-related differences in performance fatigability in neurologically healthy adults help the interpretation and referencing of performance fatigability in persons suffering from neuromuscular disorders. Even in the absence of systematic effects of sex and age on performance fatigability these factors, if not controlled, could increase variability in outcome measures.

AUTHOR CONTRIBUTIONS

IZ: designed the experiment. VS, RP, and IZ: performed the experiments and analyzed the data. VS, RP, IZ, and TH: wrote the manuscript.

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Neuromuscular Control and Performance Differences Associated With Gender and Obesity in Fatiguing Tasks Performed by Older Adults

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Obesity rates in the geriatric population have emerged as a serious health concern in recent decades. Yet, obesity-related differences in neuromuscular performance and motor control during fatiguing tasks, and how they are modified by gender, specifically among older adults, are still largely unexplored. The first aim of this study was to understand obesity and gender-related differences in endurance time among older adults. Motor variability has been linked with inter-individual differences in the rate of fatigue development, and as potentially revealing underlying mechanisms of neuromuscular control. Hence, the second and third aims of this study were to investigate to what extent motor variability at baseline could predict inter-individual differences in endurance time, and whether systematic obesity and gender differences exist in motor variability among older adults. Fifty-nine older adults (65 years or older) were recruited into four groups: obese male, obese female, non-obese male, and non-obese female. Participants performed submaximal intermittent isometric knee extensions until exhaustion. Knee extension force and muscle activation signals (surface electromyography) of a primary agonist muscle, the Vastus Lateralis (VL), were collected. Endurance time and metrics quantifying both the size and structure of variability were computed for the force and EMG signals, using coefficient of variation (within cycles and between cycles) and sample entropy measures. While group differences in endurance time were primarily associated with gender, adding individual motor variability measures as predictor variables explained significantly more variance in endurance time, thus highlighting the relevance of motor variability in understanding neuromotor control strategies. Males exhibited longer endurance times, higher EMG CV, lower EMG SaEn, lower force CV, and higher force SaEn than females. These findings are interpreted to indicate males as using a motor strategy involving better "distribution" of the neural efforts across synergists and antagonists to achieve better performance during the knee extension task. No obesity-related changes in endurance time were found. However,

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obese individuals exhibited a greater cycle-to-cycle variability in muscle activation, indicating a larger alteration in the recruitment of motor units across successive contractions and potentially increased neural costs, which may have contributed to comparable endurance time and performance as non-obese older adults.

Keywords: motor variability, muscle activation, force fluctuation, intermittent contraction, knee extension

INTRODUCTION

Muscle fatigue, defined as the decline in muscular capacity to generate force, has been the focus of numerous investigations. Fatigue has been suggested to be related to impairment of neuromuscular performance, development of musculoskeletal disorders (MSDs), and occupational injuries (Takala, 2002; Gallagher and Schall, 2017). Muscle fatigue can be caused by many different factors, ranging from the accumulation of metabolites within muscle fibers to the generation of an inadequate motor command in the motor cortex (Enoka and Duchateau, 2008). Multiple individual factors such as gender, age, body mass index (BMI), pain status, health condition (e.g., previous injury history), experience, and task-specific factors including nature of task (static/dynamic) and muscle groups used, have been recognized as influencing fatigue-related performance declines in adults (Bemben et al., 1996; Madeleine and Madsen, 2009; Cavuoto and Nussbaum, 2013a; Hunter, 2014; Mehta and Cavuoto, 2015, 2017; Shortz and Mehta, 2017).

Aging is associated with several morphological and functional impairments in skeletal muscles that lead to a decrease in muscle force production capacity, which has consequently been associated with reduced physical function and independence in aging adults. Age-related changes in muscle fiber composition and reduction of active tissues have been linked to declining physiological capabilities such as reduced muscular strength and speed (Frontera et al., 1991; Hughes et al., 1999; Kent-Braun and Ng, 1999). Declining motor performance in older adults has been observed in several studies, especially in force-control tasks where older adults have been shown to be weaker and less steady (i.e., they exhibit greater fluctuations in force around a target force) than young adults (Enoka et al., 2003; Yoon et al., 2008). As increasing numbers of older adults are staying employed, and workers in the age group 55–64 have also been reported to suffer from the highest incidence rate of occupational injuries and illnesses, a better understanding and characterization of functional performance and associated neuromuscular control mechanisms among older adults is critical. This study specifically examines the performance of force-control tasks by older adults. The effects of two relevant and likely significant factors—gender and obesity—are considered, as elaborated below.

Obesity rates in the United States have dramatically risen in the last decade. The prevalence of obesity has recently been reported to be 37.7%, with a greater prevalence in women than men (35.0% men vs. 40.4% women) (Fryar et al., 2016). Several functional impairments have been found to be associated with obesity, e.g., endurance time has been shown to be significantly decreased for obese when compared to non-obese individuals in isometric and intermittent handgrip and shoulder flexion (Eksioglu, 2011; Cavuoto and Nussbaum, 2013a, 2014) and trunk exercises (Mehta and Cavuoto, 2017). Another study found that force fluctuation was significantly higher in the obese group compared to the healthy group in intermittent hand-grip exertions (Shortz and Mehta, 2013). Kankaanpää and colleagues found that women with high BMI fatigued faster than women with normal or low BMI in isometric back endurance tests (Kankaanpää et al., 1998). However, contrary results were observed in another study conducted by Cavuoto and colleagues, involving only young people aged below 30 years, as no significant differences in endurance time were observed between obese and non-obese groups in sustained isometric torso extension (Cavuoto and Nussbaum, 2013b), thus suggesting possible interactive influences of gender and age on the association between obesity and endurance.

Fat mass has been shown to increase with age, and is higher among later birth cohorts, peaking at about age 60–75 years (Rissanen et al., 1988; Drøyvold et al., 2006; Ding et al., 2007), whereas muscle mass and strength start to decline progressively around the age of 30 with a more accelerated loss after the age of 60 (Bassey, 1998; Rantanen et al., 1998; Frontera et al., 2000; Stenholm et al., 2008). Due to such physiological changes with aging, sarcopenic obesity (i.e., obesity and low muscle mass) may be more likely to occur in older adults, resulting in reduced body strength relative to their body size (Stenholm et al., 2008). This, in turn, may expose obese older adults to more risks of suffering from neuromuscular declines, and consequently being injured. Thus, the combined effect of obesity and aging is a critical neuromuscular risk factor that deserves to be studied in more detail.

Gender differences have been widely explored in the biomechanics, occupational, and motor control research communities in terms of performance and motor control changes with fatigue. Despite previous studies claiming gender differences in endurance, there were no differences in endurance or perceived fatigue when women and men were matched for strength (Hunter and Enoka, 2001; Hatzikotoulas et al., 2004), suggesting that earlier reported differences between men and women may probably be a strength effect, and not primarily related to gender. In contrast, gender differences were found in muscle contractile function and metabolism: the majority of force potentiation occurred very rapidly (i.e., after baseline strength testing) in males, whereas potentiation reached its maximum later, during an exercise protocol, in females; in an incremental isometric exercise, males exhibited a greater reliance on non-oxidative sources of ATP compared

with females (Kent-Braun et al., 2002). Another recent study showed that although females and males did not differ in endurance time in a repetitive pointing task, there were gender differences in the relative contributions of the shoulder and elbow toward maintaining the same multi-joint movements with fatigue (Srinivasan et al., 2016). These results from healthy young individuals suggest that the underlying mechanisms of muscle response or motor control/coordination to fatigue may be different between genders, even though these may not manifest directly as difference in endurance or performance under fatiguing conditions. While this may indeed be the case among young and non-obese individuals, it is likely that such gender differences in motor control and muscle responses, when combined with obesity and old-age, may have stronger effects on performance among an older cohort of obese and non-obese individuals.

Overall, several studies have investigated functional impairments associated with obesity and gender (separately) in young adult groups. However, obesity-related differences in neuromuscular performance and motor control during fatiguing tasks among older adults, as well as how they are modified by gender, are still largely unexplored.

In understanding performance changes with fatigue, an increasing number of studies have recently emphasized the links between variations in movements, muscle activities, and coordination with fatigue development. This phenomenon, referred to as "motor variability," is the natural variation in postures, movements and muscle activity observed to different extents in all tasks, even when an individual tries to achieve identical performance across repeats (Srinivasan and Mathiassen, 2012). Motor variability has been recognized to be ubiquitous, as it has been shown to occur even in highly controlled repetitive tasks (Fethke et al., 2007; Jackson et al., 2009). An interest in motor variability has emerged in occupational research due to its associations with pain/discomfort, fatigue and performance (Srinivasan and Mathiassen, 2012); in a clinical context focusing on pain, aging, diseases (van Emmerik and van Wegen, 2000; Heiderscheit et al., 2002), in rehabilitation (Field-Fote and Tepavac, 2002; Daly et al., 2007), and in sports biomechanics because motor variability is associated with performance and injury risk (Davids et al., 2003; Bartlett et al., 2007; Preatoni et al., 2010).

Fluctuations, or variabilities, have been demonstrated to exhibit a degree of order that can be attributed to the operation of an adaptive control system (Falla and Farina, 2007). More variability in motor strategies has been suggested to be representative of new motor solutions to look for ways to reduce fatigue-induced discomfort and deterioration in performance. Studies have shown that inter-individual differences in motor variability may be an important factor in determining individual differences in susceptibility to developing fatigue, pain, and musculoskeletal disorders caused by repetitive tasks: specifically in the context that higher motor variability may be related to stronger resistance to muscle fatigue and better adaptation to task demands (van Dieën et al., 1993; Mathiassen et al., 2003; Madeleine, 2010; Srinivasan and Mathiassen, 2012). Thus, motor variability may be a useful and relevant construct to understand the neuromuscular strategies employed by different individuals during the performance of fatiguing tasks.

Given the trends of increased aging and obesity in the population, and potential gender differences on neuromuscular performance, the first aim of this study was to determine obesity and gender differences in endurance time, among older adults performing intermittent knee extension endurance tasks until exhaustion. Due to the potential for motor variability to explain individual differences in motor strategies employed to preserve performance with fatigue, the second aim of this study was to determine whether motor variability at baseline could predict individual differences in endurance time of older adults. Finally, whether gender and obesity were systematically associated with group differences in motor variability and neuromuscular control were examined, using force and muscle activation variability as the dependent measures. Knee extension tasks were specifically investigated in this study since the knee is important for controlling balance and movement, and for performing a majority of occupational and daily living tasks. Also, in many cases, particularly for older adults, lower extremity muscle function is critical for accomplishing several basic tasks of functional mobility, such as transition from sitting to standing. Variability was quantified in the force and muscle activation (i.e., surface electromyography) signals using metrics to reflect: signal steadiness (coefficient of variation over the contraction period of each cycle of contraction), cycle-to-cycle variability (quantified as a between-cycle coefficient of variation, indicative of a variable motor-unit recruitment pattern across repeated cycles) and sample entropy (quantifying the complexity of the signal, indicative of the communication/coordination across neuromuscular compartments). Based on the evidence from prior literature, we expected that endurance time would be shorter in the obese group than the non-obese group, and the extent of obesity-related differences may be different across genders. We also expected that a higher cycle-to-cycle variability and sample entropy in muscle activations at baseline may be associated with prolonged endurance among individuals. Males and females, and obese and non-obese individuals were expected to systematically differ in variability of muscle activities, reflecting different neuromuscular control mechanisms, which may potentially be associated with gender and obesity differences in force fluctuation and endurance time.

METHODS

Participants

Fifty-nine right-hand dominant older adults, 65 years or older, were recruited from the local community who formed four experimental groups: obese male ($n = 13$), obese female ($n = 16$), non-obese male ($n = 15$), and non-obese female ($n = 15$). Participants whose body mass index (BMI) were greater than 30 kg/m^2 were considered to be obese and less than 25 kg/m^2 were considered to be non-obese. The demographic data of the participants are shown in **Table 1**. All participants were self-reported to be sedentary to recreationally active individual without any musculoskeletal injuries or known disorders within the past year. The participants provided written informed

TABLE 1 | Demographic data.

Group	Number	Age (years)	Stature (cm)	Body mass (kg)	BMI (kg/m^2)	Knee extension strength (Nm)	Waist circumference (cm)	Average steps/day during previous 1 week
Non-obese male	15	74 (6)	178 (7.8)	77 (8.6)	24.45 (1.22)	107.94 (30.59)	99.06 (4.94)	7,553 (2,368)
Non-obese female	15	72 (5)	164 (5.8)	61 (6.9)	22.7 (1.89)	72.35 (13.54)	88.37 (9.32)	7,726 (2,907)
Obese male	13	73 (7)	178 (8.3)	114 (16.8)	36.0 (3.4)	104.77 (45.7)	127.49 (10.36)	4,181 (1,744)
Obese female	16	72 (5)	160 (4.6)	98 (16.9)	37.9 (5.38)	62.04 (19.67)	118.82 (11.63)	4,833 (1,558)

Note that all measures are presented as mean (SD).

consent before participation in the study, and the Institutional Review Boards at Texas A&M University and Virginia Tech approved the procedures.

Procedures

Upon consent, participants were instrumented with activPAL^{TM} physical activity monitor (Pal Technologies Ltd, Scotland, UK) on the right thigh using double-sided medical grade tape and a medical grade dressing patch, for one continuous week of measurement. Acceleration data were recorded at 20 Hz, and used to compute the number of steps per day (Tudor-Locke and Bassett, 2004). The average wear time across all participants was 6.84 days and 55 of 59 participants wore the sensor for all 7 days of monitoring.

Participants were then instrumented with relevant bio-instruments. The knee force exertions were measured using an isokinetic dynamometer (Humac NORM, Computer Sports Medicine, Stoughton, MA). Participants were seated upright with the dominant (right) hip and knee flexed to 90°. The epicondyles of their femur were aligned with the dynamometer's center-of-rotation and then locked with a dynamometer pad secured above the ankle, anterior to the tibia. The participant's upper body was secured firmly in the chair to minimize upper body motion caused by lower extremity muscle contraction. Three isometric maximum voluntary contractions (MVCs) in the posture described above, were measured prior to knee extension endurance test for each participant. Each subject was verbally encouraged to achieve maximal force. Two minutes of rest were provided in between each MVC trial to ensure adequate recovery. The greatest force achieved by the subject was taken as the MVC force. The target force level of 30% MVC was determined accordingly for the following experimental trials.

Following the MVC trials and prior to the actual experimental data collection, participants were provided with practice sessions to familiarize with the task. After familiarization and a period of adequate rest, participants performed intermittent isometric knee extension endurance test at 30% MVC until exhaustion. Each contraction lasted for 15 s with 15 s rest between each trial (**Figure 1**). Participants were asked to control their force generation against the target moment on the screen, which corresponded to a force of 30% MVC, as closely as possible based on real-time visual feedback provided. Participants continued performing the task until they were not able to maintain the 30% MVC force during the fifteen-second exertion period or until they reported as being unable to continue.

Measurements

Knee extension electromyogram (EMG) signals were recorded at 1,000 Hz during the entire exercise session (Biopac Inc., Ca, USA, Biopac MP Systems). The skin above the muscle belly was cleaned using alcohol before placing the EMG electrodes. Muscle activities of the rectus femoris (RF) and vastus lateralis (VL) were recorded using surface EMG for the knee extension exercise. Knee extension force was recorded at 100 Hz (Humac Norm Isokinetic Dynamometer, Computer Sports Medicine, Stoughton, MA). The recorded signals were transmitted to a dedicated PC using an A/D converter.

Data Analysis

For physical activity estimation, as recommended in the literature, the acquired acceleration data from activPAL^{TM} were exported as 15 s epochs. The number of steps per each epoch, and the number of total steps per day for 5 days (excluding the first and last days, when measurements were less than 24 h long) were computed to estimate the physical activity level of the participants (Tudor-Locke and Bassett, 2004; Tudor-Locke et al., 2011). The data were processed and analyzed using the software provided by Pal Technologies Ltd, Scotland, UK.

Force and EMG data of the knee were processed in Matlab R2017a (The MathWorks, Inc., Natick, MA, USA). Force data were filtered using a first-order, low-pass Butterworth filter at a cut-off frequency of 15 Hz. EMG signals from each muscle were band-pass filtered (20–450 Hz) using a sixth-order Butterworth filter. The root mean squared (EMG RMS) value of the EMG signal was calculated using 100 ms moving windows, and normalized with EMG RMS of the MVC trials. The first 1/3 task-period of each individual was referred to as the "baseline" period, and the force and EMG signals from this period were used for computing baseline measures of force fluctuations and motor variability.

The middle 10 s of each 15-s contraction were extracted from the force and EMG data respectively for each subject and used

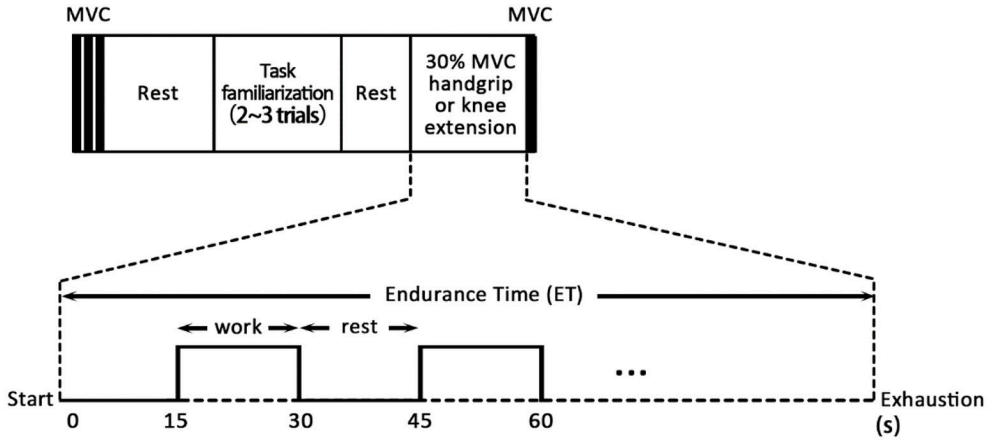

FIGURE 1 | Experiment Protocol.

in the data analysis. Exertions that were extremely irregular, including twitches, jerks, or gaps during the contraction, were excluded from the analysis to avoid potential confounding influence on the result considering motor variability as the primary focus of this study. This procedure resulted in removal of 9 trials in total, representing less than 0.4% of data.

Variability was characterized using a combination of linear (coefficient of variation) and nonlinear techniques (sample entropy), to quantify the amount and structure of EMG and force variability.

1) For computing the **within-cycle coefficient of variation (CV)**, mean and standard deviation of the middle 10 s of each contraction were calculated for both force and EMG data. Within-cycle CV was estimated for a whole task-period by pooling the within-cycle CV from all cycles in that task-period: i.e., by dividing pooled within-cycle standard deviation of all cycles within a task-period by the average of the means from each cycle.
2) **Between-cycle CV** was quantified as standard deviation of the means from each cycle within a task-period relative to the mean across contractions in each period.
3) **Sample entropy (SaEn)** of each contraction was computed and averaged within each task-period using the middle ten-seconds of data (force and EMG. The algorithm of sample entropy employed in this study is listed step by step below, and was adapted from Richman an colleagues (Richman and Moorman, 2000). For a time series u of N points, described as $\{\mathrm{u}(\mathrm{j}) : 1 \leq \mathrm{j} \leq \mathrm{N}\}$, embedding vectors x with time lag τ can be formed as follows:

$$\mathrm{x_m}(i) = \{u(i + k^*\tau) : 0 \leq k \leq m - 1\} \tag{1}$$

In total, $N - (m-1)\tau$ embedding vectors can be formed for $\{i | 1 \leq i \leq N - (m-1)\tau\}$, where $\mathrm{x_m}(i)$ is the embedding vector of m data points from $u(i)$ to $u(i + (m-1)\tau)$.

Embedding dimension (m) was determined by applying the false nearest neighbor (FNN) approach (Kennel et al., 1992). Using a random selection of contractions from all subjects in the study, a function of the percentage of FNN vs. increasing embedding dimension was created. From this, the optimal embedding dimension of $m = 4$ was computed. Based on previous literature, the time lag τ for this study was chosen to be set at a delay at which the autocorrelation function of the time series falls by as much as 1/e (Rosenstein et al., 1993). The 8th contraction of every participant was randomly selected to be used to compute time lags, and the grand average of the computed time lags of $\tau = 5$ for the knee extension activity and $\tau = 2$ for the handgrip exercise were used for further analysis in this study. For each embedding vector $\mathrm{x_m}(i)$, $C_i^m(r)$ was calculated, which was defined as the probability that any vector $\mathrm{x_m}(j)$ is within a tolerance distance (r) of $\mathrm{x_m}(i)$.

$$C_i^m(r) = \frac{\{Number\ of\ \mathrm{x_m}(j)\ such\ that\ d[\mathrm{x_m}(i), \mathrm{x_m}(j)] \leq r\}}{N - (\mathrm{m}-1)\tau} \tag{2}$$

Where d, the distance between two vectors was defined to be:

$$d[x(i), x(j)] = \max\{|u(i + k^*\tau) - u(j + k^*\tau)| : 0 \leq k \leq m - 1,\ i \neq j\} \tag{3}$$

i.e., the maximum difference of their corresponding scalar components.

The parameter r, a positive real number, referred to as the tolerance distance, has been recommended to be chosen between 0.1 and 0.25 times the standard deviation of the time series (Richman and Moorman, 2000). 0.2 times the standard deviation was used in this study, based on prior literature (Samani et al., 2015). $\Phi^m(r)$, representing the natural logarithms of the probability of matches $C_i^m(r)$, is given by:

$$\Phi^m(r) = \frac{\sum_{i=1}^{N-(m-1)\tau} \ln[C_i^m(r)]}{N - (\mathrm{m}-1)\tau} \tag{4}$$

Based on the above steps, sample entropy (SaEn), showing the negative logarithm of the relationship between the probability that two sequences coincide for m+1 and m points was then computed as follows:

$$SaEn\,(m, r, N) = -\ln(\frac{\Phi^{m+1}\,(r)}{\Phi^{m}\,(r)}) \quad (5)$$

Statistical Analysis

A two-factor analysis of variance (ANOVA) was first performed to study the effects of gender and obesity on endurance time. This was followed by a step-wise multiple linear regression model to predict endurance time, in which the "participant group" (i.e., participant obesity and gender groupings), and relevant individual-specific factors were included as predictor variables. Individual-specific factors that were explored in these models were task-related strength measured prior to the start of the protocol and force variability and muscle activation variability at baseline. Force variability was quantified as CV and SaEn and variation in muscle activation patterns were quantified by within-cycle CV, between-cycle CV, and SaEn. Two-way ANOVA models were further used to understand whether the individual predictor variables (i.e., force and muscle activation variability) showed any systematic associations with gender and obesity. JMP® was used for all statistical analysis and a significance level of $p < 0.05$ was used to accept statistical significance.

RESULTS

Demographics and Physical Activity Measurements From Participants

While gender and obesity related differences were observed in anthropometry, no obesity differences were observed in strength (**Table 1**). Males were taller ($p < 0.001$), heavier ($p < 0.001$), exhibited greater knee extension strength ($p < 0.001$), and showed greater waist circumference ($p < 0.001$) than females. Obese participants were heavier ($p < 0.001$), had higher BMI ($p < 0.001$), and exhibited higher waist circumference ($p < 0.001$) than non-obese individuals (by design). For physical activity estimated as the average number of steps per day, according to criteria found in Tudor-Locke (2010), Tudor-Locke et al. (2011), and Tudor-Locke et al. (2016), the normal weight group were relatively low in activity level (approximately 7,500 steps/day), and the obese group were sedentary or inactive (less than 5,000 steps/day). The difference between the two groups in physical activity were statistically significant ($p < 0.001$).

Knee Extension Endurance Time, as a Function of Obesity and Gender

Overall, the average knee extension endurance time was 1,431 (SD 700) seconds across all participants. The average endurance times in each obesity and gender group, as illustrated in **Figure 2**, show that male participants had 43% longer endurance time compared to females ($p = 0.005$). No statistically significant difference between obese and non-obese groups was observed (**Table 2**). As the Vastus Lateralis and the Rectus Femoris are both knee extensor muscle groups in the thigh having very similar functions during the knee extension task, results of these two muscles presented very similar trends. Hence, only the results of the Vastus Lateralis are considered in the following sections, considering the fact that this muscle presented the strongest trends.

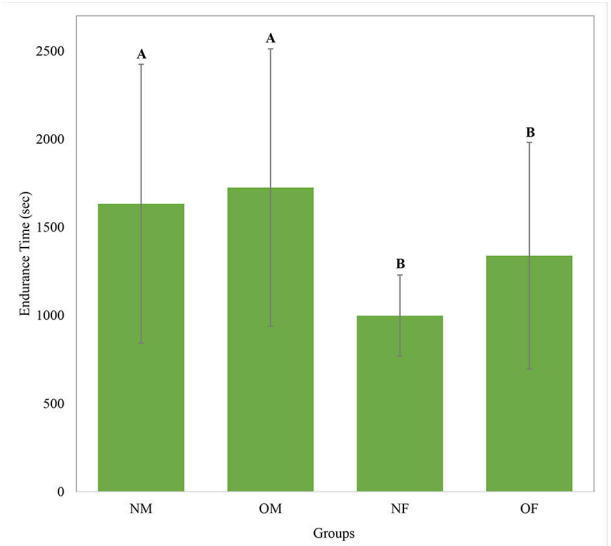

FIGURE 2 | Knee extension endurance times for each group with the between-subject standard deviation shown as error bars. NM- non-obese male; OM- obese male; NF- non-obese female; OF- obese female. Means with different letters are significantly different.

TABLE 2 | Main and interaction effects of obesity and gender on endurance time, along with effect sizes.

Source	DF	Sum of squares	F Ratio	*p*	Effect size (Partial η^2)
Obesity	1	710.97	1.47	0.23	0.03
Gender	1	3972.42	8.22	**0.006***	**0.14**
Obesity*Gender	1	233.89	0.48	0.49	0.007

Statistically significant results highlighted in bold.

Results of Multiple Linear Regression Functions for Predicting Endurance Time

A regression model with only participant group (coded using gender and obesity variables: i.e., NM, NF, OM, and OF as in **Figure 2**) as an explanatory variable and endurance time as the outcome measure was significant ($p = 0.03$) with a coefficient of determination (R^2) of 16.2%. When the individual-specific variables of knee extension strength, force variability (i.e., CV and SaEn) at baseline, and muscle activation variability (i.e., within-cycle CV, between-cycle CV and SaEn of vastus lateralis) were included as explanatory variables in a multiple regression procedure, the model R^2 increased to 49% (i.e., 49% of the variance in endurance time was predicted by the model) and the model was statistically significant [$F_{(9, 44)} = 4.3$; $p = 0.0005$]. Knee extension strength, force fluctuation CV at baseline, and

between-cycle CV of vastus lateralis EMG were significant in the resultant model (statistical results reported in **Table 3**).

When individual correlations between each of the significant predictor variables and endurance time were computed, knee extension strength did not exhibit a significant correlation with endurance time. Force fluctuation CV at baseline was negatively correlated with endurance time ($r = -0.37, p = 0.005$), and between-cycle CV of VL EMG was positively correlated with endurance time ($r = 0.47$, $p = 0.0003$). The individual correlations between force CV and endurance time (ET), as well as the between cycle CV of EMG with endurance time (ET) are plotted in **Figures 3A,B**.

Associations of Force and Muscle Activation Variability at Baseline With Obesity and Gender

The means and within-group standard deviations of force and EMG CV during the baseline period of the knee extension task, as a function of participant obesity and gender are shown in **Figure 4**; and those of force and EMG sample entropy are shown in **Figure 5**. In general, males exhibited lower force CV (i.e., lower fluctuation in force control at baseline), higher force entropy, lower EMG within-cycle CV, and higher EMG sample entropy than females. The results of the statistical analysis are shown in **Table 4**. In terms of obesity differences, obese individuals exhibited significantly greater between-cycle CV in VL EMG than non-obese individuals. No other differences were statistically significant.

DISCUSSION

The present study investigated motor performance, neuromuscular control, and endurance differences with obesity and gender among older adults performing intermittent submaximal knee extension exercises. Motor performance and control were characterized by variability in force and muscle activity. Both the amount and structure of variability were quantified using the coefficient of variation (CV) and sample entropy (SaEn) metrics. In addition, variability in muscle activation within each contraction cycle as well as the cycle-to-cycle variability were quantified by computing within-cycle and between-cycle CV.

TABLE 3 | Multiple linear regression results for predicting knee extension endurance time as a function of gender and obesity group, and individual-specific factors.

Model terms (independent variables)	Endurance time (dependent variable)		
	Estimated coefficient	*p*	Effect size (partial η^2)
Intercept	141.25		
Group	NF: −14.44; NM: 10.53; OF: −8.21	0.07	0.15
Knee extension strength	−0.24	**0.02**	**0.13**
Force CV	−713.5	**0.03**	**0.10**
Force SaEn	−233.7	0.66	0.01
VL EMG within cycle CV	263.89	0.08	0.07
VL EMG between cycle CV	−21.27	**0.006**	**0.16**
VL EMG SaEn	−22.06	0.40	0.02

NM, non-obese male; OM, obese male; NF, non-obese female; OF, obese female (statistically significant results highlighted in bold).

Gender Differences

Significant differences in endurance time were observed with gender, with males showing longer endurance time than females, in the knee-extension task. The majority of previous studies have reported either the same endurance time for both genders, especially at higher contraction intensities (Maughan et al., 1986), or females exhibiting better fatigue resistance than males when performing knee extensions (Clark et al., 2005; Albert et al., 2006), in contrast with what was found in the current study. Numerous other studies involving various types of exercises performed by different muscles also mostly reported a longer endurance time for female participants (Fulco et al., 1999; Hunter et al., 2004a,b). However, it is noteworthy that nearly all studies examining gender difference in fatigability focused on only young healthy adults. Our study suggests that older males particularly showed longer endurance than older females in knee extension.

Aging has been suggested to be associated with enhanced fatigue resistance, but there is a lack of research targeting the older population specifically and exploring fatigue characteristics as a function of gender. One of a few studies investigating gender and age effects on fatigability, involved a thumb adduction task and found that older adults were significantly less fatigable than young adults, and older males benefited from such age-related rise of fatigue resistance more than older females (Ditor and Hicks, 2000). The occurrence of changes in muscle fiber type distribution with aging has been demonstrated to account for the maintenance and enhancement of fatigue resistance. Older adults possess higher proportion of type I muscle fibers (slow-twitch), that help enable long endurance tasks, and fewer type II muscle fibers (fast-twitch) that are used for fast high force production but prone to fatigue. However, the amount of age-related increase in fatigue resistance can probably be modified by certain factors, such as gender. As a loss in estrogen has been seen in older females, their endurance advantage obtained from greater representation of type I muscle fibers may be mitigated, while muscular endurance of older males may predominantly benefit from histological changes alone (Ditor and Hicks, 2000). In addition to the unclear gender differences, whether the slightly greater proportion of type I muscle fiber observed in young females persists during the aging process is yet known (Hicks et al., 2001). Thus, the longer endurance time presented among males in this study could possibly result from gender differences in the age-related changes in muscle fiber distribution. There may also be other factors such as obesity, physical activity, lifestyle as well as cognitive factors, such as attitudes and beliefs about self-efficacy, that may play a role in explaining gender-related endurance differences (Weinberg et al., 1981; Cavuoto and Nussbaum, 2013a,b; Mehta and Cavuoto, 2015).

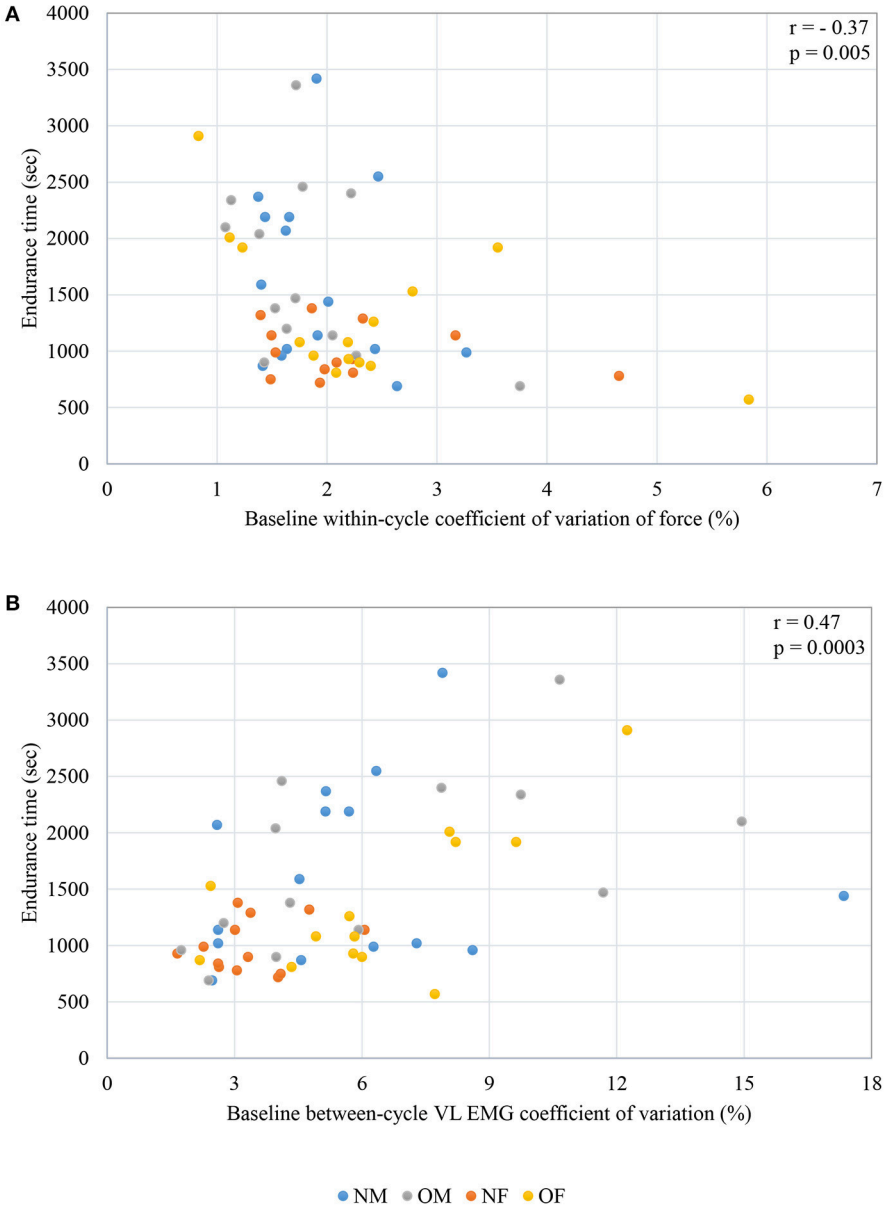

FIGURE 3 | Correlations between **(A)** force CV and endurance time **(B)** between-cycle EMG CV at baseline in the Vastus Lateralis and endurance time; NM- non-obese male; OM- obese male; NF- non-obese female; OF- obese female.

From a motor control perspective, gender differences in both force and muscle activity variability were observed, indicating that males may use a more flexible motor strategy, thus being able to prolong endurance. The force CV at baseline (inverse of force "steadiness") was found to significantly explain inter-individual differences in endurance time, and force CV was negatively correlated with endurance time across all participants. The significant gender difference in force CV further indicated a steadier force output for males compared to females during the baseline period. We also examined force SaEn differences between genders at baseline, and force SaEn was significantly lower among females compared with males. It has been suggested that a reduction of complexity in physiological time series is associated with system dysfunction and loss of adaptability to physiological stress (Lipsitz and Goldberger, 1992). In addition, Pincus pointed out that less complexity corresponded to greater component autonomy and isolation (Pincus, 1994). As force was the product of complex interactions of neuromuscular system components, and was influenced by the pattern of activation within a muscle and across a group of synergistic and antagonistic muscles, smaller complexity in the force fluctuation may imply weaker neural compartments communication, less muscle

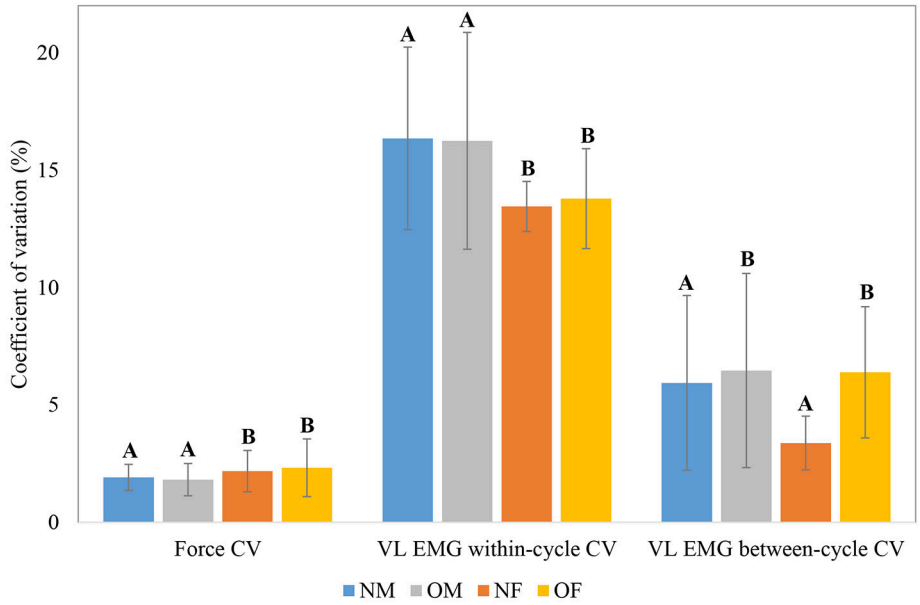

FIGURE 4 | Group level means and within-group standard deviations (error bars) of force CV, VL EMG within-cycle CV and VL EMG between-cycle CV; Means with different letters are significantly different.

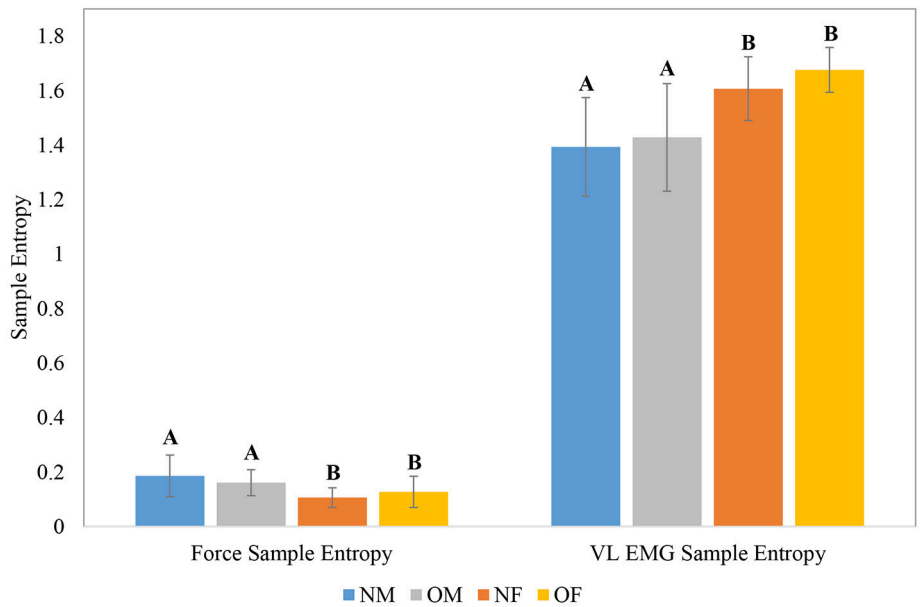

FIGURE 5 | Group level means and within-group standard deviations (error bars) of force sample entropy and VL EMG sample entropy; Means with different letters are significantly different.

coordination and less alterations in motor unit recruitment during static muscle contraction. Thus, a lower complexity of the force output observed among females may reflect poorer motor control and adaptation.

We interpreted the force CV and SaEn findings as jointly indicating that males controlled their force output more "tightly" than females, as reflected by the lower CV at baseline, and that they achieved this through greater corrections of the force signal, as reflected in the higher complexity of the signal as quantified by SaEn. However, we expected that such a tighter control on the force output by males would also imply that males would consequently fatigue at a faster rate,

TABLE 4 | Main and interaction effects of obesity and gender on force and EMG variables.

	Force CV		Force SaEn		VL EMG within cycle CV		VL EMG between cycle CV		VL EMG SaEn	
	p	Effect size (partial η^2)	*p*	Effect size (partial η^2)	*p*	Effect size (partial η^2)	*p*	Effect size (partial η^2)	*p*	Effect size (partial η^2)
Obesity	0.92	<0.001	0.9	<0.001	0.9	<0.001	**0.04**	**0.08**	0.21	0.03
Gender	**0.05**	**0.08**	**0.0006**	**0.21**	**0.0036**	**0.15**	0.14	0.04	**<0.0001**	**0.38**
Gender*Obesity	0.62	0.005	0.14	0.04	0.81	0.001	0.16	0.04	0.67	0.003

Statistically significant results highlighted in bold.

thus leading to shorter endurance times. The finding that despite more controlled force outputs, males actually showed longer endurance times than females, was unexpected and intriguing.

As for variability in muscle activations, males presented higher EMG CV in the vastus lateralis muscle (knee extensor muscle) and lower sample entropy than females. When these findings are integrated with the findings on force control and endurance time, males thus presented with higher EMG CV, lower EMG SaEn, lower force CV, higher force SaEn, and longer endurance time than females. This indicates that males somehow achieved a motor strategy in which they controlled the primary agonist muscle (vastus lateralis) to a "lower" extent, as reflected through higher CV and lower SaEn, while at the same time, achieving better force control than females. The lower SaEn observed in the extensor muscle group activation indicates that the knee extensor muscle was controlled to a lower extent among males than females, and a consequent lower neuromuscular effort by the CNS in extensor muscle control. Higher variability in muscle activation during an isometric contraction implies a more flexible motor control strategy. One possible strategy may be that alternate motor units within the same muscle, as well as other muscles with redundant function, may have been recruited and de-recruited to different extents to achieve the same overall force levels (note that the vastus lateralis is one of four knee extensor muscles in the quadriceps muscle group, indicating that this is a feasible motor control strategy). This explains both the longer endurance time that would then be achieved by not over-exerting the same motor units continually, and also the higher force SaEn as such muscle recruitment patterns would be reflected as higher complexity of the resultant force signal.

Finally, our results indicate that despite controlling a primary agonist muscle to a lower extent, males were still able to achieve better force control (lower force CV) than females. This may have been made possible by expending more effort in better antagonistic muscle control (flexor groups in this case) among males. Thus, the knee flexor muscle groups of males may obtain greater distribution of the neural effort, resulting in the lower sample entropy in the extensor muscle activity, so that the antagonists would do a better job in stabilizing the joint and assisting the control of the force output. This may have allowed the VL muscle activity to be more variable, which increased the fatigue resistance of the primary extensor, without affecting performance. Even though this hypothesis could not be verified in this study as the knee flexors were not included here, it is supported by findings from previous studies that demonstrated that women exhibited greater variation in antagonistic muscle activations and motor performance in spatial control tasks (as opposed to force control tasks here) than men (Casamento-Moran et al., 2017). From a control perspective, other studies (Granata et al., 2002) have also observed lower active stiffness of the quadriceps muscle in females during isometric knee extension when compared to males, which may in turn cause gender-based differential recruitment of agonists and antagonists in order to maintain sufficient joint stiffness.

Thus, male and female older adults differed in motor control patterns during intermittent submaximal knee extension exercises. Males seem to have employed motor strategies that better "distributed" the neural efforts across synergists and antagonists to achieve better performance, so that the primary extensors would gain more freedom to seek for less fatigable motor solutions to slow down exhaustion.

Obesity Differences

Obesity has been found to be associated with impaired functional performance such as shorter endurance, faster development of discomfort, greater fatigue, inefficient motor control, reduced relative strength, and task performance compared with normal weight people (Kankaanpää et al., 1998; Maffiuletti et al., 2007; D'Hondt et al., 2008; Eksioglu, 2011; Shortz and Mehta, 2013; Cavuoto and Nussbaum, 2014). Thus, we expected the obese group to exhibit less variable and complex muscle activity as a reflection of poorer motor control and adaptation, which would finally result in poorer force control and shorter endurance time. However, we did not observe any obesity-related differences in endurance time or force fluctuation CV in this study. Force sample entropy was lower among the obese than non-obese participants during the knee extension exercise, indicating a dysfunction and reduced effectiveness of neuromuscular control (Lipsitz and Goldberger, 1992; Pincus, 1994) within each constant contraction interval. On the muscle activation side, no difference in the within-cycle muscle variability (VL EMG CV) was observed between obese and non-obese individuals. How older obese participants achieved the same performance as the non-obese participants when bearing the physiological and motor control disadvantages described above, thus emerged as a critical question that needed to be addressed.

Obesity has been shown to be linked with poorer motor performance in terms of lower motor unit activation (as elicited by electrical stimulation) during knee extension (Blimkie et al.,

1990) and ankle dorsiflexion (Pajoutan et al., 2016), for obese when compared to non-obese individuals. One study conducted by Shortz and Mehta involving intermittent handgrip and elbow flexion reported that while obesity decrements in motor performance (quantified as force fluctuation) was found during handgrip, no obesity differences were seen during elbow flexion (Shortz and Mehta, 2013). The authors explained that obesity-related declines in performance may be muscle dependent, and that obesity-related performance declines during handgrip exertions could potentially be influenced by lower neural control (Shortz and Mehta, 2013). While the above studies involved young adults, older obese adults have been shown to maintain motor performance by increasing neural control as compared to non-obese adults, as found in a gait study (Osofundiya et al., 2016), however, as tasks become more difficult (i.e., increase in effort over time), neural control may not be sufficient to offset obesity-related performance differences.

In the present study, our finding of lower complexity (SaEn) in the force signal, and no differences between obese and non-obese groups in within cycle variability or complexity of muscle activations, seem to contradict the previous speculations of increased neural control in obese older adults. However, considering that the test was an intermittent task involving regular rest periods between exertions, cycle-to-cycle muscle variability also deserved attention as it may reflect the neuromuscular control from a different perspective. It was observed that obese people displayed a significantly more variable muscle activation pattern between cycles. The increased variability across contractions among obese individuals can be interpreted as a neuro-motor strategy that they used, to prolong endurance, especially as between-cycle variability was significantly positively correlated with endurance time. As suggested in previous studies, motor variability may be a representation of the motor unit recruitment pattern (Newell and Corcos, 1993; Davids et al., 2003; Stergiou, 2004). A previous study examining the motor unit recruitment pattern in the Vastus Lateralis during submaximal intermittent knee extensions found a monotonic decrease in the recruitment threshold of all motor units, and that an increasing number of motor units were continuously active in subsequent contractions, all without a change of the recruitment order (Adam and De Luca, 2003). Thus, the reason for a varying cycle-to-cycle muscle activity could be that, during a cyclic endurance task, new motor units are progressively recruited after the activation of old motor units in subsequent contractions following the same recruitment order, due to a decrease in the recruitment threshold of the motor units. Therefore, it was reasonable to speculate that the speed of such decrease was faster among obese people, leading to a faster increase in the number of motor unit recruitment along contractions, which was reflected by the greater cycle-to-cycle variability of EMG.

Through the recruitment of more (and different) motor units than non-obese people, individual motor units of the obese participants would be able to be more "relaxed" while still maintaining the required effort output at the same time. A greater cycle-to-cycle variability in motor activation was thus reflective of a stronger neural control strategy that is likely to be beneficial in terms of decelerating fatigability among obese older adults. This finding from our study is, thus, in agreement with that from Osofundiya and colleagues that obesity was associated with higher neural costs that may contribute to comparable performance observed in obese and non-obese groups among old people (Osofundiya et al., 2016). Whether such differences in neural control strategies between the obese and non-obese groups to achieve similar endurance time is evident in neural activation patterns as observed through brain imaging studies, and what the consequences of higher neural costs of movements would be, to obese older adults in the long-term, would be significant avenues for further research.

Limitations

There are some limiting factors that reduced the generalizability of the current study. Various methods have been used as criteria to determine obesity, such as body fat percentage, hip-to-waist ratio, body density, and BMI. Different methods may yield opposite results (e.g., some people who have high body fat percentage may also have an ideal hip-to-waist ratio). As BMI was chosen as the only approach in this study to determine obesity, the grouping, and results obtained may be biased. Another limitation was that the antagonistic muscle activities during the knee extension were not recorded, which left the coordination patterns between muscles unclear, also made the interpretation of the results and getting the full picture of neuromuscular controls more difficult. This limited our ability to completely explain our findings, thus needing further test and demonstration.

Future Directions

Submaximal isometric contractions were investigated in this study with a fixed work cycle and intensity of exertion. Future studies could continue this investigation by examining motor variability and neuromuscular control patterns under different cyclic patterns and force intensities. Moreover, as the vast majority of jobs and activities in the workplace and daily life involve dynamic motions and various levels of force exertions, future research should consider using more realistic and representative tasks to obtain more generalizable results. To gain a more complete picture of the neuromuscular control and coordination strategies used by different individuals, it is also recommended to incorporate measurements from, and activities involving agonistic, synergistic, and antagonistic muscles, to the most feasible extent.

Finally, based on our own and previous researches of others, it is clear that there is a need for a comprehensive and holistic model that brings together both basic and higher level factors to understand control and performance. We recognize that this is a very complex problem as there are multiple such factors, including personal factors (e.g., age, gender, obesity), biological factors (e.g., muscle physiological, neurological, hormonal factors), behavioral factors (e.g., motor control and coordination, strength, physical fitness), environmental, psychological, and social factors. This would require major efforts across multiple and currently-independent research disciplines but this now

seems a necessary and critical requirement for major advances in this field.

CONCLUSIONS

This study was a basic investigation on obesity- and gender-related differences in endurance among a cohort of older adults, and inter-individual differences in motor variability that may explain differences in endurance time. Males and females who were obese or non-obese, differed in the neuromuscular control mechanisms to resist fatigue and prolong endurance during intermittent submaximal muscle contractions. Males exhibited stronger fatigue resistance than females during the knee extension task, which was probably attributed to a greater antagonistic/synergistic control that slowed down the development of fatigue by allowing higher muscle variability in the primary knee extensor, while still maintaining the required force output. A motor control pattern with a greater cycle-to-cycle muscle variability at baseline was found to be associated with longer endurance time for the whole group, and the obese group exhibited significantly higher between-cycle variability than the non-obese group. We argue that this is reflective of stronger neural control exercised by the obese individuals to achieve similar endurance as non-obese older adults. Our findings enhance the theoretical understanding of the underlying neuromuscular control patterns and their relationship with fatigue for different individuals. Given that both aging and obesity rates are rising continuously and becoming a substantial health and safety priority for the society, the results from this study are both timely and critical.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Federal Regulations for Protection of Human Research Subjects (45 CFR 46). The protocol was approved by the Institutional Review Boards at Texas A&M University and Virginia Tech. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

XD was primarily responsible for analyzing the data and preparing the manuscript. JR was responsible for collecting and processing the data. RM was responsible for conceptualizing and designing the study. DS was primarily responsible for directing the data analysis, interpreting the findings, and manuscript writing. All authors contributed to critically reading and editing the manuscript content and language.

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Relationship Between Toe Clearance Strategy and Regional Regulation of Rectus Femoris Muscle During Swing Phase in Prolonged Walking in Young and Older Adults

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The toe clearance strategy during leg swinging while walking is closely associated with the risk of tripping and/or falling and is influenced by aging and a fall history. However, it remains unclear how the toe clearance strategy is regulated by the neuromuscular system. The present study investigated the effect of aging and fall/tripping history in the older adults on the toe clearance strategy and neuromuscular regulation of the rectus femoris (RF) muscle, which plays an important role in leg swinging, during prolonged walking. Thirteen older adults (age: 71.3 ± 5.7 years) and nine young adults (age: 20.9 ± 0.8 years) men volunteered for the present study. The older adults were divided into those with (n = 6) and without (n = 7) a fall/tripping history. Subjects walked on a treadmill at their preferred gait speed for 20 min, and lower extremity kinematics and multi-channel surface electromyography along the RF muscle were recorded. Variability of the minimum toe clearance (MTC) and central locus activation (CLA) of the RF muscle in older adults was significantly greater than in the young adults ($p < 0.05$). MTC significantly decreased with time in the older adults ($p < 0.05$), but not in the young adults ($p > 0.05$). There were no significant correlations between any parameters of MTC and CLA in the older adults or young adults ($p > 0.05$). MTC and variability of CLA significantly decreased with time in the older adults without a fall/tripping history ($p < 0.05$), but not in the older adults with such a history ($p > 0.05$). These results suggest that aging and a fall/tripping history in the older adults alter the toe clearance strategy and regional neural regulation of the RF muscle during prolonged walking.

Keywords: neuromuscular compartment, bi-articular muscles, multi-channel surface electromyography, aging, tripping

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INTRODUCTION

The risk of trip-related falls is maximal when the distance between the foot of the swing leg and the surface being walked on, i.e., minimum foot clearance (MFC), is reduced to zero or very small (Winter, 1992; Barrett et al., 2010). Variability of MFC during repeated gait cycles increases with aging and the presence of a fall history, and is known as a risk indicator for trips and related falls in the older adults (Karst et al., 1999; Mills and Barrett, 2001; Begg et al., 2007;

Mills et al., 2008; Barrett et al., 2010). While Mills et al. (2008) reported detailed relationships between lower extremity kinematics and MFC during gait in the young and older adults (Mills et al., 2008), the relationship with neuromuscular regulation is not fully understood.

It is well known that the rectus femoris (RF) muscle is closely associated with the gait function, and some pathological gait patterns are caused by abnormality of RF muscle activity (Sung et al., 2003; Chantraine et al., 2005; Reinbolt et al., 2008). We previously reported the unique nature of neuromuscular regulation in the RF muscle during gait. While the whole RF muscle is activated during the stance phase, its proximal region is selectively recruited during the swing phase (Watanabe et al., 2014b). This phenomenon can be explained by the region-specific functional role of the RF muscle, i.e., the proximal region of the RF muscle preferentially contributes to the hip flexion joint moment (Hagio et al., 2012; Watanabe et al., 2012, 2014a). Since the RF muscle contributes to two different joint moments, knee extension and hip flexion, regional neuromuscular control of the proximal RF muscle plays a role in minimizing unexpected knee extension joint moment induced by RF muscle activation during the swing phase. On the other hand, we also noted that this regional regulation of the RF muscle during the swing phase of gait is affected by aging. In the older adults, additional activation at distal region of the RF muscle was observed with activation at proximal regions during the swing phase (Watanabe et al., 2016). This may lead to unexpected knee extension joint moment during the swing phase and alteration in the toe clearance strategy.

The gait pattern and toe clearance strategy are modified during prolonged walking. Yoshino et al. (2004) reported that prolonged walking leads an increase in the gait cycle and its variability and mediolateral acceleration of the center of gravity (Yoshino et al., 2004). Nagano et al. (2014) showed that MTC is reduced due to prolonged walking-induced fatigue in the older adults, but not in young adults (Nagano et al., 2014). On the other hand, Barbieri et al. (2014) found that the effect of fatigue on heel clearance pattern during obstacle avoidance was not directly related with age (Barbieri et al., 2014). There are differences in the findings for relationship between age and foot clearance strategy during walking with fatigue. Also, older adults with a history of trip-related falls show a unique toe clearance strategy (Khandoker et al., 2008a,b), higher position of and greater variability of MFC (Barrett et al., 2010). However, no study has investigated the relationship between neuromuscular regulation and the toe clearance strategy during prolonged walking or in the older adults with a fall history.

The present study aimed to clarify the effect of aging and a fall/tripping history in the older adults on the toe clearance strategy and neuromuscular regulation of the RF muscle during prolonged walking. The following hypothesis were tested during prolonged walking: 1) MFC variability is associated with variability of regional activation of the RF muscle in the older adults, and 2) older adults with a fall/tripping history show a unique toe clearance strategy and neuromuscular regulation of the RF muscle.

MATERIALS AND METHODS

Subjects

Thirteen older adults (age: 71.3 ± 5.7 years, height: 167.3 ± 5.1 cm, body mass: 62.6 ± 7.1 kg) and nine young adults (age: 20.9 ± 0.8 years, height: 174.0 ± 6.7 cm, body mass: 63.0 ± 6.6 kg) men volunteered for the present study. Since women generally have thicker subcutaneous fat tissue that decreases surface EMG signal and increases signal-noise ratio in surface EMG signal, only men were chosen as the subjects in this study. The subjects gave written informed consent for the study after receiving a detailed explanation of the purposes, potential benefits, and risks associated with participation. All subjects were healthy with no history of any musculoskeletal or neurological disorders. All study procedures were conducted in accordance with the Declaration of Helsinki and research code of ethics of Chukyo University and were approved by the Committee for Human Experimentation of Chukyo University (2014-001 and 2017-004).

Experimental Design

Subjects were familiarized with walking on treadmill for 6∼16 days before the experimental day. On a trial day, the preferred gait speed was measured while walking a distance of 10 m with a normal gait along a flat surface. On the experimental day, the subjects walked on a treadmill (MEDTRACK ST65, Quinton Instrument Co., WA, United States) at their preferred gait speed for 20 min and lower extremity kinematics and neuromuscular activation of the RF muscle were recorded. The right leg was used to analyze joint kinematics and neuromuscular activation in this study. We directly questioned the trip history including fall and dragging for the older adults. The present study set that the elderly with fall/tripping history was who experienced a tripping (dragging) lately or a falling within a year.

Lower Extremity Kinematics

Coordinates on the sagittal plane obtained by placing reflective markers on the lower extremities were obtained using a three-dimensional motion capture system with six cameras (Vicon Bonita 3, Vicon Motion Systems Ltd., Oxford, United Kingdom) at a sampling rate of 100 Hz. While reflective markers were attached to the right acromion, greater trochanter, lateral femoral epicondyle, lateral malleolus, fifth metatarsal bone, toe, and heel, the markers on the toe and heel were used to determine heel contact and toe-off and analyze the toe clearance trajectory. To identify heel contact and toe off timings, vertical coordinates of heel and toe were measured during static standing before prolonged walking. The timings of heel contact or toe off were defined as beginning of stance or swing phases when vertical coordinate of heel or toe was lesser or greater than the vertical coordinates at the static standing. The detected coordinates on the sagittal plane for each marker were filtered with a fourth order Butterworth low-pass filter (6 Hz). To assess the individual characteristics of toe clearance, we calculated the MFC for each stride, i.e., lowest displacement between two highest peaks of vertical toe position from toe-off to heel contact (swing phase)

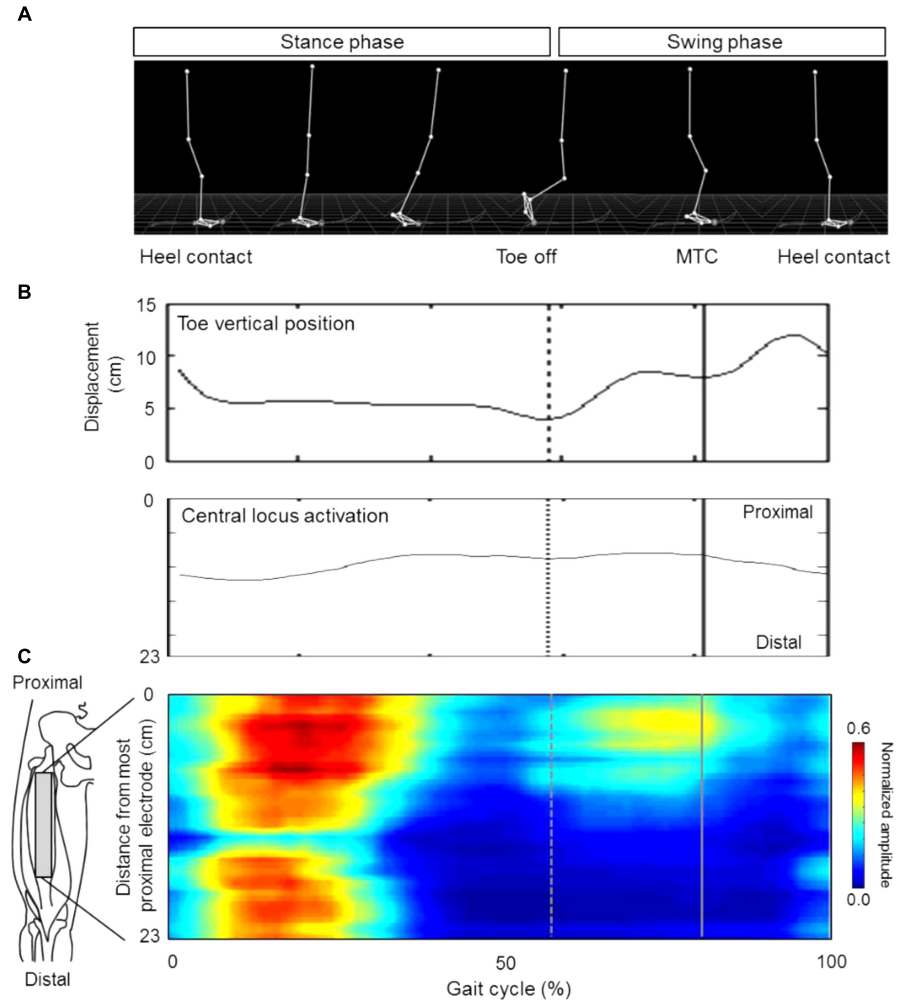

FIGURE 1 | Representative data on the lower joint kinematics **(A)**, toe vertical position **(B)** and normalized multi-channel surface electromyography amplitude of the rectus femoris muscle **(C)** for calculating minimum toe clearance (MTC) and central locus activation (CLA). Vertical solid and broken lines indicate the timings of MTC and toe off, respectively.

(**Figure 1**). Toe clearance strategy was assessed by this parameter. MFC values from 5 to 10 min and 15 to 20 min were used for further analysis. To synchronize the motion capture and EMG data, infrared radiation light-emitting diode with electrical signals were used.

Surface EMG Recording

Neuromuscular activation of the RF muscle was assessed by multi-channel surface EMG. Since regional EMG responses along the longitudinal axis of the RF muscle were noted in a previous studies (Watanabe et al., 2012, 2014b), 24 electrodes, with a 6 × 4 electrode arrangement (1 × 5 mm detection area, 10-mm inter-electrode distance; ELSH004, OT Bioelectronica, Turin, Italy) were attached along the line between the anterior superior iliac spine and superior edge of the patella (Watanabe et al., 2016). Surface EMG signals were recorded at 2,048 Hz with an eighth order Bessel band pass filter at 10–750 Hz (anti-aliasing filter) (EMG-USB, OT Bioelectronica, Torino, Italy). Bipolar surface EMG signals were calculated from the electrode pairs between neighboring electrodes along the rows in each array, rectified, and normalized by the peak value for each channel in each stride. Using the eighteen EMG signals from 3 pairs × 6 array electrodes along the longitudinal axis of the RF muscle, the centroid of the normalized rectified EMG along the muscle, i.e., central locus activation (CLA), was calculated in inter-electrode distance units at the time of MFC for each stride. This variable reflects regional neuromuscular regulation of the RF muscle. The results for CLA are shown as the distance (cm) from the most proximal edge of electrodes (**Figure 1**). CLA values from 5 to 10 min and 15 to 20 min were used for further analysis and to test the relationship with MFC.

Statistics

In the present study, non-parametric tests were used since the sample size was small and data distribution was partly non-gaussian. MFC, CLA, and gait parameters such as cadence, toe

off timing, and timing of MFC were compared between the older and young groups using the Mann-Whitney test to clarify the effect of aging and compared between 5–10 and 15–20 min using the Wilcoxon rank sum test to determine the effect of time for each subject group. Also, these variables were compared between the older adults with and without fall/tripping history using the Mann-Whitney test. Spearman's rank correlation coefficient was calculated between MFC and CLA at 5–10 min and 15–20 min to test the association between toe clearance and regional neuromuscular regulation of the RF muscle. The level of significance was set at $p < 0.05$. Statistical analysis was performed using SPSS (version 15.0, SPSS, Tokyo, Japan) and MATLAB (MATLAB R2008a, MathWorks, MA, United States).

RESULTS

Gait parameters used in this study are shown in **Table 1**. There were no significant differences in these gait parameters between the older and young adults ($p > 0.05$) (**Table 1**). Cadence in the older adults significantly decreased with time ($p < 0.05$), but no other parameters changed over time in either group ($p > 0.05$) (**Table 1**). There were no significant differences in the mean MTC or CLA at 5–10 min and 15–20 min between the older and young adults ($p > 0.05$) (**Figures 1A,C**). There were significant differences in SD of MTC at 5–10 min and 15–20 min between the older and young adults ($p < 0.05$) (**Figure 2B**). In the older adults, a significant effect of time was found in mean of MTC ($p < 0.05$) (**Figure 2A**). No significant correlations were found between parameters of MTC and CLA at 15–20 min in the older and young adults ($p > 0.05$) (**Table 2**).

There were no significant differences in gait parameters, MTC, or CLA between the older adults with and without fall/tripping history ($p > 0.05$) (**Table 3** and **Figure 3**). A significant effect of time on the mean MTC was noted in the older adults without a fall/tripping history ($p < 0.05$), but not in the older adults with such a history ($p > 0.05$) (**Figure 3A**). SD of CLA was significantly influenced by time in the older adults with fall/tripping history ($p < 0.05$) (**Figure 3D**). There were significant positive correlations between mean values of MTC and CLA at 5–10 min and 15–20 min in the older adults with fall/tripping history ($p < 0.05$), but not in the older adults without fall/tripping history ($p > 0.05$) (**Table 4**).

TABLE 1 | Gait parameters in older and young groups.

		Older adults *N* = 13	Young adults *N* = 9
Preferred gait speed (km/h)		4.7 ± 0.7	5.2 ± 0.7
Sample step number	5–10 min	289.1 ± 25.3	290.0 ± 15.5
	15–20 min	289.6 ± 16.1	291.0 ± 13.0
Cadence (bpm)	5–10 min	118.9 ± 8.1	119.3 ± 7.9
	15–20 min	116.8 ± 8.3*	117.8 ± 6.5
Toe off (% of stride)	5–10 min	62.1 ± 2.1	61.1 ± 2.4
	15–20 min	62.2 ± 1.9	61.7 ± 1.7
Time of MFC (% of stride)	5–10 min	83.3 ± 2.2	82.8 ± 0.8
	15–20 min	83.1 ± 2.0	83.0 ± 0.8

*$p < 0.05$ vs. 5–10 min.

DISCUSSION

The present study investigated the effect of aging and a fall/tripping history in the older adults on the toe clearance strategy and neuromuscular regulation of the RF muscle during prolonged walking. The main findings of the present study were (1) variability of MTC in the older adults was significantly greater than in the young adults (**Figure 2B**), (2) MTC significantly decreased with time in the older adults, but not the in young adults (**Figure 2A**), (3) there were no significant correlations between parameters of MTC and CLA in the young or older adults (**Table 2**), and (4) the effects of time on the mean MTC and variability of CLA were not uniform between the older adults with and without a fall/tripping history (**Figures 3A,D**). These results do not support the first hypothesis of this study that MFC variability is associated with variability in regional activation of the RF muscle in older adults. On the other hand, the second hypothesis that older adults with a fall/tripping history show a unique toe clearance strategy and neuromuscular regulation of the RF muscle was supported by our results.

As reported in a previous study (Barrett et al., 2010), while the mean MTC was not different between the older and young adults (**Figure 1A**), SD of MTC, which is a parameter of variability, was significantly higher in the older adults (**Figure 1B**). In their review, Barrett et al. (2010) suggested that mechanisms of greater MTC variability in the older adults are unclear, but it may be induced by age-related reductions in proprioceptive sensitivity and their ability to modulate muscle force (Barrett et al., 2010). The present study investigated the latter possibilities by assessing regional neuromuscular regulation of the RF muscle. In our previous study, CLA in the older adults was located at a more distal site compared with the young adults during 70–80% of the gait cycle (Watanabe et al., 2016), revealing that preferential activation of the RF muscle was attenuated during the swing phase in the older adults. We considered that this unique activation pattern in the older adults would lead to unexpected knee extension and a lower toe position during the swing phase. However, there were no significant differences in CLA between the older and young adults in the present study ($p > 0.05$) (**Figure 2** and **Table 2**). This may be partly due to differences in the gait speed, subjects' profiles, and analyzed phase between the present and previous studies. While age-related differences in CLA were noted solely with a fast gait speed and only the older adults without a fall history participated in a previous study (Watanabe et al., 2016), the present study employed a normal gait speed and the older adults subjects included those with fall/tripping history. The previous and present studies compared CLA between older and young adults at 70–80% (Watanabe et al., 2016) and approximately 83% of stride, respectively. There were no significant differences in CLA at 80–90% of stride for any gait speeds in the previous study (Watanabe et al., 2016). One of the causes of difference in the results between previous and present study could be the analyzed phase. On the other

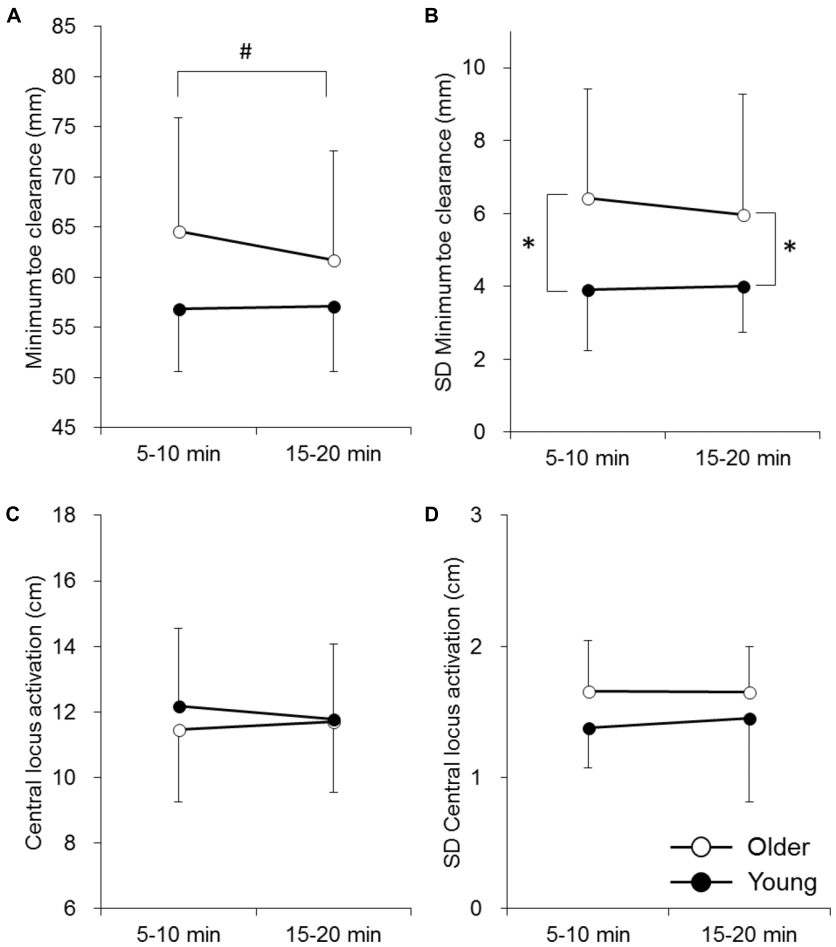

FIGURE 2 | Mean and standard deviation of minimum toe clearance (MTC) **(A,B)** and central locus activation (CLA) of the rectus femoris muscle **(C,D)** in the older adults (White circle) and young adults (Black circle). The symbols ∗ and # indicate significant differences ($p < 0.05$) between the older adults and young adults and between 5–10 min and 15–20 min, respectively.

hand, the present study also investigated the effect of prolonged walking on CLA. Although the gait pattern in the older adults was affected by prolonged walking, i.e., decreases in cadence and MTC (**Table 1** and **Figure 2A**), CLA remained unchanged between 5–10 min and 15–20 min in the older adults (**Figure 2C**). Moreover, correlations between mean values and variabilities in MTC and CLA were not detected in either the older or young adults subjects (**Table 2**). These findings suggest that the age-related toe clearance strategy was not associated with the regional neuromuscular activation pattern in the RF muscle. This is the answer to major question in the present study. During gait, large number of the muscles including the RF muscle are recruited and other muscles such as tibialis anterior or triceps surae muscles would have greater contribution to toe clearance strategy. It would be difficult to explain toe clearance strategy by only the RF muscle and combination of recording surface EMG from other key muscles provide further understanding of toe clearance strategy and its aging.

In the present study, the effect of fall/tripping history on the toe clearance strategy and regional neuromuscular activation pattern in the RF muscle was investigated. First, it must be noted that this study combined histories of fall and tripping while these are clearly different events. Fall history directly affect motor behavior due to anxiety and/or fear (Young and Mark Williams, 2015), however, this could not be presented by tripping history. Therefore, comparison of the results in this study with those in the previous studies using the subjects with fall history only would be needed to pay attention. There were no significant differences in the mean or variability of MTC

TABLE 2 | Correlation coefficients between minimum toe clearance and central locus activation.

		Older adults	Young adults
		r	r
Mean	5–10 min	0.209	−0.417
	15–20 min	0.418	−0.517
SD	5–10 min	0.148	0.200
	15–20 min	0.258	0.000

TABLE 3 | Profiles and gait parameters in the older adults with and without fall/tripping history.

		Older adults with fall/tripping history *N* = 6	Older adults without fall/tripping history *N* = 7
Age (years)		69.0 ± 3.7	73.3 ± 6.5
Height (cm)		164.6 ± 5.6	169.6 ± 3.5
Body mass (kg)		59.8 ± 4.6	65.0 ± 8.2
Preferred gait speed (km/h)		4.6 ± 0.9	4.8 ± 0.5
Sample step number	5–10 min	283.3 ± 22.6	294.0 ± 28.3
	15–20 min	286.7 ± 19.0	292.1 ± 14.2
Cadence (bpm)	5–10 min	118.1 ± 10.7	119.6 ± 6.0
	15–20 min	116.2 ± 10.4	117.3 ± 7.0
Toe off (% of stride)	5–10 min	63.2 ± 1.4	61.1 ± 2.2
	15–20 min	63.3 ± 1.6	61.2 ± 1.7
Time of MFC (% of stride)	5–10 min	84.3 ± 1.4	82.4 ± 2.4
	15–20 min	84.0 ± 1.6	82.3 ± 2.0

between the older adults with and without fall/tripping history ($p > 0.05$) (**Figures 3A,B**). In previous studies, greater mean values and variabilities in the older adults with a fall/tripping history were reported, and it was suggested that the change in the toe position may be a strategy to reduce the risk of falls associated with greater MTC variability (Khandoker et al., 2008a,b; Barrett et al., 2010). Although differences in the mean and variability of MTC were not observed in the present study, a difference in the time course of MTC during prolonged walking was noted on comparing the older adults with and without fall/tripping history (**Figure 3A**). MTC was significantly decreased with time in the older adults without fall/tripping history ($p < 0.05$), but not in the older adults with such history ($p > 0.05$) (**Figure 3A**). Considering the reduced MTC after prolonged walking in all older adults in this study (**Figure 2A**) and normal older adults in a previous study (Nagano et al., 2014), the unchanging MTC over time could be a characteristic toe clearance strategy in the older adults with a fall/tripping history during prolonged walking (**Figure 3A**). While reduction of the vertical toe position during the swing phase would increase the fall risk, maintaining a higher toe position during prolonged walking may increase

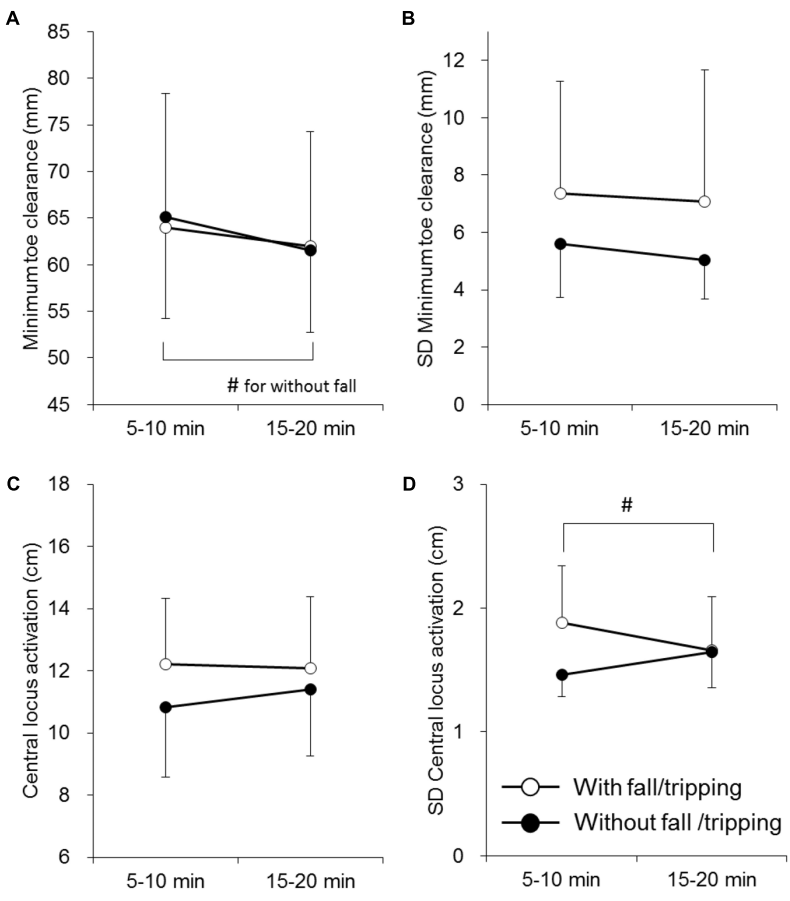

FIGURE 3 | Mean and standard deviation of minimum toe clearance (MTC) **(A,B)** and central locus activation (CLA) of the rectus femoris muscle **(C,D)** in the older adults with (White circle) and without (Black circle) fall/tripping history. The symbol # indicates a significant difference ($p < 0.05$) between 5—10 min and 15–20 min.

TABLE 4 | Correlation coefficients between minimum toe clearance and central locus activation for older adults with and without fall/tripping history.

		With fall/tripping history	Without fall/tripping history
		r	r
Mean	5–10 min	0.829*	0.036
	15–20 min	0.829*	0.143
SD	5–10 min	0.486	−0.286
	15–20 min	0.257	0.464

*$p < 0.05$.

the metabolic cost (Barrett et al., 2010). We think that the older adults with and without fall/tripping history adopt strategies that minimize the fall risk and metabolic energy, respectively. The present study also showed a difference in regional neuromuscular activation of the RF muscle between the older adults with and without a fall/tripping history. A significant decrease with time in variability in CLA was observed only in the older adults with a fall/tripping history (**Figure 3D**). While it is difficult to link this with the results regarding the toe clearance strategy, this neural activation pattern may be characteristic of the older adults with fall/tripping history. CLA is determined by the spatial distribution of the neuromuscular activation levels in proximal to distal regions of the RF muscle. Our previous studies already revealed that the regional neuromuscular activation pattern along the RF muscle is modified by motor tasks: knee extension or hip flexion (Watanabe et al., 2012), fatigue (Watanabe et al., 2013), and the joint angle (Watanabe et al., 2014a). From the results of these previous studies, the regional neural regulation of the RF muscle is modulated and integrated by many factors. Although the physiological mechanisms are unclear, decreased CLA variability over time in the older adults with a fall/tripping history could be due to reduced variability of these modulations. Significant correlation was found between mean values of MTC and CLA in the older adults with fall/tripping history at 5–10 min and 15–20 min ($p < 0.05$) (**Table 4**). This relationship was not observed in the analysis for all older adults ($p > 0.05$) (**Table 2**) and the older adults without fall/tripping history ($p > 0.05$) (**Table 4**). Positive relationship between MTC and CLA means that higher toe vertical position in the subjects with more distal position of CLA. This relationship is not reasonable, because our previous studies suggested that neuromuscular activation at proximal regions of the RF muscle contributes to hip flexion joint torque that should lead higher vertical toe position (Watanabe et al., 2012, 2014b, 2016). While it is difficult to clarify physiological/biomechanical mechanisms of this characteristic relationship between MTC and CLA in the older adults with fall/tripping history in this study, this may reflect unique gait strategy in the older adults with fall/tripping history. Also, it should be noted that the present study investigated the effect of fall/tripping history by including subjects with such a history and history of tripping and dragging, while the previous studies only included older subjects with a fall history. Differences in results between the present and previous studies may be partly explained by variations in subjects' gait ability. The subjects with fall/tripping history in this study may be categorized as showing milder gait dysfunction when compared with those of previous studies (Khandoker et al., 2008a,b). On the other hand, I must note that the results in the present study were observed from small number of the subjects. This could be one of the limitations and interpretation of the results is also restricted in current study.

The present study focused on only the RF muscle, since this study performed to clarify the hypothesis that regional neuromuscular activation within the RF muscle is associated with gait parameters. However, many muscles are recruited during gait and the muscles around ankle joint would strongly contribute to toe clearance strategy. The further study that covers key muscles with the RF muscle could be needed to understand the effect of aging and fall/tripping history on the toe clearance strategy. Also, this study analyzed neuromuscular activation of the RF muscle and toe clearance strategy only in right leg. From the older adults may have asymmetry in the leg movements during walking, analyses of both legs could be needed for further understanding.

CONCLUSION

The present study investigated the effect of aging and fall/tripping history in the older adults on the toe clearance strategy and neuromuscular regulation of the RF muscle during prolonged walking. To achieve this, we compared indicators of the toe clearance strategy and regional muscle activation along the RF muscle: MTC and CLA, between the older and young adults and between the older adults with and without a fall/tripping history during 20 min walking at normal speed. We noted a difference in MTC between the older and young adults, but not in CLA, and a difference in MTC and CLA during prolonged walking between the older adults with and without a fall/tripping history. Also, there were no significant correlations between parameters of MTC and CLA in the older adults. These results suggest that aging and a fall/tripping history in the older adults alter the toe clearance strategy and regional neural regulation of the RF muscle during prolonged walking, but toe clearance strategy and regional neural regulation of the RF muscle are not associated in the older adults.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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REVIEW
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Fatigue in Chronic Respiratory Diseases: Theoretical Framework and Implications For Real-Life Performance and Rehabilitation

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Fatigue is a primary disabling symptom in chronic respiratory diseases (CRD) with major clinical implications. However, fatigue is not yet sufficiently explored and is still poorly understood in CRD, making this symptom underdiagnosed and undertreated in these populations. Fatigue is a dynamic phenomenon, particularly in such evolving diseases punctuated by acute events which can, alone or in combination, modulate the degree of fatigue experienced by the patients. This review supports a comprehensive inter-disciplinary approach of CRD-related fatigue and emphasizes the need to consider both its performance and perceived components. Most studies in CRD evaluated perceived fatigue as a trait characteristic using multidimensional scales, providing precious information about its prevalence and clinical impact. However, these scales are not adapted to understand the complex dynamics of fatigue in real-life settings and should be augmented with ecological assessment of fatigue. The state level of fatigue must also be considered during physical tasks as severe fatigue can emerge rapidly during exercise. CRD patients exhibit alterations in both peripheral and central nervous systems and these abnormalities can be exacerbated during exercise. Laboratory tests are necessary to provide mechanistic insights into how and why fatigue develops during exercise in CRD. A better knowledge of the neurophysiological mechanisms underlying perceived and performance fatigability and their influence on real-life performance will enable the development of new individualized countermeasures. This review aims first to shed light on the terminology of fatigue and then critically considers the contemporary models of fatigue and their relevance in the particular context of CRD. This article then briefly reports the prevalence and clinical consequences of fatigue in CRD and discusses the strengths and weaknesses of various fatigue scales. This review also provides several arguments to select the ideal test of performance fatigability in CRD and to translate the mechanistic laboratory findings into the clinical practice and real-world performance. Finally, this article discusses the dose-response relationship to training and the feasibility and validity of using the fatigue produced during exercise training sessions in CRD to optimize exercise training efficiency. Methodological concerns, examples of applications in selected diseases and avenues for future research are also provided.

Keywords: performance fatigability, perceived fatigability, muscle function, exercise training, ecological momentary assessment, chronic obstructive pulmonary disease, cystic fibrosis, obstructive sleep apnea

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INTRODUCTION

Fatigue is an important debilitating symptom which concerns virtually all chronic respiratory diseases (CRD). Fatigue is a leading cause of consultations in CRD with major clinical implications. Despite its well-acknowledged negative consequences on patient's life, fatigue is still a misunderstood and underdiagnosed symptom in CRD. As a consequence, there is currently no intervention that has been developed specifically to treat all aspects of this ambiguously defined symptom in CRD. Fatigue is rather often considered as a secondary outcome in interventions aiming primarily to increase physical fitness and/or health-related quality of life.

Previous research on fatigue in CRD has been based on many dichotomies and no consensus as yet emerged on how to define and measure this symptom in these specific populations. The present review adopts a terminology of fatigue adapted from Enoka and Duchateau (2016) that includes the subjective sensations of fatigue (i.e., perceived fatigability) and the objectives changes in performance (i.e. performance fatigability), both being closely interrelated and inseparable. Most studies in CRD evaluated perceived fatigability as a trait characteristic. Using multidimensional scales, such studies provided important insights on the prevalence and the clinical consequences of fatigue in these populations (e.g., Stridsman et al., 2015; Nap-Van der Vlist et al., 2018). However, these scales do not permit to capture and understand fatigue over time and across contexts and environments. Evaluating fatigue as a state is thus fundamental to shed light on the dynamics of fatigue experienced by CRD patients in real-world settings.

Fatigue as a state can be evaluated both at rest at a specific moment of the day (e.g., before bedtime, after lunch) and during a physical activity. Surprisingly, only very few studies evaluated fatigue as a state at rest in CRD and there are no specific validated tools available for that purpose in these populations. During an ongoing physical activity, the fatigue experienced by a patient will be determined by the rates of changes in both perceived and performance fatigability. Various tests have been used to evaluate performance fatigability in CRD. Performance fatigability depends on the ability of the peripheral muscles and the central nervous system to meet the demands of the prescribed task. Both systems can exhibit abnormal changes in response to exercise in CRD (e.g., Maltais et al., 2014; Marillier et al., 2018a) and contribute to increased performance fatigability. Thus, a performance fatigability test should allow an easy implementation of measures of both peripheral and central contributors of fatigue. However, with the aim to be used in clinical trials and even routine practice, the test should also demonstrate satisfactory feasibility and reliability. Importantly, mechanistic studies on the neurophysiology of CRD-related fatigue often display poor external and ecological validity. This is notably the case for local fatiguing exercises (e.g., Marillier et al., 2018a). It is often unknown whether the results from a performance fatigability study could be generalized to circumstances beyond the actual research setting and how such results could be translated to real-life performance and rehabilitation. Can the results of a specific fatiguing task in a given subgroup of CRD patients be extrapolated to another task in patients with different disease severity? And, at least as important, can the same results be relevant in the real daily-life? The real challenge of a performance fatigability test is to cumulate all the aforementioned characteristics to be suitable in most CRD patients in both clinical and research settings.

A better knowledge of the determinants of fatigue is a prerequisite to develop new strategies aiming to reduce the influence of each underlying factor in the daily life of the patients. However, such knowledge may also paradoxically enable to produce more fatigue in the specific context of exercise training. Following the principle of muscle loading, seminal reports in chronic obstructive pulmonary disease (COPD) (e.g., Burtin et al., 2012) demonstrate that quantifying the production of fatigue following an acute exercise training session was an effective strategy to identify future responders and non-responders to an exercise program. The key issue is then to understand why some CRD patients are not able to exhibit significant fatigue following a given exercise training session and then to propose individualized countermeasures.

This review aims first to clarify the terminology of fatigue and considers the strengths and weaknesses of the current models of fatigue and their applicability in CRD. This article then briefly reviews the prevalence and impact of fatigue in CRD and considers the advantages and drawbacks of the scales intending to assess fatigue as a trait and as a state in these patients. This review then proposes a step-by-step approach to identify the ideal test of performance fatigability in CRD and to translate the mechanistic laboratory findings into the clinical practice and real-life performance. Finally, this article discusses the viability of using the fatigue produced during an acute exercise training session in CRD to detect the future responders to an exercise program. The present review is enriched by several practical examples of application in various CRD and provides directions for future research.

TRADITIONAL DICHOTOMIES, LIMITATIONS OF CURRENT KNOWLEDGE, AND NEW MODELS OF FATIGUE

Many works on fatigue, in both clinical and sports research areas, have been based on traditional dichotomies. The usual way is to consider *mental*, *psychological, cognitive*, *perceived* fatigue distinctly from *physical, physiological, muscle* fatigue or fatigability. It is also common to adopt a *peripheral* vs. *central* (*spinal* vs. *supraspinal*) dichotomy to suggest a locus of the observed *muscle* fatigue (e.g., Gruet et al., 2013). Other distinctions based on temporality or methodologies are also usually made (e.g., *chronic* vs. *acute* fatigue, fatigue as a *trait* vs. fatigue as a *state*, *subjective* vs. *objective* fatigue) (Enoka and Duchateau, 2016). The word "fatigue" is thus most of the time preceded by one of the aforementioned adjectives, leading to as

Abbreviations: 6MWT, six-minute walk test; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; CRD, chronic respiratory diseases; EMA, ecological momentary assessment; MVC, maximal voluntary contraction; OSA, obstructive sleep apnea; PFC, prefrontal cortex; QIF, quadriceps intermittent fatigue; ROF, rating-of-fatigue; RPE, ratings of perceived exertion.

many different definitions as adjectives. Although each definition may be relevant in isolation, such compartmentalization does not favor the emergence of a comprehensive interdisciplinary approach of fatigue and rather confines the study of fatigue to a monodisciplinary research. Each discipline has developed its own corpus of knowledge, taxonomy, experimental models, and methodologies. For instance, neurophysiologists often consider a neuromuscular approach of fatigue. *Muscle* fatigue is then defined as a reduction in maximal force of power generated voluntary by a muscle or a muscle group and/or a reduction in twitch force elicited by nerve stimulation (Gandevia, 2001). This condition is reversible by rest and should be differentiated from muscle weakness which can be defined as an impaired capacity to generate force (NHLBI Workshop summary, 1990). Study of muscle fatigue is relevant in CRD as many patients present a peripheral muscle dysfunction (e.g., muscle atrophy, inflammation, metabolic abnormalities; Maltais et al., 2014; Gruet et al., 2017) and even sometimes cerebral abnormalities (e.g., gray matter decrease; Esser et al., 2016). A neuromuscular approach of fatigue, giving consideration to both central (i.e., corticospinal drive) and peripheral (i.e., peripheral muscle transmission and contractility) factors is thus relevant in these patients to understand the mechanisms underlying increased fatigability during a physical task. However, such approach is clearly irrelevant to capture the fatigue experienced by patients at "rest," independent of any ongoing physical activity. On the other hand, perceived fatigue experienced at rest and captured by questionnaires is not sufficient to understand how and why fatigue progressively develops during a given physical activity of daily living (e.g., walk up several flights of stairs). Thus, a multidimensional approach of fatigue is clearly warranted, especially in multi-systemic and progressive diseases that are CRD, with the aim to understand the fatigue experienced by patients in various contexts and at different times during the course of the disease.

Spruit et al. (2017) recently proposed a model of fatigue in patients with COPD. Moderate to severe fatigue can be perpetuated by various factors, grouped into three categories: systemic factors (e.g., cardiovascular disease, exercise-induced oxidative stress), physical and psychological factors (e.g., breathlessness, symptoms of anxiety and/or depression) and behavioral (e.g., nocturnal awakening, low social support). Fatigue can be precipitated by infectious COPD exacerbation and its treatment. This model suggests that the fatigue experienced by these patients is not simply the consequence of the COPD disease and cannot be predicted by the sole degree of airflow obstruction. Fatigue is rather the consequence of multiple factors that may act alone or in interaction, at rest and during/after a physical exercise. If some factors such as physical activity levels and exacerbation rate have been demonstrated to play a significant role in perpetuating and precipitating fatigue in COPD (Baghai-Ravary et al., 2009; Andersson et al., 2015), the influence of some other factors still has to be demonstrated. It is of note that this model mixes, at the same level, factors at a macro- (e.g., physical deconditioning, physical inactivity, cardiovascular disease) with factors at a more micro-level (e.g., systemic inflammation, breathlessness), the latter being often dependant on the former. This approach also does not make a clear distinction between factors influencing perceived and performance fatigue and thus does not rely on a unified taxonomy of fatigue. This model may thus be challenging to be experimentally tested but is so far the most comprehensive model of fatigue in COPD.

Contemporary models of fatigue have criticized the traditional peripheral/central dichotomy and rather suggested that fatigue is the result of a complex interaction between physiological activity and psychological state. For instance, in their Integrative Governor theory, St Clair Gibson et al. (2018) proposed that the competitive, dynamic interplay between physiological and psychological homeostatic drives regulates exercise performance and the fatigue process. In the same vein, Enoka and Duchateau (2016) proposed a definition of fatigue that includes (1) the "perceived" component, referring to the sensations about fatigue, and (2) the "performance" component, referring to the capacity of the neuromuscular system to meet the requirements of a given task. Importantly, the definition also suggests the interdependence relationship of the two components. The authors defined fatigue as "a disabling symptom in which physical and cognitive function is limited by interactions between performance fatigability and perceived fatigability." The term "fatigability" is used here to normalize the level of fatigue experienced by a person relative to the requirements of a given task that produces it. Based on this taxonomy, the same authors proposed a generic model of fatigue (adapted and modified from Kluger et al. (2013), initially developed for neurological diseases). In this model, perceived fatigability depends on two domains: maintenance of homeostasis (e.g., blood glucose) and psychological state (e.g., mood). Performance fatigability also depends on two domains: contractile function (e.g., calcium kinetics) and muscle activation (e.g., activation patterns). This model has the advantage of being universal and can be virtually adapted for every disease including CRD, the relative weight of each factor and their reciprocal interaction depending on the disease.

The model proposed in the present review and adapted for CRD is based on this taxonomy (**Figure 1A**). The designation of the domains of perceived and performance fatigability was slightly modified. "Psychological state" was replaced by "psychosocial state" to underline the possible influence of coping with social identity threats on fatigue. Indeed, copying with negative stereotypes (which can be prevalent among CRD, e.g., Johnson et al., 2007) may increase fatigue (Inzlicht and Kang, 2010; Chalabaev et al., 2013). The factors of perceived fatigability are those described by Enoka and Duchateau (2016), with the addition of "stereotypes" and "cardiovascular hemodynamic" (which can also impact fatigue levels, e.g., blood pressure, cardiac output, stroke volume; Freeman and Komaroff, 1997; Nelesen et al., 2008). "Central factors" and "peripheral factors" were chosen to designate domains of performance fatigability. Four macro-factors which are particularly prevalent in CRD (i.e., dyspnea, anxiety/depression, cognitive failure, and physical deconditioning) can exert an important influence on several of the micro-factors underlying domains of perceived and performance fatigability (**Figure 1A**). The present model also mentions the potential modulating factors and consequences of fatigue and suggests a step-by-step approach to develop specific countermeasures. The different parts and components

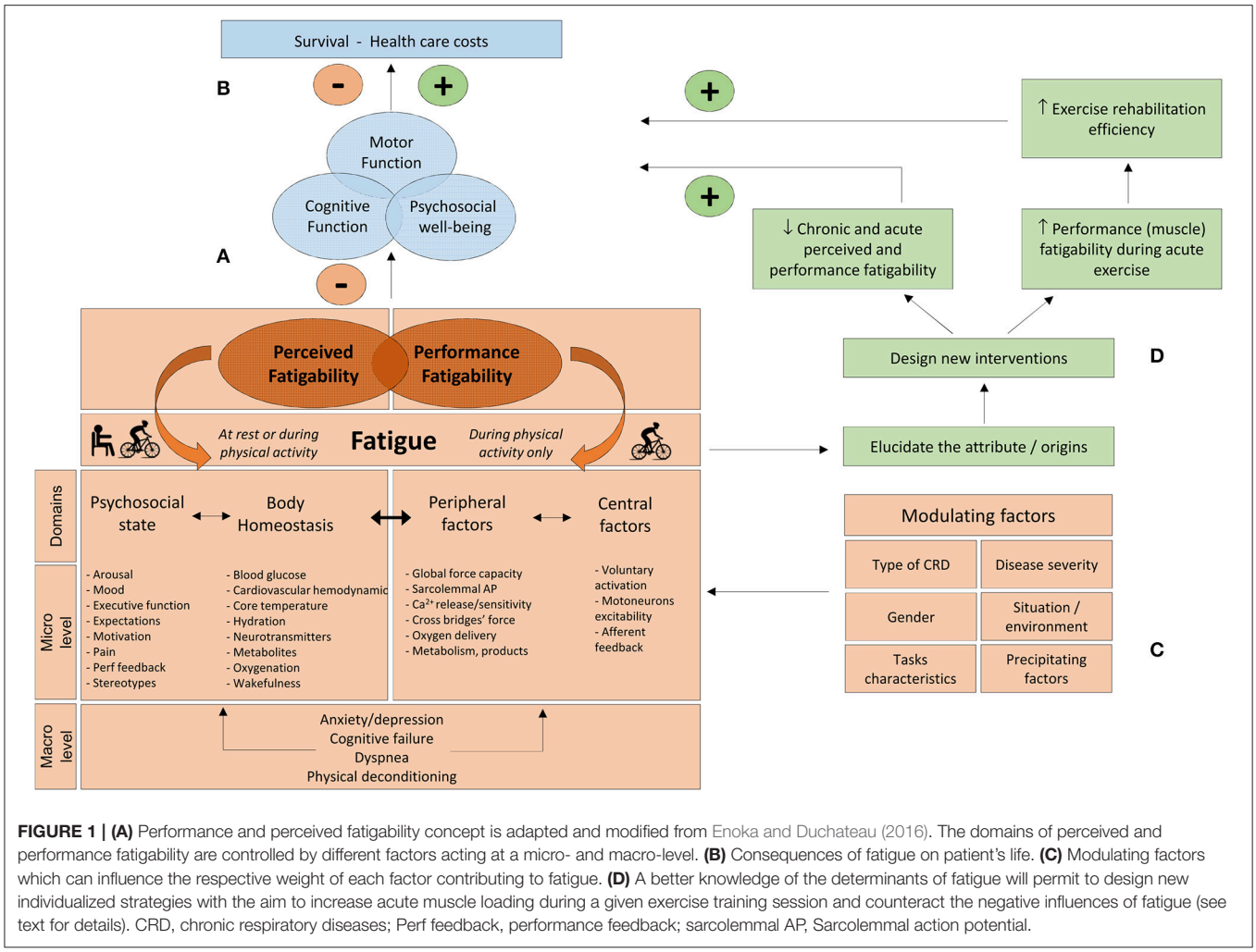

FIGURE 1 | (A) Performance and perceived fatigability concept is adapted and modified from Enoka and Duchateau (2016). The domains of perceived and performance fatigability are controlled by different factors acting at a micro- and macro-level. **(B)** Consequences of fatigue on patient's life. **(C)** Modulating factors which can influence the respective weight of each factor contributing to fatigue. **(D)** A better knowledge of the determinants of fatigue will permit to design new individualized strategies with the aim to increase acute muscle loading during a given exercise training session and counteract the negative influences of fatigue (see text for details). CRD, chronic respiratory diseases; Perf feedback, performance feedback; sarcolemmal AP, Sarcolemmal action potential.

of this model will be developed throughout the subsequent sections.

Perceived and performance fatigability can both exert a negative influence on motor, cognitive, and psychosocial functioning, all of which, in isolation and/or combination, may in turn compromise survival and increase medical care costs (**Figure 1B**). However, various modulating factors must be considered when investigating fatigue, each potentially influencing the relative contribution of perceived and performance fatigability underlying factors. Thus, elucidating the origins of fatigue is context-specific and the etiology of fatigue must be considered according to patients (i.e., type of disease, disease severity, gender), tasks (i.e., nature, duration and intensity of the tasks) and situation/environment characteristics (e.g., rest vs. exercise; work vs. home) and precipitating factors (i.e., hospitalization and associated treatments) (**Figure 1C**). For instance, "oxygenation" and "metabolites" are probably important attributes in severe COPD during exercise. Early activation of the anaerobic metabolism during exercise can result in elevated lactic acid production, precipitating exercise-induced hyperventilation and dyspnea (Maltais et al., 1998), which in turn can contribute to increased perceived fatigability. However, these factors have probably a minor influence at rest in patients with mild cystic fibrosis (CF). Each of the modulating factors presented in **Figure 1C** can be tested experimentally (e.g., specific inclusion criteria, stratification for disease severity, gender, pre vs. during vs. post hospitalization).

Shedding light on the attributes of fatigue will permit to create new individualized interventions, aiming to (1) increase acute muscle loading during a given exercise session (a prerequisite for training efficiency, see section Fatiguers as Responders: Experimental Evidences and Exercise Training Strategies) and, (2) reduce both chronic and acute perceived and performance fatigability under various conditions. Achieving both of these goals can in turn improve patients' health and thus reduce medical care costs (**Figure 1D**). This model clearly suggests that fatigue should be evaluated in different ways to reflect the diversity of contexts and environments in which fatigue can emerge over the natural history of the disease. Fatigue can be assessed in four different ways. Perceived fatigability can be evaluated as a trait characteristic (section Fatigue as a Trait: Useful Information on Prevalence and Impact), but also

as a state, in the present moment, both at rest and during ongoing physical activity (section Fatigue as a State: Time for Ecological Momentary Assessment). Performance fatigability is evaluated during physical activity (section Fatigability and Performance: Theoretical Concepts and Applications and Performance Fatigability: Which Test With Which Fundamental Characteristics?). **Table 1** summarizes four selected methods to evaluate perceived and performance fatigability in CRD. These methods will be discussed in details in the next sections.

PERCEIVED FATIGABILITY

Fatigue as a Trait: Useful Information on Prevalence and Impact

The trait level of fatigue refers to the amount of fatigue experienced by patients over a preceding period of time, usually several days or few weeks. It is evaluated with multidimensional scales, which constitute by far the most common way to assess fatigue in studies involving CRD patients. These scales reveal that the prevalence of fatigue is elevated in CRD, including COPD (Stridsman et al., 2013), CF (Nap-Van der Vlist et al., 2018), bronchiectasis (Hester et al., 2012), obstructive sleep apnea (OSA) (Mills et al., 2008), lung cancer (Graves et al., 2007), chronic pulmonary aspergillosis (Al-Shair et al., 2016b), sarcoidosis (Bosse-Henck et al., 2017), and idiopathic pulmonary fibrosis (Atkins et al., 2016). These multidimensional scales also provide evidence that fatigue in CRD is distinguishable from other related symptoms also prevalent in these populations, such as sleepiness, dyspnea, anxiety, and depression (Baghai-Ravary et al., 2009; Jackson et al., 2011; Al-Shair et al., 2016a; Atkins et al., 2016; Nap-Van der Vlist et al., 2018). Elevated trait level of fatigue has major clinical implications. Fatigue is associated with reduced quality of life, increased rates of hospitalization, reduced physical activity levels, and exercise intolerance (Baghai-Ravary et al., 2009; Paddison et al., 2013; Andersson et al., 2015; Al-Shair et al., 2016a; Nap-Van der Vlist et al., 2018). Fatigue has also been identified as a predictor of mortality in COPD (Stridsman et al., 2015). No less importantly, fatigue is only partially explained by disease severity and symptoms related to shortness of breath. For instance, apnea severity accounted for only a very small percentage of variance in fatigue score in patients with OSA, whereas factors such as inflammation and depression symptoms were found to be important independent predictors (Bardwell et al., 2003; Mills et al., 2008). Strategies aiming to treat breathing impairments may thus not be sufficient to reduce fatigue and other factors affecting body homeostasis and psychosocial state may be important to consider.

However, methodological considerations should also be taken into account, especially when comparing studies and the clinical implications of these findings. The first reason is related to the variety of scales used to investigate the trait level of fatigue. Hjollund et al. (2007) identified 156 multi-symptom scales (from 670 studies) and 71 scales (from 416 studies) which have been used to specifically measure perceived fatigability, irrespective of the disease. The number of scales used in CRD is certainly much lower but remains important. For instance, Antoniu and Ungureanu (2015) identified 8 multidimensional scales which are commonly used to assess perceived fatigability in COPD. **Table 2** summarizes the unidimensional, multidimensional and specific-disease scales which are frequently used in CRD ($n = 16$). Such diversity precludes accurate comparisons between studies as the scores produced by the scales are, most of the time, not interchangeable, as indicated by poor to moderate correlations between scales in previous reports (Vasconcelos et al., 2006; Panitz et al., 2015). It should also be mentioned that CRD are progressive diseases and some questionnaire items may turn inappropriate with disease progression. This should be considered when selecting a fatigue questionnaire, especially for long-term longitudinal studies.

There is also still a debate whether the trait level of fatigue should be evaluated from generic or disease-specific scales. On one hand, fatigue can be considered as an unspecific symptom as a whole, thus not requiring the development of specific scales for each disease (Hjollund et al., 2007). The use of generic scales may thus allow a better comparison of this symptom between diseases. On the other hand, fatigue can still have distinct features depending on the disease, making a disease-specific assessment important. For instance, pain can be an important correlate of fatigue in rheumatoid disorders whereas it may not specifically be the case in CRD, the opposite being certainly true for dyspnea. Some factors may also play a greater role in causing or maintaining fatigue in a given CRD compared to the other (e.g., sleep-related breathing disorders in OSA). Considering these elements, assessment of perceived fatigability as a trait should ideally be performed by using both disease-specific and generic fatigue scales. Admittedly, the use of two questionnaires may not always be feasible in daily clinical practice. Nonetheless, the few additional minutes to complete a second questionnaire are most certainly worthwhile, at least for research purposes. To date, fully validated CRD-specific fatigue scales are available for COPD and asthma (Al-Shair et al., 2009; Revicki et al., 2010) and further studies should develop and validate disease-specific scales in CRD for which fatigue is an important issue.

The vast majority of studies investigating the trait level of fatigue in CRD used cross-sectional designs. In most studies, the scores of fatigue are linked to the scores of other symptoms and some clinical data (e.g., Stridsman et al., 2013; Atkins et al., 2016; Nap-Van der Vlist et al., 2018). Such designs have the advantage to demonstrate excellent feasibility, resulting in the completion of large studies across the disease spectrum, even in rare CRD (e.g., sarcoidosis, Bosse-Henck et al., 2017). However, such studies have the disadvantage to assess fatigue only at a single time point and thus may not precisely reflect the level of fatigue experienced by the patient over the course of his long-lasting disease. Moreover, the cross-sectional association between two parameters does not permit to infer on the causes and consequences. For instance, previous reports demonstrated a link between physical activity levels and fatigue scores across numerous CRD, including COPD (Andersson et al., 2015) and CF (Nap-Van der Vlist et al., 2018). Lack of physical activity can be a mechanism through which fatigue occurs (notably via peripheral muscle deconditioning and reduced force capacity) but an elevated trait of fatigue

TABLE 1 | Summary of four selected methods to assess perceived and performance fatigability in CRD.

Fatigue attribute	Trait/State	Capture condition	methods/tests	Main applications/advantages	Disadvantages	Main future directions
Perceived fatigability	Trait	At rest	Combination of multidimensional generic scale and disease-specific scale	Elucidate predictors of fatigue. Obtain information about prevalence and clinical consequences of elevated levels of perceived fatigability.	Limited ecological validity. Recall bias. Not optimal for multiple repeated assessments.	Validate disease-specific fatigue scales. Conduct observational and interventional longitudinal studies.
	State	At rest	ROF scale	Capture changes in fatigue over time in various contexts and environments. Impact of specific events and their temporality on perceived fatigability. Ecological validity, feasibility.	Limited details on the attributes of fatigue. Absence of normal values. Long-term compliance.	Assess diurnal and seasonal changes in fatigue. Asses fatigue pre-post acute treatment (e.g., physiotherapy session) and throughout hospitalization for exacerbation or over the course of a new long-term treatment.
	State	During physical activity	ROF scale	Assess the kinetics of perceived fatigability severity during a given physical task. Obtain insight into the global level of fatigue produced by an exercise training session.	Absence of mechanistic insights into fatigue development.	Assess fatigue kinetics during standardized physical activities of daily living (e.g., stair-climbing). Usefulness in combination with markers of muscle fatigue to identify responders to exercise training.
Performance fatigability	State	During physical activity	Intermittent isometric graded contractions	Obtain insight into the neuromuscular factors limiting performance and contributing to elevated state of fatigue during a given physical task.	Ecological validity, feasibility	Assess supraspinal mechanisms in fatigue-related force loss by implementing brain investigations techniques. Assess performance fatigability with concomitant cognitive tasks. Quantify the association between performance fatigability and real-world performance (e.g., walking tests). Determine the effectiveness of specific interventions in reducing performance fatigability.

For each method is given the main applications and advantages, disadvantages and some directions regarding the future use of these methods. ROF, rating-of-fatigue.

TABLE 2 | Scales commonly used to assess perceived fatigability in CRD patients.

Name of the scale	Example of study	Example of population
Borg VAS scale	Al-Shair et al., 2011	COPD
Single question, Likert scale	Chervin, 2000	OSA
Fatigue Severity Scale (FSS)	Ozalp et al., 2012	Bronchiectasis
Short Form Health Survey 36 (SF-36), vitality domain	Antoniu et al., 2016	COPD
Functional Assessment of Chronic Illness Therapy - Fatigue scale (FACIT-F)	Andersson et al., 2015	COPD
Multidimensional Fatigue Inventory (MFI)	Orava et al., 2018	CF
Profile of Mood States (POMS), fatigue subscale	Jackson et al., 2011	OSA
Brief Fatigue Inventory (BFI)	Chen et al., 2018	COPD
Checklist Individual Strength-20 (CIS-20)	Nap-Van der Vlist et al., 2018	CF
Fatigue Assessment Scale (FAS)	Lingner et al., 2018	Sarcoidosis
Identity-Consequences Fatigue Scale (ICFS)	Paddison et al., 2013	COPD
Chalder Fatigue Scale	Jarad et al., 2012	CF
Multidimensional Assessment of Fatigue (MAF)	Belza et al., 2001	COPD
Fatigue Impact Scale (FIS)	Hester et al., 2012	Bronchiectasis
Manchester COPD Fatigue Scale (MCFS)	Al-Shair et al., 2016a	COPD
COPD and Asthma Fatigue Scale (CAFS)	Miravitlles et al., 2013	COPD

The current list is not intended to be all-inclusive. The light gray indicates unidimensional scales. The intermediate gray indicates multidimensional generic scales. The dark gray indicates specific-disease scales. CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea.

can also prevent some patients to engage in regular physical activities. Longitudinal observational and interventional studies, controlling for confounding factors are clearly warranted to obtain further insights on the factors underlying elevated trait of fatigue and on its development and evolution over the natural history of the disease. Some recent clinical trials demonstrated the effectiveness of multidisciplinary pulmonary rehabilitation programs to reduce perceived fatigability. For instance, both a 3- and 12-week program have proven effective in reducing fatigue, in patients with sarcoidosis (Lingner et al., 2018) and COPD (Peters et al., 2017), respectively. However, in both studies fatigue was chosen as a secondary outcome and it is not known which component of these multimodal programs actually reduced fatigue. Importantly, multidimensional scales may not be well-suited for longitudinal studies, especially when conducting repeated assessment of fatigue over a short-time period. Other scales are thus necessary to conduct repeated measurements of perceived fatigability over a short period of time, for instance to capture diurnal changes in fatigue or throughout hospitalization for exacerbation.

Fatigue as a State: Time for Ecological Momentary Assessment

As discussed above, measuring the trait level of fatigue of CRD patients is essential to shed light on the prevalence, the etiology and the clinical consequences of fatigue as well as to assess its changes in response to therapeutic interventions. However, retrospective self-reports of fatigue, as measured by multidimensional scales during clinical routine or research visits are subject to recall bias and are not well-adapted to capture changes in fatigue over time in various contexts and environments. Fatigue assessment at a specific moment in time refers to the state level of fatigue.

Ecological momentary assessment (EMA) is a range of methods collecting real-time data on individuals' current behaviors and experiences in real-world situations (Stone and Shiffman, 1994). This method is an alternative to retrospective reports which fail to capture the dynamics of patients' everyday life, on both long-term (e.g., month by month) and short term basis (e.g., day-to-day, hour by hour). EMA methodology seems particularly adapted to capture the state level of fatigue in CRD and that for several reasons. First, perceived fatigability varies with context and environment and thus should be captured during real-life situations. Moreover, CRD are progressive diseases punctuated by several particular events which can exert, alone or in combination, substantial changes in fatigue. Fatigue is not a stable symptom over time and can fluctuate in an unpredictable manner within and between days. In healthy subjects, the state level of fatigue measured at rest during several time points (7 times from 10-min after waking until bedtime) augments linearly throughout the day whereas the daily average amount of fatigue augments linearly throughout the working week (Monday to Friday) and decreases to reach its minimal values during the weekend (Micklewright et al., 2017). This scenario may not apply in CRD patients, as the state level of fatigue may be modulated by several factors within and between days (e.g., diurnal variation in mucus accumulation, schedule and sequence of the treatment, adherence to the treatment, occurrence of an exacerbation).

Treatment regimens have considerably evolved over the years to manage CRD, with the development of complex strategies which require increasing time and effort. For instance, many children and adults with CF spend more than 2 h/day on respiratory therapy (i.e., including nebulized, oral, airway clearance and exercise therapies as well as maintenance of materials), even exceeding 30 h/week in some patients (Sawicki

et al., 2009; Hafen et al., 2013). However, increased treatment burden is associated with poor adherence, which is common among CRD patients and associated with many clinical issues (e.g., increased rates of morbidity, hospitalizations, health care costs, reduced quality of life) (Bourbeau and Bartlett, 2008; Bishay and Sawicki, 2016).

According to the working-capacity model of Heckman et al. (2015), the fatigue related to treatment can be modulated by four different factors: 1- increased general demands (i.e., daily-life tasks) and 2- increased treatment burden (i.e., amount of effort required for a given treatment), which define, in combination, "patient demands"; and 3- reduced general resources (i.e., psychosocial and cognitive functions) and 4- illness burden (i.e., disease symptoms), which define, in combination, "patient capacity." The balance between patient demands and capacity will modulate the fatigue related to treatment which in turns determines patient adherence. For instance, when patient capacity decreases for a given demand, treatment fatigue will increase and patient adherence will decrease. Perceived fatigability is determined by rates of changes in body homeostasis and psychosocial state (see traditional dichotomies, limitations of current knowledge, and new models of fatigue and **Figure 1**). Now let's consider the following scenario. A treatment may reduce perceived fatigability through improvements in body homeostasis. For instance, continuous positive airway pressure treatment improves some attributes of body homeostasis (e.g., oxygenation, blood pressure, sleepiness) in patients with OSA (Antic et al., 2011; Gottlieb et al., 2014). However, in the long-term, the treatment loses some effectiveness whereas the psychosocial state is affected (for instance because alterations in some of its attributes, e.g., motivation, mood, expectations). The positive changes in body homeostasis do not compensate enough for alterations in psychosocial state, leading to increased perceived fatigability. In the model of Heckman et al. (2015), it translates to increased treatment fatigue because patient demands exceed coping capacity, eventually resulting in decreased treatment adherence. Within this framework, the repeated assessment of the state level of fatigue throughout the duration of a treatment may help in predicting future changes in health behavior. Small changes in fatigue may indicate the need to reconsider the ratio between demands and capacity, with the aim to redress the balance. This can be achieved for instance by reconsidering patients' preference for a given treatment especially when several strategies displaying only small differences in term of effectiveness are available. This is for instance the case of some contemporary airway clearance therapies (Bott et al., 2009; Flume et al., 2009). Thus, other factors than effectiveness should guide the individual's choice of techniques. Increasing patient's satisfaction may reduce treatment burden, improve psychosocial state, reduce perceived fatigability and in turn promote sustained changes in health behavior (e.g., long-term adherence).

Repeated EMA of fatigue may also have interest during an exacerbation-related hospital admission. For instance it would be beneficial to determine the suitability of exercise training during severe exacerbations to reduce the state level of fatigue at discharge, both at rest and during activities of daily-living. Long-term EMA assessment (i.e., month-by-month) of fatigue should also be conducted to determine whether fatigue displays seasonal variation in CRD. It can be speculated that higher state levels of fatigue are encountered during winter, mirroring the seasonal variations of pulmonary exacerbations and/or hospital admissions and/or acquisitions of respiratory pathogens (Psoter et al., 2013, 2017; Donaldson and Wedzicha, 2014; Williams et al., 2017). The knowledge of a potential seasonality of fatigue in CRD may increase our understanding of the mechanisms underlying elevated perceived fatigability in these populations and may guide the development of prevention strategies.

The fundamental question is now to determine which scale should be used for EMA of fatigue in CRD. Despite all the aforementioned potential applications, the state level of fatigue has only been scarcely investigated in CRD and not in the context of EMA. Instead, the state level of fatigue has been evaluated in specific acute situations. For instance, two studies (Al-Shair et al., 2009, 2016a) used Borg's ratings of perceived exertion (RPE) scale (Borg, 1982) before and after a six-minute walk test (6MWT) as a measure of a state level of fatigue. However, perceived exertion should be distinguished from perceptions of fatigue. Perceived exertion refers to the subjective experience of how heavy/laborious it feels to work/to exercise and should be viewed as an indicator of physical strain (Borg, 1982; Micklewright et al., 2017). Perceived fatigability refers to the sensation of reduced ability to cope with mental and physical stressors in relation to a given task and environment (Micklewright et al., 2017). As a consequence, perceived exertion can only be experienced during acute episodes of physical exercise, and RPE scores should immediately drop to zero right after exercise cessation. On the opposite, perceived fatigability can be evaluated both at rest, during and after an exercise (with a gradual decrease during post-exercise recovery). Such assumptions are supported by the high correlation between RPE and fatigue scores during graded cycling exercise, which disappears during a 30-min recovery period (Micklewright et al., 2017).

In view of these elements and of the absence of specific validated fatigue scales which can be used in various contexts, environments and populations, Micklewright et al. (2017) developed and validated the rating-of-fatigue (ROF) scale. The ROF scale consists of 11 numerical points, ranging from 0 ("not fatigued at all") to 10 ("total fatigue and exhaustion—nothing left"), with 5 descriptors and 5 pictures. This scale demonstrated satisfactory face validity and high levels of convergent validity during graded cycling exercise to exhaustion, resting recovery and activities of daily living. The ROF should thus be perfectly adapted for repeated EMA in all the above-described situations in CRD. An important next step will be to validate the ROF scale in the specific context of CRD and then to implement this scale in dedicated software in order to benefit from the multiples advantages of using mobiles technologies for EMA. Some available software may be customized to the needs of a specific study (e.g., capturing ROF scores at a precise time of the day). The advantages of using mobile-EMA platforms over paper-and pencils methods for EMA are discussed elsewhere (Shiffman et al., 2008; Wen et al., 2017). Briefly, it may reduce non-compliant behaviors such as backfilling and thus augment the ecological validity of the data. Mobile-EMA platforms can also

ascertain the timeliness of patients' responses and thus provide an objective measure of response compliance. Pending the development/customization of software to implement specific validated fatigue scales, existing EMA dedicated software can be used to collect responses to various questions, including patients' fatigue. This is notably the case of a large multicenter ongoing study investigating the trait and the state level of fatigue in patients with COPD and its associations with exacerbation-related hospitalizations and mortality (see study protocol in Goertz et al., 2018). This is the first study using EMA to capture fatigue in COPD. This study uses an EMA application (i.e., PsyMate^{TM}, https://www.psymate.eu/, installed on an iPod) allowing to record answers about fatigue, context and surroundings, at eight random moments of the day, for 5 consecutive days at baseline and then at 4, 8 and 12 months.

Fatigue as a state can also be measured during a physical task. Capturing and understanding the state level of fatigue during physical tasks is essential for at least two reasons: first, physical activities represent an important part in the everyday occupations. Second, a greater modulation of the attributes of perceived and performance fatigability is expected during physical tasks and severe fatigue can emerge rapidly in these situations. The level of fatigue experienced by a patient during a physical task will be determined by the rates of changes in body homeostasis and psychosocial state, but will also be modulated by alterations in peripheral muscle function and the ability to voluntary activate the involved muscles (i.e., central activation) (see **Figure 1** and traditional dichotomies, limitations of current knowledge, and new models of fatigue).

As a symptom, the intensity of fatigue that develops during a given physical task can be captured by specific scales. Again, ROF scores should be differentiated from RPE scores, although they correlate during graded exercise (Micklewright et al., 2017). During whole-body exercise such as running or cycling, it is possible to report perceived exertion as differentiated "feelings," with the difficulties of breathing (i.e., dyspnea) reported separately from the perceived effort in the active limb muscles (Bolgar et al., 2010). For instance, some reports have demonstrated that many patients with CF, despite their important ventilatory limitation, had subjective symptoms of muscle effort in excess of symptoms of dyspnea during submaximal and maximal cycling exercise (Moorcroft et al., 2005; Gruet et al., 2010a, 2018; Quon et al., 2015). These observations provide indirect, subjective evidences of an important implication of the peripheral muscles in the exercise intolerance experienced by these patients. It is also possible, beyond measuring the intensity of dyspnea with a RPE scale (e.g., 0–10 Borg Scale) to report qualitative dimensions of dyspnea during graded exercise. For instance, Quon et al. (2016) demonstrated that the onset of "unsatisfied inspiration" occurred at a lower relative exercise intensity in CF compared to controls and that the qualitative descriptors "chest tightness" and "inspiratory difficulty" were selected more often by CF patients compared to controls at exhaustion. In contrast, a single fatigue score, for instance captured by the ROF scale, provides only information on the severity of the symptom experienced during exercise at a given intensity. Such scales capturing perceived fatigability are however unable to shed light on the attributes of performance fatigability, i.e., the peripheral and central factors which modulate the level of fatigue experienced during a physical exercise. Peripheral muscle dysfunction and cerebral abnormalities are commons features in patients with CRD (Maltais et al., 2014; Oliveira et al., 2014; Gruet et al., 2017). Such abnormalities may be exacerbated during a physical task and contribute to exercise intolerance in these patients. Studies on performance fatigability are thus mandatory to clarify the relative role of central and peripheral mechanisms underlying increased fatigability during physical exercise in CRD.

PERFORMANCE FATIGABILITY: TRANSLATION TO PERFORMANCE AND REHABILITATION

Fatigability and Performance: Theoretical Concepts and Applications

A myriad of protocols have been used over the past thirty years to investigate performance fatigability in CRD. As detailed in the next part, each protocol may have its own advantages and limits and may justify in part such degree of diversity. However, this has also lead to major impediments in understanding the causes of fatigue in CRD and translating the mechanistic research knowledge into the clinical practice. Mechanistic studies on fatigue, because they are not designed for that purpose, lack of both external and ecological validity. It is often uncertain whether the findings pertaining to a specific fatiguing task in a given CRD can be generalized to another task in patients with different phenotype severity. Another important issue is to determine whether the same laboratory findings may predict the performance of functional tasks in the real-life.

In an attempt to resolve these issues, Enoka and Duchateau (2016) recently proposed the following three-level experimental strategy (with examples of application in athletes and patients with multiple sclerosis): (1) identify a test and its main outcome of performance as reflective as possible of patients' daily activities (e.g., walking test); (2) identify a laboratory fatigability test which can strongly predict the aforementioned main outcome and (3) perform a mechanistic study to determine how a given factor (e.g., central muscle activation) underlying perceived/performance fatigability may limit performance in the laboratory test. Such approach is clearly attractive as it directly aims at translating complex mechanistic fatigue findings to the real-world performance, reducing the gap between research and clinical practice. Ultimately, a better understanding of the factors underlying reduced real-world performance will help to develop specific countermeasures.

Admittedly, the application of such model in CRD is far from being straightforward. First, it implies to identify a relevant test reflecting daily physical activities which can be influenced by performance fatigability. Both cycling and walking tests are strong indicators of health status in CRD patients. For instance, outcomes of maximal graded cycling test (e.g., peak oxygen uptake) and walking tests (e.g., 6MWT) have been repeatedly associated with quality of life and risk of death in a wide range

of CRD (Nixon et al., 1992; Cote et al., 2007; Lee et al., 2009; Martin et al., 2013; Polkey et al., 2013; Hsieh et al., 2017; Layton et al., 2017). However, contrary to walking, cycling cannot be considered as a daily activity for most CRD patients. This activity notably involves a specific recruitment of leg muscles which cannot be extrapolated to daily walking.

Marquis et al. (2009) found a progressive reduction in electromyographic median frequency recorded from the *vastus lateralis* and *rectus femoris* during 6MWT in patients with severe COPD. They attributed this shift toward low frequencies as a progressive development of lower-limb fatigue during walking. However, it should be pointed out that the physiological load imposed by the 6MWT significantly varies from one patient to another, in part because of its self-paced nature. This test is thus submaximal in many CRD patients. The walk distance can even be normal in young patients with mild lung disease (e.g., patients with mild CF) and thus do not reflect the disabilities that can experience some patients during daily living. Most CRD patients choose their walking speed (i.e., preferred walking speed) in order to keep a tolerable sensation of dyspnea (Sanseverino et al., 2018) but still often present symptom of breathlessness in excess of symptoms of muscle effort. It is also important to note that walking requires the activations of many muscles groups (e.g., knee flexors and extensors, hip and ankle extensors; Franz and Kram, 2012). Considering these elements, it is unlikely that submaximal walking performance, at least on flat ground in mild to moderate CRD patients, has a significant dependence upon performance fatigability involving a specific muscle group (e.g., quadriceps). However, walking is not limited to self-paced slow speed on a flat ground and much higher muscle recruitment is required with increasing speeds and grade. This may be the case for instance during stair-climbing which is very common in and beyond the home. Dreher et al. (2008) demonstrated that physiological changes during 6MWT were not related to those during stair-climbing in severe COPD. For instance, stair-climbing resulted in higher blood lactate production (Dreher et al., 2008). This may reflect in part differences in muscle recruitment between walking on level ground and walking up, the latter likely being associated with increased muscle susceptibility to fatigue. Treadmill exercise testing with increasing grades such as the Bruce protocols or modified versions, commonly used worldwide in a variety of CRD (Klijn et al., 2003; Przybylowski et al., 2007; Cooper et al., 2010; Hebestreit et al., 2015) may thus be an ideal alternative as a reflect of real-world performance.

To date, no tests of performance fatigability have been identified as strong predictors of walking endurance in CRD. In contrast, some studies performed a fatigability test and tried to establish an a posteriori correlation with a measure of whole-body exercise capacity. For instance, Gruet et al. (2016a) found a significant association between local quadriceps endurance and peak oxygen uptake determined during graded cycling exercise in adults with CF. However, such approach is based on single and/or multiple regression analyses which are particularly sensitive to sample size and may thus suffer from lack of power. Indeed, it is often complicated to conduct large cohort studies when using complex and time-consuming mechanistic laboratory studies on fatigue. On a short-term basis, future large studies should investigate the association between one or more well-accepted measures of daily functioning and a laboratory fatigability test. This latter should be, at this preliminary stage, performed in its simplest form to increase feasibility and power sample (i.e., without the addition of complex physiological measures (e.g., EEG, neurostimulation techniques) or cognitive manipulations (e.g., addition of a concomitant cognitive task, see section Future Directions for Mechanistic Studies). Beyond walking or cycling tests, it would be also important to consider the 1-min sit-to-stand-test as an easily implementable measure of daily functional capacity in CRD. Indeed, this test reflects a movement frequently performed in daily life and has recently received increasing attention in CRD (Gruet et al., 2016b; Radtke et al., 2016; Reychler et al., 2017) with a specific multicenter validation in COPD (Crook et al., 2017), making it an interesting correlate of real-world performance. The next key question is now to identify the ideal performance fatigability test which should ideally serve both research and clinical purposes.

Performance Fatigability: Which Test With Which Fundamental Characteristics?

The differences between protocols to evaluate performance fatigability in CRD rely on various factors, including the type of muscle contraction / exercise (i.e., isometric vs. isokinetic vs. whole-body exercise), the intrinsic nature of the task (i.e., based on relative vs. absolute force), its continuity (i.e., sustained vs. intermittent contractions), its intensity (i.e., maximal vs. submaximal) and the stopping criteria (i.e., fixed number of contractions vs. exhaustion). These characteristics will directly condition the possibility to gather four essential features that should demonstrate a performance fatigability test to be suitable in clinical and research settings:

1- Is the test ecologically valid?
2- Is the test reliable?
3- Is the test feasible?
4- Does this test allow easy implementation of measures of some attributes of fatigue?

Whole-Body Exercises

Performance fatigability can be evaluated from whole-body exercises which are easier to translate to real-world settings. The standard technique is to assess neuromuscular function [e.g., maximal voluntary contraction (MVC), voluntary activation, and contractile function] before and after high-intensity cycling exercise. Such studies have provided crucial insights about the relative influence of each physiological system in limiting maximal exercise capacity in CRD. They notably confirmed that, despite their ventilatory limitations, most CRD patients develop post-exercise contractile fatigue of the quadriceps, highlighting the importance of lower-limb function in the exercise intolerance experienced by these patients (Saey et al., 2005; Vallier et al., 2011; Bachasson et al., 2013c). Such methodology has also proven efficacy to detect negative response to exercise training (i.e., the absence of post-exercise contractile fatigue can mean that the exercise stimulus is not adapted to generate positive physiological adaptations, e.g., Burtin et al. (2012); see section

Performance Fatigability as an Index to Detect Responders to Exercise Training). However, this whole-body approach implies that fatigability can only be assessed from pre to post maximal exercise measurements, leading to several limits. First, the degree of fatigue is largely dependent on patients' cooperation and several extra physiological factors may limit the attainment of a true maximal exercise, influencing the total amount of fatigue. Of importance, fatigue usually develops progressively during daily activities even in the absence of a maximal effort with major cardiovascular demand. Hence, measuring fatigue at a single time point (i.e., at exhaustion) may not reflect the usual level of fatigue faced by the patient. Moreover, it has been established that both peripheral and central mechanisms of fatigue recovered quickly after short-duration exercises, in healthy subjects (Froyd et al., 2013; Gruet et al., 2014) as well as in CRD patients (Gruet et al., 2016a). Thus, the time between exercise termination and post-exercise fatigue measurements should be reduced as much as possible to appreciate the full magnitude of exercise-related fatigue. Unfortunately, transferring the subjects from the ergocycle to the chair and start the neuromuscular evaluation necessitates several minutes (i.e., usually ranging from 5 to 10 min).

In an attempt to resolve this issue, Doyle-Baker et al. (2017) recently developed a new ergometer permitting to switch from recumbent cycling to isometric set-up (i.e., to measure neuromuscular function) within 1-s. This allows the measurement of neuromuscular fatigue at any moment during a cycling protocol without any time delay, providing important insights about how fatigue progressively develops during exercise for a given metabolic intensity. Such innovative ergometer may allow in the future a better understanding of the etiology of fatigue experienced by CRD patients during whole-body exercise. However, as things stand at present, such prototype is far from being included in the routine practice and the feasibility should be evaluated in CRD patients. Of importance, the ergometer has been validated with settings (articular angles) allowing electrical stimulation of the femoral nerve to assess neuromuscular function. As such method is typically poorly tolerated in fragile patients (see Section Fatiguers vs. Non-fatiguers: Methodological Concerns), slight adjustments will be necessary to allow the use of magnetic stimulation (e.g., open hip angle).

Local Exercises

The other popular method to assess performance fatigability is to use local endurance tests involving a specific muscle group. They will be referred as "muscle fatigability" tests in the following sections. These protocols generate minimal cardiorespiratory constraint, permitting to assess muscle fatigability in isolation with oxygen delivery remaining within normal limits, as it is the case in many everyday activities. The most common maneuvers used to assess muscle fatigability are isometric and isokinetic contractions.

The isokinetic protocols used in CRD usually require the performance of repeated MVC at a given angular velocity (from 60 to 300°/s; see Evans et al. (2015b) for review). For instance Ribeiro et al. (2015) reported strong reliability of main outcomes of a quadriceps isokinetic test consisting in 30 MVC at 90°/s in moderate to severe COPD. These outcomes included total isokinetic work, peak torque and fatigue index (i.e., work performed during the last 10 repetitions/work performed during the first 10 repetitions). Such protocols may however display several disadvantages. First, the performance of repeated MVC can be largely influenced by motivational factors and osteoarticular limitations, the latter being a growing concern in the aging CRD population (Liao and Lu, 2016). This test also needs a familiarization session, costly equipment, large space requirements and trained technician, impeding its regular use in clinical practice.

Isometric protocols have also been largely utilized in CRD over the last 30 years. One of the main advantage is the low cost of an isometric set-up (i.e., custom chair and strain gauge), as compared to computerized dynamometry (i.e., at least 10 times cheaper). Strain gauge measures of quadriceps force are valid and reliable, in both healthy and CRD populations (Bachasson et al., 2013b; Machado Rodrigues et al., 2017). Isometric test have often been criticized on the basis that this muscular contraction regime is not the best reflect of daily activities of the patients. In fact, isometric contractions are often maintained for a prolonged period of time in various activities requiring the action of upper or lower limbs (e.g., holding an object, postural control). Moreover, the argument of low ecological validity could just as well work for contractions performed at constant angular velocity (i.e., isokinetic) which are non-physiological maneuvers. Isometric contractions are usually performed at a relative intensity (i.e., most often based on a given percentage of MVC) so that reduced strength of the patients will not directly influence muscle fatigability. Such methodological precaution is necessary to ensure that a specific neurophysiological abnormality related to fatigue does not only reflect a low muscle mass. This is essential when studying CRD patients as limb muscle atrophy is a common feature of these patients (Maltais et al., 2014; Gruet et al., 2017). Some studies used sustained isometric contractions until exhaustion, with a target force level usually ranging from 50 to 80% MVC (Zattara-Hartmann et al., 1995; Allaire et al., 2004; Gruet et al., 2010b; Ju and Chen, 2014; Miranda et al., 2014). The performance on such high-intensity, non-gradual protocols is in part dependent on subjects' motivation and ability to tolerate pain and thus is typically less reliable in fragile patients compared to healthy controls (Gruet et al., 2010b). Similar to whole-body exercise or continuous isokinetic protocols, sustained contractions without breaks also have the major drawback of not allowing repetitive neuromuscular evaluation throughout the task, impeding the possibility to describe the kinetics of peripheral and central mechanisms of fatigue.

A growing number of mechanistic neurophysiological investigations seek to identify the central and peripheral mechanisms contributing to increased fatigability in healthy subjects and in various chronic diseases (see Enoka and Duchateau, 2016; Twomey et al., 2017 for recent reviews). There is now accumulating evidences of brain abnormalities in CRD patients (Macey et al., 2008; Canessa et al., 2011; Dodd et al., 2012; Esser et al., 2016), notably in cortical areas implicated in motor control. Some studies in OSA and COPD demonstrated

abnormalities in the premotor and primary motor cortex (e.g., altered excitability) at rest and during the performance of voluntary muscle contractions (Grippo et al., 2005; Alexandre et al., 2014, 2016). One may expect that decreased muscle performance in CRD is related in part to exaggerated and/or early exercise-induced central fatigue (i.e., abnormalities located at the spinal and/or supraspinal levels). Such hypothesis can be tested by using intermittent contractions interspaced by regular neuromuscular evaluations that may include measures of motor cortical voluntary activation and intracortical inhibitory networks. Some studies using intermittent contractions of the quadriceps have provided indirect arguments in favor of this hypothesis by showing an increased contribution of supraspinal mechanisms in fatigue-related force loss when healthy subjects faced increasing severities of acute hypoxia (Goodall et al., 2010; Rupp et al., 2015). It is only very recently that studies sought to determine whether the cortical abnormalities observed at rest in CRD patients could contribute to increased muscle fatigability and reduced endurance performance. Marillier et al. (2018a) evaluated corticospinal responses to fatiguing intermittent quadriceps contractions in patients with severe OSA and matched healthy controls. The task consisted in 17 intermittent isometric knee extensions (5-s contraction/4-s relaxation) at 35% MVC interspaced by neuromuscular evaluations (duration ∼40 s) including cortical voluntary activation and intracortical inhibition assessments using single and paired transcranial magnetic stimulations (TMS). Target force was increased by 5% every two sets of contractions until task failure. Endurance time was lower in OSA patients. This was associated with lower MVC and cortical voluntary activation as well as increased silent period and long-interval inhibition throughout the fatiguing task. However, short-interval intracortical inhibition kinetics was similar between OSA and controls. Thus, exaggerated muscle fatigability in OSA can be explained in part by increased intracortical inhibitory activity of $GABA_B$ receptors which can contribute to reduced voluntary activation from the motor cortex. It is of note that such cortical adjustments in OSA were present from the beginning of the task and persisted until exhaustion. This means that cortical voluntary activation deficit may be present in these patients even without a high amount of muscle fatigue.

This example illustrates the potential of intermittent isometric protocols interspaced with neuromuscular evaluations to provide important mechanistic insights into how and why fatigue develops during exercise in CRD. Further investigations should extend this paradigm to other CRD. It is also worth noting that the use of isometric contractions may facilitate the investigation of brain adaptations with fatigue by minimizing body and head movement (as compared for instance to whole-body exercises) which is essential for reducing artifacts in the data. The next issue is to determine whether an intermittent isometric test, beyond having the first attribute (i.e., easy implementation of mechanistic measurements) may also combine the three other mentioned earlier (i.e., ecological validity, reliability and feasibility) to be included in routine patients' assessments.

Bachasson et al. (2013b) developed a quadriceps intermittent fatigue (QIF) test. This test consisted in intermittent isometric knee extensions (5-s contraction/5-s relaxation) beginning at 10% MVC with a 10%-MVC increment every 10 contractions until task failure. Visual (i.e., for maintaining a target force level) and audio (i.e., soundtrack indicating the contraction-relaxation rhythm) feedbacks are provided throughout the test. Central and peripheral contributors of muscle fatigability are assessed between each set and at task failure with single and paired femoral magnetic nerve stimulations. Main outcomes are the total number of contractions performed (i.e., relative endurance index), the total force-time product (i.e., absolute endurance index) and changes in MVC (i.e., muscle fatigability index), voluntary activation (i.e., twitch interpolation technique; index of central function), M-wave, twitch and doublets at 10 and 100 Hz (i.e., indices of peripheral function). The QIF test cumulates several advantages. First, by permitting muscle reperfusion during relaxation periods (i.e., 5-s off phases), such intermittent contractions may better reflect usual muscle functioning as opposed to sustained isometric contraction which leads to muscle ischaemia. Moreover, by using progressive loading (instead of a constant-load), multiple assessments (instead of only pre vs. task failure assessments), and non-volitional contractions (i.e., induced by magnetic stimulation which induces less discomfort than electrical stimulation), this test limits the influence of pain and motivation confounding factors. The evaluation focuses on a large muscle group (i.e., quadriceps) which plays a major role in various locomotor tasks (e.g., walking, cycling). Moreover, some fatigue (i.e., reduction in twitch at set 50%MVC) and endurance (i.e., total force-time product) indices measured during this test have been significantly correlated with peak oxygen uptake measured during cycling cardiopulmonary exercise test (Bachasson et al., 2013a; Gruet et al., 2016a). The QIF test has demonstrated excellent feasibility in healthy subjects (i.e., male and female, young and older, sedentary and athletes) (Bachasson et al., 2013b, 2016) but also in various chronic conditions including fibromyalgia (Bachasson et al., 2013a), fascioscapulohumeral dystrophy, Charcot-Marie-Tooth disease (Bachasson et al., 2014) and CF (Gruet et al., 2016a), with no adverse effects. The aforementioned outcomes of the QIF test demonstrated high absolute and relative test-retest reliability with typical error expressed as a coefficient of variation and ICC ranges of 4–7% and 0.81–0.90, respectively (Bachasson et al., 2013b).

In summary, an intermittent fatiguing isometric test such as the QIF test should offer a good compromise between ecological validity, reliability and feasibility. In its current form, this test is virtually suitable for most patients with CRD and could be widely spread out in clinical settings. As mentioned earlier, the next important steps will be to determine how measures of performance fatigability as determined by this test may predict the performance of functional tasks which are good correlate of real-world performance (e.g., walking tests, 1-min sit-to-stand test, see section Fatigability and Performance: Theoretical Concepts and Applications) and then, to conduct mechanistic studies aiming to elucidate the neurophysiological underpinnings

of altered performance fatigability in CRD and its interactions with perceived fatigability. The next section provides some directions for conducting such research.

Future Directions for Mechanistic Studies

In its current form, the QIF test is performed using voluntary contractions and contrations evoked by femoral magnetic nerve stimulations. Peripheral nerve stimulation can distinguish for peripheral vs. central adaptations during exercise. However, this technique does not allow appraising the adaptations that occur at the cortical level with fatigue. As mentioned above, many CRD patients may present various brain abnormalities in cortical areas involved in motor control, making important the exploration of cortical functioning during exercise. Further investigations should examine the role of supraspinal mechanisms in fatigue-related force loss in CRD by coupling peripheral nerve stimulation with TMS over the motor cortex (e.g., Gruet et al., 2013; Marillier et al., 2018a). However, it is well-acknowledged that several mechanisms upstream from the motor cortex influence the execution of the motor command (see Tanaka and Watanabe (2012) for review). Different brain areas exchange information and synchronize their activities during exercise (Hilty et al., 2011; Ushiyama et al., 2011) and their complex interactions influence motor cortical functioning. It would therefore be a significant step to evaluate, besides the motor cortex, the role of other brain structures such as the premotor, the primary somatosensory and the prefrontal cortex (PFC) (e.g., Marillier et al., 2018b) in perpetuating fatigue during exercise in CRD patients. This could be achieved by augmenting neurostimulation techniques (e.g., TMS) with neuroimaging (e.g., multichannel functional near-infrared spectroscopy) and corticomuscular coherence (EEG-EMG coupling) methods. These non-invasive techniques all demonstrated good feasibility during isometric contractions in both healthy and pathological conditions and can detect small changes in brain activity with fatigue (Ushiyama et al., 2011; Gwin and Ferris, 2012; Abeln et al., 2013; Perrey, 2013; Alexandre et al., 2014; Cremoux et al., 2017; Marillier et al., 2018a). Such techniques could thus be implemented in the future during local exercises such as the QIF test, in various CRD populations.

Virtually every study investigating performance fatigability in CRD used single motor tasks. In these laboratory situations, the influence of perceived fatigability on performance fatigability is limited, notably because of the absence of any specific cognitive stress. Another possibility is thus to investigate performance fatigability with the addition of a concomitant cognitive task. Cognitively demanding motor tasks are relevant to functional activities in daily-life and investigating performance fatigability in such conditions would thus increase ecological validity of the findings. In healthy subjects, the addition of a concomitant cognitive task to a motor task impaired motor performance, notably by reducing the time to task failure in the dual-task compared to the motor task performed alone, implying increased performance fatigability (Yoon et al., 2009; Mehta and Agnew, 2011; Keller-Ross et al., 2014). It is proposed that this effect could be even more pronounced in CRD and cognitive-motor dual tasks may represent situations particularly prone to induce exaggerated fatigability in CRD patients. Cognitive impairments are frequent in CRD, with higher prevalence compared to the general population. For instance, high level of cognitive failure was found in 35% of the patients with sarcoidosis and only in 14% of the age- and sex-matched healthy controls (Elfferich et al., 2010). Fairly similar prevalence was found in COPD (Villeneuve et al., 2012; Torres-Sanchez et al., 2015). These cognitive deficits, and notably the loss of executive functions (Andrianopoulos et al., 2017), will make more difficult to maintain the performance of both cognitive and motor tasks and will require greater brain resources to execute them simultaneously. Such assumptions are supported by recent findings in old healthy subjects (assumed to be more prone to cognitive abnormalities), who demonstrated reduced endurance during a motor task (i.e., handgrip at 30% MVC until exhaustion) as compared to young healthy subjects, but only when this motor task was performed with a concomitant cognitive task (i.e., mental arithmetic) (Shortz and Mehta, 2017). Previous studies demonstrated that some brain regions, such as the PFC, play an important role in regulating performance during cognitive-motor dual tasks. Reduction in PFC activity has been associated with reduced time to task failure during exercises with elevated cognitive demands (Mehta and Parasuraman, 2014; Shortz et al., 2015). This effect can be more pronounced in CRD patients as they need greater mobilization of brain resources to execute the same task. Blunted PFC activity and even disengagement may occur during cognitive-motor dual tasks in CRD, affecting the functioning of other interconnected brain regions such as the motor cortex. It can be thus speculated that alterations in performance fatigability in CRD would be even more marked during cognitive-motor dual tasks due to early central abnormalities impacting the ability to sustain a high level of voluntary activation. Moreover, the addition of a cognitive task (that is harder to perform for CRD patients) may exacerbate the influence of most factors of the psychosocial domain of perceived fatigability (see **Figure 1**). For instance, reduced motivation, negative mood, decreased executive functions and negative performance feedback may all, alone or in combination, contribute to increased muscle fatigability through earlier disengagement from the motor task. These assumptions could be tested by implementing concomitant cognitive tasks and assessments of perceived fatigability throughout the QIF test. For instance, mental arithmetic (e.g., subtraction from a 4-digit number by 13; Yoon et al., 2009) or memory tasks (e.g., memorize a sequence of numbers) could be superimposed during the 5-s contraction period with the answer expected during the 5-s recovery period. Perceived fatigability could be assessed using the ROF scale every 10 contractions. Motor cortex and PFC activations could be assessed by TMS and functional near-infrared spectroscopy, respectively.

It is also worth noting that cognitive failure has recently been demonstrated as an important predictor of elevated perceived fatigability (evaluated by the Fatigue Assessment Scale at baseline and then at 6 and 12 months) in patients with sarcoidosis (Hendriks et al., 2018). Thus, it is proposed that cognitive impairments may contribute to both the trait and the state level of fatigue in CRD. Cognitive-motor dual tasks may

also serve rehabilitation purposes as producing more fatigue during a given session may further trigger positive physiological adaptations in CRD (see section Fatiguers as Responders: Experimental Evidences and Exercise Training Strategies). Mechanistic studies aiming to clarify the neurophysiological adaptations to cognitively demanding motor tasks in CRD may thus help to design future interventions for these patients.

Performance Fatigability as an Index to Detect Responders to Exercise Training

Fatiguers as Responders: Experimental Evidences and Exercise Training Strategies

Exercise training has already proven several beneficial effects in various CRD (McCarthy et al., 2015; Aiello et al., 2016; Radtke et al., 2017) and is an integral part of the package of care offered to most patients. However, there is still large inter-individual variability regarding its effectiveness, especially for cardiorespiratory fitness, and some CRD patients receive only few or no benefit at all from exercise training. This has led to the so-called concept of "responders" and "non-responders" to exercise training, in both healthy (e.g., Mann et al., 2014) and pathological conditions (e.g., CRD, Troosters et al., 2001). Several studies tried to elucidate the factors associated with inter-individual differences in response to standardized exercise training. Much attention has been directed toward the role of genetic factors (Bouchard et al., 2011; Bouchard, 2012; Sarzynski et al., 2017). In their HERITAGE Family Study, Bouchard et al. (2011) found that 21 single-nucleotide polymorphisms explained 49% of the variance in maximal oxygen uptake trainability following a 20-week exercise training program in 473 sedentary adults. Some reports involving CRD patients also suggest an influence of genetic determinants in trainability. For instance, Jarosch et al. (2016) found an increase in the oxidative myofibre type I proportion in COPD patients with PiMM genotype but not in those with PiZZ genotype following a 3-week exercise training program, suggesting a better trainability for the PiMM genotype. However, this study was small and cardiorespiratory fitness was not evaluated. Moreover, it is still unknown whether the outcomes from the large HERITAGE study can be extrapolated to CRD patients. It is likely that hereditary influences the pre-training (i.e., baseline) phenotype buy has only a minor influence on the subsequent training response (see Mann et al., 2014 for review). Individual variation in trainability that cannot be explained by hereditary can thus probably be related to the characteristics of the training program.

Montero and Lundby (2017) recently challenged the notion of non-response to exercise training in healthy adults. They allocated 78 subjects into five groups that performed one, two, three, four and five 1-h endurance training sessions per week, for a 6-week period. Non-response to the intervention was defined as a change in maximal incremental exercise power output within the typical error of measurement (i.e., ±3.96%). Non-responders participants were then enrolled in another 6-week endurance training period which included two additional sessions per week. The main result is that after the second period of training, the non-response was abolished in all individuals. This means that the non-response to exercise training is mainly dependant on the dose of exercise, and then increasing the overall load (≥240 min per week in the study by Montero and Lundby, 2017) should be sufficient to trigger positive adaptations. Even though such findings are robust in healthy individuals, it is currently unknown whether they can be extrapolated to CRD patients. First, it may be complicated to increase the overall dose of training in some patients groups due to logistical issues (e.g., time spent to treatments, see also section Fatigue as a State: Time for Ecological Momentary Assessment), especially in the hospital setting. Moreover, several psychosocial and physiological factors may impede the patients to reach training intensities which are compatible with positive adaptations. Thus, even with an assumed optimal overall training dose, the exercise program may not be effective due to inadequate training characteristics (e.g., duration, intensity) at the level of a given training session. As acknowledged by Montero and Lundby (2017), their study was designed to investigate the independent contribution of overall training dose but not its components, at a given exercise session level, which may exert an important influence in CRD patients. This is particularly true when considering the likely phenotypic heterogeneity in a given group of CRD patients involved in a pulmonary rehabilitation program (e.g., patients with/without limb muscle weakness, with/without substantial ventilatory limitation (e.g., Troosters et al., 2001). The large heterogeneity in factors limiting exercise tolerance in CRD patients and the resulting individual variations in homeostatic stress induced by a training session clearly warrants a careful individualized approach. The next fundamental question is now how to determine whether a given session is effective for a given CRD patient?

Following the well-known principle of muscle loading, production of acute muscle fatigue (i.e., increase in performance fatigability) can be viewed as a positive response to a given exercise training session. Conversely, the absence of exercise induced-muscle fatigue implies that the stimulus may not be sufficient to trigger positive physiological adaptations (e.g., structural adaptations within the muscle fibers). Within this theoretical framework Burtin et al. (2012) thought to determine whether the muscle fatigue exhibited by patients with COPD after an acute exercise session could be used as an indicator to detect the future responders to a whole exercise program. Forty six patients with COPD completed a 3-month multimodal exercise program. Exercise capacity (e.g., 6MWT, peak workload during graded cycling exercise test), quadriceps strength and quality of life were assessed before and after the program. The training consisted in various exercise modalities including cycling, treadmill walking, stair climbing and quadriceps resistance exercise. Muscle fatigue was evaluated after 1 month of training following a single exercise session. Significant contractile fatigue was defined as a drop in resting quadriceps potentiated twitch (elicited by femoral nerve magnetic stimulation) ≥15% after the exercise session. Twenty-nine patients (63%) developed contractile fatigue after exercise according to this criterion. This subgroup of patients demonstrated greater improvements in both exercise capacity and quality of life after the 3-month program, as compared to patients who did not exhibit post-exercise fatigue.

These results will be subsequently confirmed in a larger cohort (n = 132), with patients capable to develop quadriceps contractile fatigue having greater improvements in 6-min walk distance after exercise training (Mador et al., 2014). In practice, identifying non-fatiguers patients may prevent to enroll them in a long-term ineffective exercise program. Measurement of post-exercise muscle fatigue is clearly a promising technique in that respect and future studies should extend the use of such methodology to other CRD.

The fundamental issue is now to understand why a substantial percentage of patients are not able to develop significant muscle fatigue following an exercise session. First, following the dose-dependent principle of Montero and Lundby (2017) and applying it at the session level, it is still possible that the intensity and/or duration of the session is not optimal. However, in the study by Burtin et al. (2012), training intensity was high and not different between the fatiguers and non-fatiguers groups. Some patients may not develop muscle fatigue of the active limbs because major ventilatory constraints impede the achievement of a sufficient training stimulus. Such hypothesis is partially supported by findings showing that COPD patients exhibiting less ventilatory limitation to acute exercise are more prone to improve following a whole exercise program (Troosters et al., 2001). However, the percentage of variability explained by this factor is limited and there was no evidence of different patterns of ventilatory limitation during exercise between fatiguers and non-fatiguers in the study by Burtin et al. (2012). Additional factors may thus limit the susceptibility to develop muscle fatigue. These may include intrinsic muscles adaptations such as poor skeletal muscle glycolytic enzyme activity (Saey et al., 2005). However, beyond physiological factors, it is also possible that psychosocial factors may alter the ability of some patients to produce muscle fatigue, notably through poor motivation to push themselves during each session of the program. Some patients may present several barriers to physical exercise linked to self-efficacy beliefs and symptom severity. In particular, negative outcome expectations (e.g., increased perceived fatigability, worsening symptoms, dyspnea-related fear) and disregard of the potential benefits of exercise training (e.g., lack of a clear positive effect on resting lung function), associated with the negative feeling of being too old to exercise (e.g., COPD patients, many OSA patients) (Kosteli et al., 2017) may all impact immediate engagement in a given exercise session. Importantly, such negative beliefs can be associated over time with feeling of weariness due to lack of exercise diversity. This can affect long-term engagement and thus the ability to produce repeated fatigue from one session to another over the whole program duration.

In view of the multitude of factors potentially contributing to the absence of exercise-induced muscle fatigue, it seems essential to promote an inter-disciplinary approach assessing the relative influence of physiological, psychological and sociological factors in impeding muscle susceptibility to fatigue. Various alternatives to classic exercise rehabilitation sessions can thus be proposed and, by limiting the negative influence of a given factor or symptom, they should theoretically lead to optimal muscle loading. Such strategies (**Figure 2**) may directly aim at:

1- Modulating patients' personal barriers and enablers to exercise training (e.g., therapeutic education) and motivation (e.g., use of self-paced exercise to increase patients' autonomy and long-term adherence to exercise through the promotion of a more intrinsically motivated exercise behavior). The use of specific exercise preference inventory (e.g., such as the SEPI questionnaire by Bonner et al., 2016, specifically validated in stroke, but with items easily adjustable to CRD patients) may also guide the choice of specific exercise modalities.
2- Acting against the negatives feelings associated to dyspnea through desensitization techniques (e.g., listening self-selected music, Lee et al., 2018);
3- Reducing the demand imposed on the cardiopulmonary system allowing to reach higher training intensities that would not be normally possible for patients with important ventilatory limitation. They may include exercise with supplemental oxygen (Emtner et al., 2003) or non-invasive ventilation (Ambrosino and Xie, 2017), one-legged cycling (Evans et al., 2015a) or combination of aerobic training with respiratory muscle training (Santana-Sosa et al., 2014).
4- Increasing limb muscles mass and force, especially in very deconditioned patients to facilitate the completion of a subsequent whole-body exercise program. For instance, 6 weeks of neuromuscular electrical stimulation training conducted prior 8 weeks of endurance training in severe patients with CF was effective to increase quadriceps muscle force which in turn was related to decreased ventilatory requirement during exercise (Vivodtzev et al., 2013). The ability of some of these strategies to induce significant acute muscle fatigue remains to be confirmed.

The addition of concomitant cognitive tasks to these strategies may also be a promising lead for the future. As proposed above, it may help to produce more fatigue for the same intervention duration (see section Whole-Body Exercises). Moreover, in addition to the playful aspect which may promote long-term adherence, cognitive-motor dual tasks may also serve to practice various cognitive aptitudes, notably executive functions which are impaired in many CRD patients (Andrianopoulos et al., 2017).

Fatiguers vs. Non-fatiguers: Methodological Concerns

As discussed above, these experimental findings clearly demonstrate the relevance of measuring muscle fatigue to predict the effectiveness of exercise training in CRD. However, several methodological concerns should be addressed before thinking to implement this technique into clinical practice. The method to distinguish fatiguers from non-fatiguers is based on the fall in potentiated twitch >15% measured few minutes after the end of an exercise session. The use of a non-volitional index such as potentiated twitch for stratification is clearly relevant in patients as it should be more sensitive than a volitional index of muscle fatigue (i.e., MVC) which depends on patient's cooperation and motivation. However, the use of this unique index may also have some inconvenient. First, it implies the use of costly equipment (i.e., magnetic

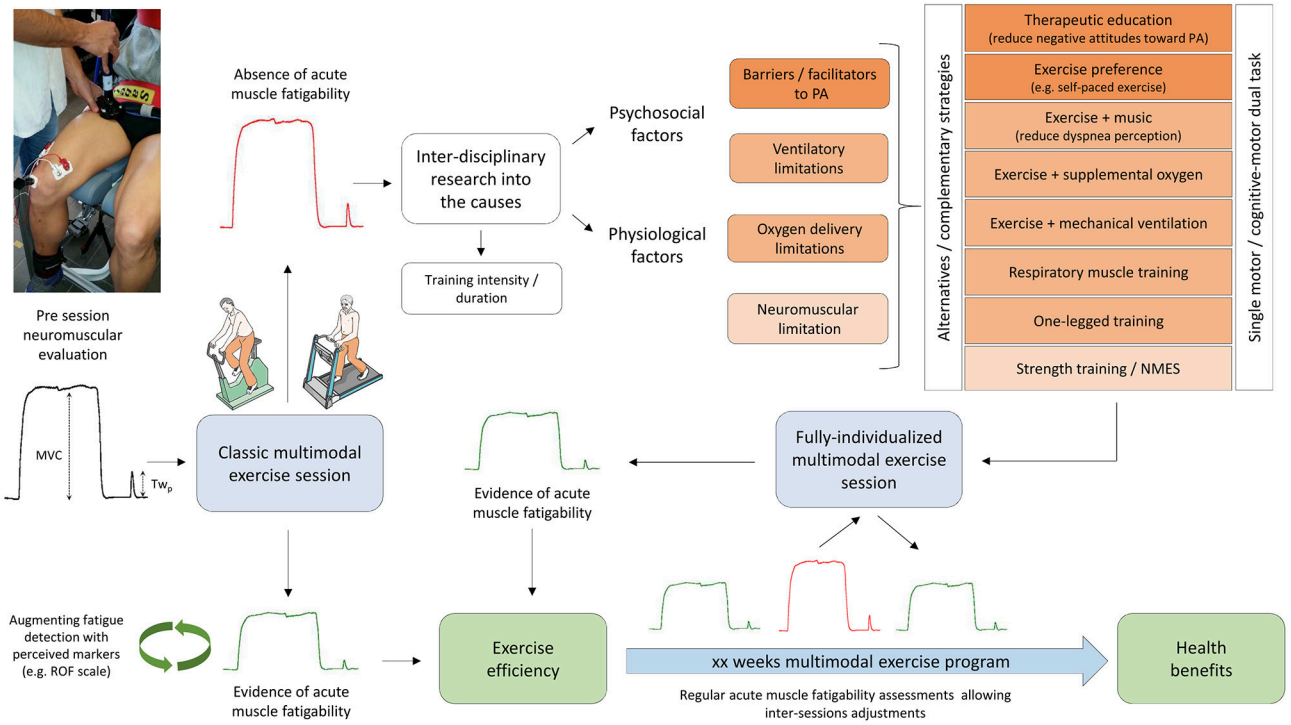

FIGURE 2 | An important clinical application of the measurement of performance fatigability is to evaluate the acute muscle fatigability following an exercise rehabilitation session as a surrogate of efficient muscle loading. Such technique may help identifying future responders and non-responders to an exercise program of several weeks/months. Patients who exhibit fatigue [e.g., reduction in the amplitude of the potentiated twitch (Tw_P) elicited by femoral magnetic nerve stimulation] following an acute exercise session can be classified as responders to the intervention and are more likely to develop positive adaptations following the whole program than patients who do not exhibit fatigue. For these latter, the next step is to identify the factors preventing the development of acute muscle fatigue on an individual basis. The proposed inter-disciplinary approach should permit to evaluate the relative influence of physiological, psychological and sociological factors. Various alternatives strategies can be offered to trigger optimal muscle loading. The effectiveness of some of these strategies to produce acute muscle fatigue remains to be confirmed, as well as the potential additional benefits of incorporating a concomitant cognitive component to these strategies. The current list is thus proposed as an initial framework that should be modified and/or completed according to future experimental results. A given exercise strategy may be effective over a short time period. However, it may become less effective in the long term. Thus, regular acute muscle fatigability assessments should be performed with the aim to adjust training modalities if necessary and then promote long-term adherence and health benefits. Treadmill and cycling exercise illustrations were modified from Smart Servier Medical Art on April 2018, available online at https://smart.servier.com/category/general-items/equipment/, licensed under the CC BY 3.0 license. MVC, maximal voluntary contraction; NMES, neuromuscular electrical stimulation; PA, physical activity; ROF, rating-of-fatigue.

stimulator and coil) and trained investigators to obtain reliable measurements. Second, potentiated twitch was measured in both studies from femoral nerve stimulation. This seems logical as lower-limbs muscles are particularly affected in CRD (Maltais et al., 2014; Gruet et al., 2017) and a large component of exercise programs is designed to predominantly solicit this muscle group (e.g., cycling, walking, climbing stairs). Nevertheless, arm muscles are also affected in many CRD patients and upper-limb exercise training is also sometimes incorporated in pulmonary rehabilitation programs (McKeough et al., 2016). Thus, the use of the sole femoral potentiated twitch may not be representative of the fatigue experienced during a multimodal (i.e., involving both lower and upper limbs) exercise session. In addition, it is unknown whether the 15% threshold could be applied for other muscles groups. It is also worth noting that potentiated twitch cannot be measured for every muscle groups due to the induction of the co-contraction of the antagonist muscles, affecting the mechanical response (e.g., see Millet et al., 2011 for review). Moreover, supramaximal stimulation is necessary to ensure full spatial recruitment even with slight changes in electrode (i.e., electrical stimulation) or coil positioning (i.e., magnetic stimulation). As such, a stimulation intensity ranging from 120 to 150% of optimal intensity is usually chosen for electrical stimulation. Unfortunately, contrary to electrical stimulators, current magnetic stimulators are limited in power output and it has been demonstrated that excessive fat thickness in the femoral region could preclude the achievement of supramaximal stimulations (Tomazin et al., 2011), making this technique inoperable in some patients. This is of particular importance in chronic respiratory disorders since overweight and even obesity are important and growing concerns in various CRD, including COPD (Rutten et al., 2013), OSA (Romero-Corral et al., 2010), and even CF (Hanna and Weiner, 2015). Next generation of magnetic stimulators should address this important issue. Making this technique usable on a larger sample-scale would

undoubtedly further foster its implementation into the clinical practice.

As multiple nerve assessments may be complicated for methodological and logistical reasons, it may also be of interest to add an indicator of perceived fatigability when a whole-body exercise session is intended. For instance, the ROF scale (Micklewright et al., 2017; see also section Fatigue as a State: Time for Ecological Momentary Assessment), which also demonstrates high convergent validity during post-exercise recovery, may be used in conjunction to femoral magnetic nerve stimulation to obtain further insights on the fatiguing aspect of an exercise session. Further studies are warranted to identify the usefulness and potential implementation of perceived indicators of fatigue. An important last notion is that a fatiguer, as determined from one single session, may not inevitably be a good training responder on a long-term basis. Although a given exercise modality may be effective at a single time point, it is possible, even when adjusting for the intensity according to patients' improvements, that such modality loses effectiveness over time (because of motivational factors, for instance). Thus, acute muscle fatigability assessments should be conducted on a periodic basis, allowing regular inter-sessions adjustments for optimal long-term adherence and health benefits (**Figure 2**).

SUMMARY AND FUTURES DIRECTIONS

Fatigue is prevalent in CRD and negatively impacts the daily lives of the patients. A better knowledge of the modulators and attributes of fatigue is thus fundamental to design appropriate countermeasures. To this end, fatigue must be regarded as a multifaceted phenomenon that should be described with an inter-disciplinary approach, giving consideration to both its perceptual and performance components. Most studies in CRD evaluated perceived fatigability as a trait characteristic using multidimensional scales. Such studies provided important insights regarding the prevalence, the etiology and the clinical impact of an elevated trait level of fatigue. However, fatigue is an unstable, dynamic phenomenon which can arise from various real-life situations with varying degrees of severity. This is particularly the case for CRD which are evolving diseases characterized by frequent events (e.g., hospitalizations, changes in medication, new long-term treatment) that may dictate the fatigue level. Evaluating fatigue as a state, at several time points in various contexts and environments is critical to improve our understanding of how fatigue affects the daily-life of CRD patients in real-world settings. Thus, traditional scales of fatigue should be supplemented with ecological assessment of fatigue. Future studies should implement valid fatigue scales (e.g., ROF scale) into mobile-EMA platforms and determine how fatigue is modulated within and between days, according to specific events (e.g., occurrence and treatment of an exacerbation). The state level of fatigue must also be considered during a physical task. This specific situation can induce substantial deviations in the attributes of perceived and performance fatigability and severe fatigue can be expected during exercise in CRD patients. Performance fatigability is determined by the neuromuscular adjustments that occur to meet the demands of the motor task. Both peripheral and central systems may exhibit abnormalities in CRD and future studies should elucidate whether neuromuscular alterations observed at rest may be exacerbated during physical exercise and could negatively impact performance in these patients. To this end, an isometric laboratory test such as the QIF test could represent an ideal compromise between feasibility, reliability and ecological validity, while being able to implemental neurophysiological and neuroimaging methods. A better understanding of the neurophysiological underpinnings of performance and perceived fatigability and their impact on real-world performance (e.g., walking performance, sit-to-stand capacity) will foster the development of new strategies mitigating the influence of the attributes of fatigue on patients' performance. Such knowledge will also serve to develop new strategies promoting the development of acute muscle fatigue, a surrogate of efficient muscle loading during exercise training sessions. Various factors may limit the ability to produce muscle fatigue during exercise training in CRD patients. They should by identified by adopting a comprehensive inter-disciplinary approach giving consideration to physiological, psychological and sociological factors that may potentially hinder the development of muscle fatigue in these patients. Future fatigue research should determine whether a given individualized exercise intervention which has proved its effectiveness in triggering acute muscle fatigue production will ultimately leads to reduced levels of perceived fatigability into the everyday lives of the patients.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Force Steadiness During a Cognitively Challenging Motor Task Is Predicted by Executive Function in Older Adults

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Motor performance and cognitive function both decline with aging. Older adults for example are usually less steady for a constant-force task than young adults when performing low-intensity contractions with limb muscles. Healthy older adults can also show varying degrees of cognitive decline, particularly in executive function skills. It is not known, however, whether age-related changes in steadiness of low-force tasks and cognitive function are independent of one another. In this study, we determined if executive function skills in aging are associated with the steadiness during a low-force muscle contraction performed with and without the imposition of a cognitive challenge. We recruited 60 older adults (60–85 years old, 34 women, 26 men) and 48 young adults (19–30 years old, 24 women, 24 men) to perform elbow flexor muscle contractions at 5% of maximal voluntary contraction (MVC) force in the presence and absence of a difficult mental-math task (counting backward by 13 from a four-digit number). Force steadiness was quantified as the coefficient of variation (CV) of force and executive function was estimated with the Trail-making Test part A and B. The cognitive challenge increased the CV of force (i.e., decreased force steadiness) with greater changes in older adults than young adults (5.2 vs. 1.3%, respectively, cognitive challenge × age: $P < 0.001$). Older adults were 35% slower in both parts A and B of the Trail-making Test ($P < 0.001$), and to eliminate the effects of age and education on this variable, all further analyses were performed with the age-corrected *z*-scores for each individual using established normative values. Hierarchical regression models indicated that decreased force steadiness during a cognitive challenge trial was in part, explained by the performance in the Trail-making Test part A and B in older ($r = 0.53$ and 0.50, respectively, $P < 0.05$), but not in young adults ($P > 0.05$). Thus, healthy community-dwelling older adults, who have poorer executive function skills, exhibit reduced force steadiness during tasks when also required to perform a high cognitive demand task, and are likely at risk of reduced capacity to perform daily activities that involve cognitively challenging motor tasks.

Keywords: force fluctuations, sex differences, gender differences, aging, Trail-making Test

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INTRODUCTION

Many activities of daily living require precise control of force during static or dynamic contractions (e.g., eating, cooking, and interacting with touch screen devices). Most of these motor tasks require not only an intact musculoskeletal system, but they also depend upon integral neural function (Scherder et al., 2008; Overdorp et al., 2016). Cognitive processes such as attention, memory, and executive function are essential neural constructs often involved during motor tasks (Spirduso, 1980; Scherder et al., 2008; Corp et al., 2013). More specifically, executive function which encompasses working memory and attention, enables an individual to plan, organize, and integrate neural processes to achieve a goal (Elliott, 2003). Executive functioning, for example, is essential during activities of daily living that require divided attention (i.e., dual task activities) because a dual task often requires planning, integration of information and the capacity to switch attention between tasks (Strauss et al., 2006).

It is well established that both motor and cognitive function decline with aging (Buckner, 2004; Salthouse, 2009; Hunter et al., 2016). In the laboratory setting, motor function and the resultant force fluctuations (force steadiness) can be quantified for a force-matching task of a muscle group as the variability of the force around the mean force [Coefficient of variation of force (CV) = standard deviation/mean × 100] (Enoka et al., 2003). Using this metric older adults and women frequently exhibit a greater CV of force (reduced force steadiness) compared with young adults and men, respectively, at lower intensities of contraction (Tracy and Enoka, 2002; Enoka et al., 2003; Brown et al., 2010). Greater maximal strength can partially account for some of the reduced CV of force with aging in men and women (Christou and Carlton, 2001; Marmon et al., 2011).

Force steadiness, however, is altered with the requirement of greater cognitive demand during the motor task. Imposing a cognitive challenge during a force-matching motor task, for example, resulted in greater CV of force in older adults, particularly older women, for both upper and lower limb muscles (Voelcker-Rehage et al., 2006; Vanden Noven et al., 2014; Pereira et al., 2015; Shortz and Mehta, 2017), although the mechanism is not well defined. We also found larger variability between trials in motor performance among older men and women compared with young adults when a cognitive challenge was imposed during a low-force, steadiness task for the lower limb (Vanden Noven et al., 2014). Furthermore, when the difficulty in the cognitive challenge increased, steadiness reduced (i.e., CV of force increased) markedly for the older adults and less for the young (Voelcker-Rehage et al., 2006; Vanden Noven et al., 2014; Pereira et al., 2015). One possible explanation is that older men and women who have age-related reductions in executive functions, have lower capacity to multi-task and thus poorer performance on a motor task while also performing a cognitive challenge. However, the influence of baseline cognitive constructs, such as executive function, on motor function such as a task that requires force steadiness in young and older adults are poorly understood. One of the several executive function tests available to target this construct is the Trail-making Test (Reitan, 1958; Tombaugh, 2004) (see better description in the section "Materials and Methods"), which is frequently used in neuropsychological batteries (Strauss et al., 2006).

The purpose of the study therefore, was to determine if executive functioning, estimated with the Trail-making Test, was associated with force steadiness (CV of force) during an upper extremity task both with and without the imposition of cognitive challenge in young and older men and women. Our *hypothesis* was that poorer executive functioning would predict the CV of force during a motor task when performed simultaneously with a cognitive challenge because of the greater reliance on executive functioning during the increased cognitive demand task.

MATERIALS AND METHODS

Sixty older (60–85 years old, 34 women and 26 men) and 48 young adults (19–30 years old, 24 women and 24 men) participated in the study (**Table 1**). Each participant provided written informed consent to participate in the study and the protocol was approved by the Institutional Review Board of Marquette University and all experimentations were performed in accordance with the Declaration of Helsinki. All participants were healthy without known neurological, orthopedic or cardiovascular conditions and they were naive to the protocol. All older women were post-menopausal and none were on hormone replacement therapy at the time of the study.

Each participant attended three sessions, an introductory session and two randomized experimental sessions. At the introductory session, each participant completed surveys to evaluate handedness (Oldfield, 1971), physical activity levels (Kriska and Bennett, 1992), and trait anxiety (Spielberger

TABLE 1 | Descriptive statistics [mean (SD)] of young and older men and women.

	Young men	Young women	Old men	Old women
n	**24**	**24**	**26**	**34**
Age (years)	22.1 (3.1)	21.6 (2.6)	69.6 (5.5)	68.2 (6.4)
Education (years)	16.2 (2.3)	15.6 (1.9)	16.8 (2.7)	15.7 (3.5)
GDS (a.u.)	–	–	1.22 (1.3)	1.7 (1.9)
MMSE (a.u.)	–	–	28.5 (1.6)	28.9 (1.6)
Trait anxiety (a.u.)	35.7 (8.2)	32.7 (8.6)	30.2 (6.8)	28.9 (6.4)
PAQ (MET-h/week)	66.1 (56.6)	55.6 (47.8)	37.5 (30.9)	31.5 (23.1)
Handedness (a.u)	0.6 (0.4)	0.7 (0.2)	0.8 (0.3)	0.7 (0.4)
MVC (N.m)	71.5 (19.1)*	42.3 (10.0)	62.2 (12.7)†	33.1 (6.4)
Trails A (s)	15.7 (3.3)	16.7 (5.8)	23.9 (6.1)	23.1 (6.8)
Trails B (s)	35.5 (11.6)	35.9 (9.3)	58.5 (23.4)	55.8 (20.6)

*GDS, Geriatric Depression Scale short version raw score (possible range = 0–15); MMSE, Mini Mental State Exam raw score (possible range = 0–30); Trait Anxiety, State-Trait Anxiety Inventory raw score (possible range = 20–80); PAQ, Physical Activity Questionnaire; Handedness, Edinburgh Handedness Inventory [range = −1 (left) to +1 (right)]; MVC, maximal voluntary contraction; Trails, Trail-making Test; *sex difference for young adults; †sex difference for older adults.*

et al., 1970). To screen for dementia and depression, each older individual completed the Mini-Mental State Examination (Folstein et al., 1975) (all participants scored >24) and the Geriatric Depression Scale (Sheikh and Yesavage, 1986) (all participants scored <5). Executive functioning was measured using the Trail-making Test, and each participant was familiarized with the steadiness task as described later.

In separate experimental sessions, each participant performed a: (*a*) *control trial,* which involved performance of a force steadiness task with the elbow flexor muscles *without* imposition of a mental math task (cognitive challenge) and, (*b*) *cognitive challenge trial,* which involved a force steadiness task with the elbow flexor muscles while also performing a mental math task (cognitive challenge). The force steadiness task during each session was performed with the elbow flexor muscles at 5% of maximal voluntary contraction (MVC) force and the order of the sessions (control and cognitive challenge trials) was randomized.

Assessment of Executive Functioning: Trail-Making Test

The Trail-making Test (Reitan, 1958) is comprised of two parts: In part A, each participant was asked to draw a line consecutively connecting 25 encircled numbers distributed on a sheet of paper. In part B, each circle had either a number or a letter in its center, and each participant was asked to consecutively connect the circles alternating between numbers and letters (e.g., 1, A, 2, B, 3, C, 4, D, and so on), as fast as possible while maintaining accuracy. The score on each part is the time required to connect the circles without removing the pen from the paper.

Although parts A and B of the Trail-making Test are highly intercorrelated, they are differentially affected by aging (Tombaugh, 2004) due to differences in the cognitive constructs they assess (Bowie and Harvey, 2006). Specifically, part B imposes greater cognitive demand and need for flexibility by requiring switching between letters and numbers, whereas part A more simply requires the ability to maintain a cognitive set (Kortte et al., 2002). Part B measures executive control and it is less influenced by motor components, whereas part A is generally associated with attention and motor speed (Arbuthnott and Frank, 2000). Consequently, we analyzed parts A and B separately to investigate any potential distinct effects between tests when a motor task is performed simultaneously with a cognitive challenge.

Assessment of the Force Steadiness

Each participant was seated upright in an adjustable chair with the non-dominant arm abducted slightly and the elbow resting on a padded support with the elbow joint flexed to 90°. The non-dominant arm was tested to minimize variability between participants that can occur due to differences in activities performed with the dominant arm. Details of the experimental setup are described elsewhere (Pereira et al., 2015). In brief, the hand and forearm were placed in a modified wrist–hand–thumb orthosis (Orthomerica, Newport Beach, CA, United States), and the forearm was placed midway between pronation and supination. Elbow flexion force was measured with a transducer (JR-3 Force-Moment Sensor; JR-3, Woodland, CA, United States, range ± 800 N; resolution: 0.10 N or MLP – 150 Transducer Techniques, Temecula, CA, United States, resolution: 0.10 N securing that force signals were similar between transducers) and displayed on a 22″ monitor. Force was recorded online at 500 samples/s using a Power 1401 analog-to-digital (A–D) converter and Spike 2 software [Cambridge Electronic Design (CED), Cambridge, United Kingdom].

The following protocol was followed to assess force steadiness:

(1) *Assessment of Maximal Voluntary Contraction (MVC).* Each participant performed 3–4 MVCs trials with the elbow flexor muscles with 60 s rest between each trial. If the peak force achieved for two of the first three trials was not within 5% of each other, additional trials were performed until this criterion was met. The greatest force achieved with the elbow flexor muscles was taken as the MVC force and used to calculate the target force for the submaximal contractions.

(2) *Submaximal Contractions.* After the MVC was determined, an isometric contraction at 5% of MVC was performed for 40 s. A very low intensity of 5% MVC was chosen because previous studies indicated that age differences in the force steadiness with cognitive challenge are more likely at very low contraction intensity (Pereira et al., 2015; Hunter et al., 2016). During the cognitive challenge trial, once the participant increased the force to the required target force, the participant began the subtraction by 13 from a four-digit number. Only one trial was performed during the experimental session because the learning effect was minimal in a subset of participants and also to simplify the test session. During the control trial, each participant performed the submaximal contraction only.

Cognitive Challenge Task

The cognitive challenge involved mental math, such that each individual performed serial subtraction by 13 from a four-digit number with one response required every 3 s (Noteboom et al., 2001; Pereira et al., 2015). If the participant made an error in the serial subtraction or was unable to provide the correct answer within 3 s, the mental-math procedure was restarted with a new number (Noteboom et al., 2001; Yoon et al., 2009; Keller-Ross et al., 2014; Vanden Noven et al., 2014; Pereira et al., 2015). The cognitive challenge was performed at two timepoints: (1) before the submaximal contraction for 4 min for practice, and (2) during the steadiness task in a dual task. Mental math was performed during the cognitive challenge trial only, and not during the control trial.

Data Analysis

Analysis of the Trail-Making Test

Older adults are known to take a longer duration to complete the Trail-making Test (Tombaugh, 2004). Thus, age itself could serve as a confounding factor when determining the influence of executive functioning on force steadiness. Norms for the Trail-making Test are stratified by age and education to correct for the influence of both factors on performance (Tombaugh, 2004). Thus, we calculated Trail-making *z*-scores accounting

for age and education to minimize their potential impacts on the results. Average raw scores for each group are presented in **Table 1**.

Analysis of the Force Signal During MVC and the Steadiness Task

The torque was calculated as the product of force and the distance between the elbow joint and the point at which the wrist was attached to the force transducer. The MVC was quantified as the average value over a 0.5 s interval that was centered about the peak. Force steadiness was quantified with the amplitude of the force fluctuations using the coefficient of variation of the force (CV = standard deviation of the force/mean of force × 100). The CV of force was calculated over the middle 30 s period of each 40 s submaximal contraction.

Statistical Analysis

Data are reported as mean ± SD within the text and tables and mean ± SE in the figure. CV of force and MVC force were analyzed with repeated measures analysis of variance (ANOVA) with age and sex as between-subject factors. Repeated measures included the test trial (control vs. cognitive challenge). Separate two-factor (age × sex) ANOVAs were used to compare handedness, physical activity levels, Trail-making Test part A and B, trait of anxiety and years of education between young and older men and women. For each ANOVA the sphericity of data was verified with *Mauchly's* test. In cases where *F*-test was significant, *post hoc t*-tests with *Bonferroni* corrections were performed to detect differences among pairs. Independent *t*-tests were used to compare the results of Mini-Mental State Examination and Geriatric Depression Scale between men and women in the older adults group after assessing for normality with the *Shapiro–Wilk* test. Hierarchical regression models were used to determine the influence of the executive functioning on the CV of force in the control trial and the cognitive challenge trial. Age, sex, and MVC were entered as predictors in the first step, as each has known potential influence on the CV of force (the criterion variable). Trail-making Test performance part A and B were entered as predictors in step 2 (independent models as different indices of executive functioning). The statistical significance was considered as $P < 0.05$ and all analysis were performed in IBM Statistical Package for Social Sciences (SPSS) version 23.

RESULTS

Young adults were stronger than older adults (age effect: $P < 0.01$) and men were stronger than women (sex effect: $P < 0.01$), with no interaction of age and sex ($P = 0.99$, **Table 1**). Young adults reported greater physical activity levels compared with older adults (59.4 ± 50.5 vs. 33.2 ± 26.2 MET-h/week, respectively, age effect: $P < 0.001$), with no sex differences (sex effect: $P = 0.39$) and no interaction of age and sex ($P = 0.54$). There were no differences in handedness, years of education and trait of anxiety across groups (all $P > 0.05$) (**Table 1**).

Steadiness

Older adults had greater CV of force (i.e., reduced steadiness) compared with the young adults (5.5 ± 4.1% vs. 2.9 ± 1.6%, respectively, age effect: $P < 0.01$) and women had greater CV of force than men (6.3 ± 3.6% vs. 4.2 ± 3.7%, respectively, sex effect: $P = 0.01$) with a trend for greater CV of force in older women (age × sex: $P = 0.06$). CV of force was greater during the cognitive challenge trial compared with the control trial (5.8 ± 7.7% vs. 2.6 ± 1.7%, respectively, cognitive challenge effect: $P < 0.001$) (**Figure 1A**), but the older adults had a greater increase in CV of force between the control to the cognitive challenge trial (control: 2.9 ± 1.2% vs. cognitive challenge trial: 8.1 ± 5.4%) than young adults (control: 2.2 ± 1.2% vs. cognitive challenge trial: 3.5 ± 6.0%; cognitive challenge effect × age: $P < 0.001$). Women had a greater increase in CV of force from the control to the cognitive challenge trial (2.5 ± 1.2% vs. 6.8 ± 5.5%, respectively) than the men (2.7 ± 1.2% vs. 4.9 ± 5.4%, respectively, session × sex: $P = 0.03$) for both young and older adults (session × age × sex: $P = 0.57$) (**Figure 1B**).

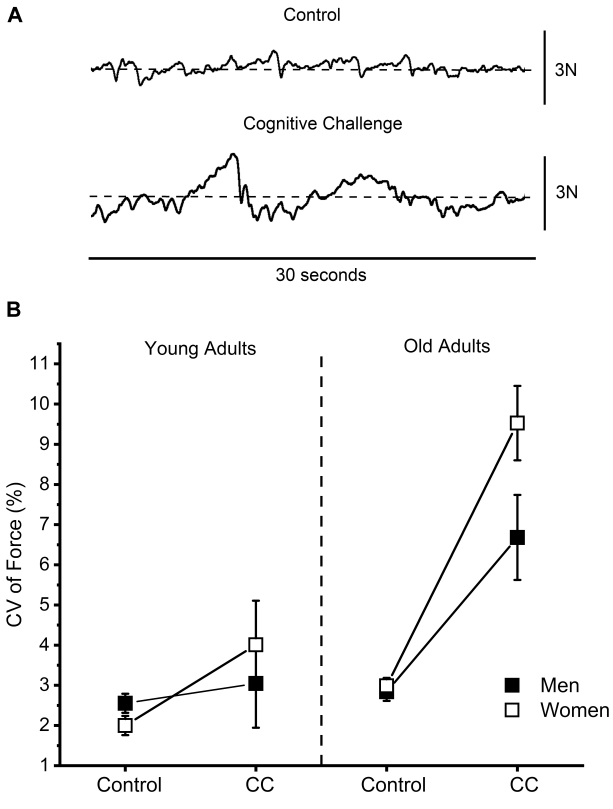

FIGURE 1 | (A) Representative force signals of the elbow flexor muscles for control and cognitive challenge trials (subtracting by 13 from a four-digit number). **(B)** Force steadiness quantified as the coefficient of variation (CV) of force during the control and cognitive challenge trials (CC) of young and older men and women. Older adults had a greater increase in CV of force (i.e., reduced force steadiness) during the CC trials than young adults ($P < 0.001$) and women had a greater increase in CV of force during the CC trials than men ($P = 0.03$).

Trail-Making Test (Raw Scores)

Part A

Older adults required a longer time to complete the test compared with young adults (25.3 ± 6.2 vs. 16.6 ± 6.3 s, respectively, age effect: $P < 0.001$), with no difference between men and women (sex effect: $P = 0.39$) in either the young or older adults (age × sex: $P = 0.43$, **Table 1**).

Part B

Time to complete the test was longer for the older adults than young adults (58.3 ± 23.7 s vs. 36.3 ± 10.5 s, respectively, age effect: $P < 0.001$), with no difference between men and women (sex effect: $P = 0.60$) in either the young or older adults (age × sex: $P = 0.73$, **Table 1**).

Predictability of Force Steadiness

Hierarchical regression models were used to identify variables that influenced the CV of force during the control and cognitive challenge trials (**Tables 2**, **3**). Step 1 showed the effects of age, sex and MVC on the CV of force, and step 2 showed the added contribution to prediction of CV by the *z*-score results for the Trail-making Test (parts A and B, independently) for young (**Table 2**) and older adults (**Table 3**).

Control Trials

The age of the participant did not predict the CV of force for the young ($P = 0.78$) (step 1 in **Table 2**) but there was a trend for the older adults ($P = 0.05$) (step 1 in **Table 3**). The sex of the participant did not predict the CV of force during control trials for the older adults ($P = 0.22$) (step 1 in **Table 3**) but did explain the CV of force in young adults ($P < 0.01$) (step 1 in **Table 2**). Greater MVC was responsible for 0.59 and 0.53% reduction in the CV of force (revealed by the beta values) for young and older adults, respectively (both groups with $P < 0.05$) (step 1 in **Tables 2**, **3**). Including the *z*-score result of the Trail-making Test part A did not alter the prediction of CV of force for young or older adults (both with $P > 0.05$) (step 2 in **Tables 2**, **3**). This was similar for the Trail-making Test part B *z*-score results for the young and older adults (both groups with $P > 0.05$) (step 2 in **Tables 2**, **3**).

Cognitive Challenge Trial

Coefficient of variation of force was predicted by age of the individual for older adults ($P = 0.01$) (step 1 in **Table 3**), but not young adults ($P > 0.05$) (step 1 in **Table 2**). For young adults, step 1 indicated that CV of force during cognitive challenge trial was not predicted by sex or MVC, and in step 2, the Trail-making Test part A or part B was also not predictive (all with $P > 0.05$). In contrast, in the older adults group, each added year in the age of the individual accounted for 0.36%, revealed by the beta value, of the increase in CV of force during the cognitive challenge trial ($P = 0.01$) (step 1 in **Table 3**). The addition of part A of the Trail-making Test improved the regression model for older adults but not young adults ($P < 0.01$ and $P = 0.65$, respectively) (step 2 in **Tables 2**, **3**, respectively). Each unit of increase in *z*-score of the Trail-making Test part A accounted for 0.32% (revealed by the beta value) of the increase in CV of force during cognitive challenge trials for older adults ($P = 0.01$), but not for young adults ($P = 0.65$) (step 2 in **Table 2**). The addition of Trail-making Test part B also improved the regression model for older adults but not young adults ($P = 0.03$ and $P = 0.20$, respectively) (step 2 in **Tables 2**, **3**, respectively). Each *z*-score unit of increase in part

TABLE 2 | Hierarchical regression analyses predicting performance on force steadiness of young adults.

	Model summary of each step					Contribution of each variable in last step				
	R	R^2	ΔR^2	***F***	***p***	**B**	**SE**	**β**	***t***	***p***
Force steadiness: control trial										
Step 1	0.49	0.24	–	4.33	**0.01**					
Age						0.02	0.06	0.04	0.28	0.78
Sex						−1.52	0.45	−0.62	−3.36	**<0.01**
MVC						−0.04	0.01	−0.59	−3.21	**<0.01**
Step 2	0.52	0.27		1.91	0.17					
Trails A						0.31	0.22	0.18	1.38	0.17
Step 2	0.49	0.24	< 0.01	0.41	0.53					
Trails B						−0.13	0.21	−0.09	−0.64	0.53
Force steadiness: cognitive challenge trial										
Step 1	0.34	0.12	–	1.91	0.14					
Age						0.19	0.11	0.25	1.72	0.09
Sex						1.00	0.81	0.25	1.23	0.23
MVC						−0.01	0.02	−0.05	−0.23	0.82
Step 2	0.36	0.13	0.05	0.21	0.65					
Trails A						0.19	0.40	0.07	0.46	0.65
Step 2	0.40	0.16	0.04	1.73	0.20					
Trails B						0.48	0.36	0.19	1.32	0.20

MVC, maximal voluntary contraction; Trails, Trail-making Test; F from change in R^2, P from change in R^2. Bold values highlight when $P < 0.05$ (i.e., statistically significant).

TABLE 3 | Hierarchical regression analyses predicting performance on force steadiness of older adults.

	Model summary of each step					Contribution of each variable in last step				
	R	R^2	ΔR^2	*F*	*p*	B	SE	β	*t*	*p*
Force steadiness: control trial										
Step 1	0.42	0.18	–	3.98	**0.01**					
Age						0.05	0.02	0.25	1.95	0.05
Sex						−0.74	0.60	−0.31	−1.25	0.22
MVC						−0.04	0.02	−0.53	−2.14	**0.03**
Step 2	0.45	0.2	0.14	1.71	0.19					
Trails A						0.28	0.22	0.16	1.31	0.19
Step 2	0.46	0.21	0.04	2.39	0.13					
Trails B						0.27	0.18	0.19	1.55	0.13
Force steadiness: cognitive challenge trial										
Step 1	0.42	0.18	–	3.98	**0.01**					
Age						0.44	0.16	0.36	2.82	**0.01**
Sex						3.13	3.58	0.22	0.88	0.39
MVC						−0.02	0.11	−0.06	−0.23	0.82
Step 2	0.53	0.28	0.11	7.45	**<0.01**					
Trails A						3.32	1.22	0.32	2.73	**0.01**
Step 2	0.50	0.25	0.07	4.98	**0.03**					
Trials B						2.30	1.03	0.27	2.23	**0.03**

MVC, maximal voluntary contraction; Trails, Trail-making Test; F from change in R^2, P from change in R^2. Bold values indicate when $P < 0.05$ (i.e., when they are statistically significant).

B of the Trail-making Test accounted for 0.27% of the increase in CV of force during cognitive challenge trial in older adults ($P = 0.03$), but not young adults ($P = 0.20$).

DISCUSSION

This study showed that (1) healthy older adults had greater CV of force (i.e., reduced force steadiness) than young adults when a difficult cognitive challenge was imposed during a low-force task with the elbow flexor muscles, (2) young and older women had greater CV of force than men with the imposition of a cognitive challenge, and (3) poor executive functioning, which is a fundamental cognitive ability that allows planning and integration of information during motor tasks, is a significant factor that predicts the age-related decline in force steadiness when a cognitively challenging task is performed simultaneously with a motor task in healthy community-dwelling older adults. To examine the influence of executive functioning on force steadiness, our participants performed the Trail-making Test that largely depends on executive function skills (Sanchez-Cubillo et al., 2009; Camilleri et al., 2015). We found that both part A and B of the Trail-making Test separately improved the prediction of CV of force during a cognitive challenge trial in older adults, but not in the young adults (**Tables 2**, **3**). Parts A and B of the Trail-making Test are highly intercorrelated, so they cannot both be effectively entered into the models. Yet, they are recognized as measuring related but separable constructs (Bowie and Harvey, 2006). Importantly, the influence of executive function on CV of force was independent of age-related changes in cognitive function or education level because we used the *z*-score of each individual Trail-making Test that is adjusted for age and education. We also found that MVC and age of the individual had a greater contribution than the sex of the individual to improve the model to predict CV of force during the cognitive challenge session in young and older adults, but sex was a main factor explaining force steadiness during control contractions of young adults (**Tables 2**, **3**).

Age and Sex Differences in Force Steadiness During Control and Cognitive Challenging Tasks

Findings of the current study agree with others showing that older adults have greater CV of force (lower force steadiness) during muscle contractions under control conditions when no cognitive challenge is imposed (Enoka et al., 2003; Oomen and van Dieen, 2017, for review). A new finding, however, is that within the older cohort, CV of force for the control contractions had a trend to be even greater in the very older compared with the younger older adults (age factor of step 1 in **Table 3**). Importantly, age-related reductions in force steadiness were further increased when a cognitive challenge was imposed during the force task, particular in women, which is consistent with previous observations for the upper limb muscles (Voelcker-Rehage et al., 2006; Pereira et al., 2015; Shortz and Mehta, 2017) and lower limb muscles (Vanden Noven et al., 2014). Our results showed that prediction of CV of force during cognitive challenge tasks in the older adults group was improved when executive functioning skills (i.e., results from Trail-making Test part A or B) were considered (step 2 in **Table 3**). Together these findings

indicate that executive functioning and the age of the individual are primary factors explaining the CV of force during cognitively challenging tasks.

Women were shown in other studies to exhibit a greater CV of force during low-to-moderate force contractions without imposition of a cognitive challenge for the upper limb (Christou et al., 2004; Brown et al., 2010) and lower limb muscles (Vanden Noven et al., 2014). Here we also showed that young and older women had greater CV of force of the elbow flexor muscles during a cognitive challenge as previously reported (Noteboom et al., 2001; Pereira et al., 2015). Furthermore, our current results indicate that during contractions without a cognitive challenge, the sex and strength (MVC) of young adults are primary factors influencing the CV of force (step 1 in **Table 2**), whereas for older adults only the MVC was a main predictor of the force steadiness (step 1 in **Table 3**). There were no sex differences in the Trail-making Test scores for either age group. Thus, sex differences in executive functioning probably do not explain the sex differences in force steadiness.

A larger CV of force is more likely to occur in weaker young and older individuals during control contractions (Brown et al., 2010; Marmon et al., 2011) and our results support these findings (step 1 in **Tables 2**, **3**). However, for a contraction with the cognitive challenge, maximal strength did not improve the model to predict CV of force compared with age of the individual or Trail-making-Test results in young or older adults (step 1 in **Tables 2**, **3**). The findings of age and sex-related differences in CV of force during a cognitive challenge task expand previous observations of impaired motor function during several motor tasks of the upper extremity such as dexterity tests, finger tapping tasks and reaction time tests in young and older adults (Zijdewind et al., 2006; Fraser et al., 2010; Toosizadeh et al., 2016). Physiological mechanisms driving the differences in motor performance during cognitive challenging tasks in men and women are not fully understood, but alterations in cognitive function with aging may partly explain these findings as discussed below.

Executive Function Influence on Motor Performance

Executive functioning was previously shown to be crucial for *dynamic* contractions such as maintenance of speed in older adults during attention-demanding walking (Ble et al., 2005; Coppin et al., 2006; Springer et al., 2006), a finger tapping task (Fraser et al., 2010), a dexterity task (Corti et al., 2017), and a motor sequencing task with the upper extremity (Niermeyer et al., 2017). The current study shows that the Trail-making Test performance predicted the force steadiness during *static* contractions performed simultaneously with a cognitively challenging task in older adults, but not in young adults. The greater influence of executive functioning on the motor task in the older adults only, may indicate neuroanatomical alterations with aging. More specifically, older adults are known to use additional cortical areas to compensate for the reduced volume of the cortex that is known to occur with aging (Grady, 2012; Reuter-Lorenz and Park, 2014). The mental math performed during the elbow flexion contraction increased the demand of the task by taxing executive function (Menon et al., 2002) and the prefrontal cortex (Baddeley, 2003). Because of the recruitment of additional cortical areas with aging (Grady, 2012; Reuter-Lorenz and Park, 2014), any interference input of the prefrontal cortex on the pre-motor areas (Tanji and Hoshi, 2008) is more likely to occur in older adults. Support for this hypothesis also comes from a greater corticomuscular coherence in the alpha and beta bands of older adults when they perform a mental math task simultaneously with an index finger abduction (Johnson and Shinohara, 2012). However, our data extend the literature to indicate it is those older adults who have greater difficulty with executive function skills who also exhibit the largest impairment in CV of force during cognitive challenge trials. Additionally, all the individuals in the current and previous studies (Ble et al., 2005; Coppin et al., 2006; Springer et al., 2006) were within the range of normal MMSE values (>24), indicating that none of the individuals had severe cognitive impairment. These findings also indicate that older individuals with declines in cognitive processes, although not enough to be considered with a clinical diagnosis, may be at risk of low motor function when performing cognitively challenging motor tasks.

There are other factors that were not tested in this study but that can influence force steadiness in old adults. For example, practice of a force task can improve force steadiness (Laidlaw et al., 1999; Griffin et al., 2009; Onushko et al., 2014) and greater visual feedback was reported to reduce force steadiness particularly in older adults (Christou, 2011; Baweja et al., 2015). Both these factors were not investigated in the current study, although were held constant for both age groups across the different conditions. Other factors such as production of nitrogen and oxygen species and noradrenergic concentration that are known to increase during stressful events (Sessa et al., 2018) such as a cognitively challenging task, may effect young and old adults differently. Reactive oxygen species for example, may impair force production by inhibiting calcium sensitivity (Debold, 2015) although its effects on force steadiness with aging are not known. In contrast, increased noradrenergic concentration may improve force steadiness in young men (Klass et al., 2018), but its effects among older adults is also not understood.

CONCLUSION

Healthy community-dwelling older adults, who have lower executive functioning skills, exhibit the greatest reduction of force steadiness (greater CV of force) during an upper extremity motor task when required to perform a cognitively challenging task. Because everyday tasks are frequently performed with the requirement of a dual task involving a cognitive and motor task, healthy community-dwelling older adults, who have poorer executive function skills, are likely at risk of reduced capacity to perform daily activities that involve cognitively challenging

motor tasks. Maintenance of executive functioning in older age may impact the performance of steadiness tasks in the presence of greater cognitive demand.

AUTHOR CONTRIBUTIONS

HP, SH, and KN designed the study. HP and BS-D collected the data. HP, BS-D, and KN analyzed the data. All authors interpreted the results, contributed to the drafting, and revised the manuscript. SH and KN raised funding for the study.

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REVIEW
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Perceived Versus Performance Fatigability in Patients With Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is a chronic, inflammatory disease that affects 1% of the general population. Fatigue is a common complaint of patients with RA, however their perceived fatigue may be more exacerbated than objective measures of fatigue may indicate. The assessment of fatigue is made complex due to inconsistent and vague terms used to define fatigue, and the task dependence of fatigability. Fatigue is defined as a state of exhaustion and decreased strength, while fatigability indicates an individual's susceptibility to fatigue. In order to offer some clarity to the manifestation of fatigue in clinical populations, in this review we outline that fatigue should be described with subsections that are related to the symptom, such as: perceived fatigability and performance fatigability. Where perceived fatigability indicates the subjective state of the individual and thus involves the individual's subjective measure of fatigue, performance fatigability would be measured through clinical and laboratory-based assessments that quantify the functional decline in performance. This review describes RA and the various neuromuscular changes associated with the disease that can lead to alterations in both perceived and performance fatigue. From there, we discuss fatigue and RA, how fatigue can be assessed, effects of exercise interventions on RA symptoms and fatigue, and recommendations for future studies investigating subjective and objective measures of fatigability.

Keywords: inflammation, rheumatoid arthritis, performance fatigability, perceived fatigability, fatigue, fatigability, cytokines

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Rheumatoid arthritis (RA) is a chronic, inflammatory disease that affects many individuals regardless of their demographic (Veldhuijzen Van Zanten et al., 2015). Fatigue, or the state of exhaustion and increased acute weakness, is a common symptom reported by 40–80% of individuals with RA and its co-morbidities: rheumatoid cachexia and sarcopenia (Cooney et al., 2011; Nikolaus et al., 2013; Louati and Berenbaum, 2015). Attempts have been made to study fatigue within the rheumatoid population, yet there are still considerable knowledge gaps regarding the underlying mechanisms of fatigue. Furthermore, in RA populations, a commonly accepted definition of fatigue does not exist (Nikolaus et al., 2013). Amongst primary care providers, there has been a great deal of confusion regarding the topic of fatigue and the various types of fatigue that individuals experience possibly because terminology surrounding 'fatigue' is fairly ambiguous – ranging from general malaise and tiredness to transient impairments in neuromuscular function and muscle force production. The multifactorial etiology of fatigue has driven researchers to describe

fatigue based on its likely origin; however, the descriptions have been depicted as too unclear and have only led to confusion regarding clinical populations (Enoka and Duchateau, 2016).

Owing to the multiple origins of fatigue, it has been difficult to determine the best ways to measure fatigue in clinical populations. Moreover, there has been confusion regarding whether or not self-reported measures of fatigue reflect laboratory-based objective measures (do Espírito Santo et al., 2017). Some studies assess only the psychological factors that contribute to feelings of fatigue and tiredness (Hewlett et al., 2011) while others assess the specific muscular, peripheral, and central nervous system impairments reducing neuromuscular performance (Enoka and Duchateau, 2016). In order to grasp a true understanding of fatigue in the rheumatoid population, it is critical for researchers and clinicians to assess both perceived and performance fatigability and draw parallels between these findings. The purpose of this review is to explore the relationship between RA and fatigue, the different types of fatigue that have been explored in literature, the measures of fatigue that are used to assess both performance and perceived fatigue, what clinicians and researchers are recommending to manage the symptoms of RA, and lastly, future directions of evaluating fatigue in RA populations.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic, multi-system, autoimmune disease that affects approximately 1% of the general population (Veldhuijzen Van Zanten et al., 2015). Women are more commonly targeted with a peak onset between the ages of 40 and 60 years of age; however, RA can affect individuals of all demographics (Londhe and Guttridge, 2015). It is a debilitating disease that is often characterized by joint pain, swelling, and stiffness due to persistent inflammation (Londhe and Guttridge, 2015; Veldhuijzen Van Zanten et al., 2015). Sustained synovitis can lead to permanent structural damage, which in turn reduces the everyday functionality of patients with RA (Cooney et al., 2013; Londhe and Guttridge, 2015).

The synovial membranes of individuals with RA are often characterized by increased vascularity and intrusion of inflammatory cells, which are suspected to be the key mediators of the disease (Londhe and Guttridge, 2015). There is an approximate 3–100 fold increase in the levels of pro-inflammatory cytokines, specifically interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-a), and interleukin 1-B (IL-1B) (Cooney et al., 2011). IL-6 perpetuates RA by stimulating the secretion of vascular endothelial growth factor (VEGF), enhancing angiogenesis in the synovium. IL-6 also works synergistically with IL-1B to increase the production of matrix metalloproteinases (MMPs), leading to joint and cartilage destruction (Londhe and Guttridge, 2015). TNF-a and IL-1 are potent stimulators of mesenchymal cells that release matrix MMPs, which are involved in degradation of tissue and prevent production of tissue inhibitors of metalloproteinases (TIMPs) (Londhe and Guttridge, 2015). Increased catabolism of muscle tissue coinciding with the downregulation of anabolic factors that accompany RA, such as insulin-like growth factor (IGF-1), drastically alters muscle-protein turnover to a net catabolic state (Cooney et al., 2011; Dogan et al., 2015; Londhe and Guttridge, 2015). Increased net catabolism causes an increase in resting energy expenditure (REE), efflux of amino acids from the muscles to the liver, and an increase in acute phase reactants, fibrinogen, and C-reactive protein (CRP) (Londhe and Guttridge, 2015).

A hypothetical model of the disablement process in patients with RA was proposed (Balsamo et al., 2014), suggesting there are many relationships between multiple variables that will impact the disability levels in RA. The main disease-disability pathway follows a series of stages including pathology, impairment, functional limitation, and lastly, disability (Balsamo et al., 2014). Inflammation and long-term joint damage lead to symptoms of impairment, including muscle pain and weakness as well as self-reported fatigue, resulting in functional limitations in mobility, strength and dexterity (Escalante and Del Rincón, 2002; Alomari et al., 2012). These limitations lead to physical disability and, ultimately, cause patients to suffer a reduced quality of life (Alomari et al., 2012).

SARCOPENIA AND RHEUMATOID CACHEXIA: CO-MORBIDITIES OF RA

Chronic inflammatory diseases such as RA have been linked with various co-morbidities such as rheumatoid cachexia and sarcopenia Matschke et al. (2010a). Both conditions lead to muscle wasting and may influence fatigability in RA patients (Cooney et al., 2011). Rheumatoid cachexia is reported in approximately two-thirds of the RA population (Cooney et al., 2011). This condition presents as an accelerated loss of lean muscle mass while maintaining a normal or increased fat mass, contributing to disability and a poorer quality of life (Cooney et al., 2011). The total mass associated with muscle and bone within the body, known as body cell mass (BCM), was decreased by 13% in adults with RA compared to controls (Roubenoff et al., 1994). The loss of BCM was primarily caused by cytokine-mediated catabolism, a decrease in physical activity, inadequate nutrition and effects of medication (Roubenoff et al., 1994). However, the fundamental feature of rheumatoid cachexia appears to be an excess of the pro-inflammatory cytokines that are involved in RA (TNF-a, IL-1B, IL-6, and IFN-y) which leads to increased muscle wasting and protein degradation (Cooney et al., 2011; Masuko, 2014; Londhe and Guttridge, 2015). In older patients, in addition to RA cachexia, muscle loss can also occur through the process known as sarcopenia. Sarcopenia is a condition currently defined as "an age-related loss of functional quality (of muscle) in addition to muscle weakness and muscle protein mass loss" (Power et al., 2013; Dogan et al., 2015) While sarcopenia is classically associated with aging, it is believed that accelerated muscle loss in RA patients occurs due to chronic inflammation and the effects that are associated with sarcopenia (Masuko, 2014). The primary driver of age-related muscle wasting appears to be a loss of functional motor units (α motor neuron and the muscle fibers it innervates). Following the death of a parent motor neuron, the

muscle fibers previously innervated are orphaned, and although some are recaptured via collateral reinnervation, whole muscle atrophy is inevitable. (Power et al., 2014; Power et al., 2016). Additionally, increased inflammatory mediators, particularly cytokines, and other immunological changes due to aging may contribute to the loss of lean muscle mass (Dogan et al., 2015). Therefore, it has been proposed that changes to the inflammatory environment and lifestyle modifications accompanying RA, such as increased cytokine levels and reduced physical activity due to immobilization from pain, stiffness, and joint damage, accelerate the progression and the occurrence of sarcopenia in the RA population (Dogan et al., 2015; Krajewska-Wlodarczyk, 2016). Both rheumatoid cachexia and sarcopenia are involved in a vicious cycle of disease progression in RA patients, causing further deleterious effects. It has been demonstrated that exercise as a form of therapy is very beneficial (discussed below) in reducing the progression and risk of sarcopenia and rheumatoid cachexia, as well as alleviating some of the physical limitations commonly experienced by patients with RA (Cooney et al., 2011). These co-morbidities can be reduced and safely managed through the completion of regular physical activity (Cooney et al., 2011).

NEUROMUSCULAR CHANGES IN RA PATIENTS

Histopathological analysis of muscle from patients with stable RA [stable disease activity due to no flare or change in medication for the previous 3 months (Matschke et al., 2010b)] tend to report characteristics of 'normal' muscle (Lundberg and Nader, 2008). However, even with similar whole muscle properties, in two-thirds of patients with RA there is often a 25–50% reduction in muscle strength (Stenstrom and Minor, 2003). Some human trials reveal muscle weakness is often a consequence of skeletal muscle mass loss as opposed to changes in muscle quality (i.e., force/contractile properties) or voluntary activation (Matschke et al., 2010b). In contrast, other studies suggest that muscle mass loss cannot account for the decrease in muscle strength alone (Helliwell and Jackson, 1994), proposing that the contractile function of muscles affected by RA are impaired, thus causing muscle weakness (de Palma et al., 2000; Yamada et al., 2009; Yamada et al., 2015). Therefore, muscle weakness in patients with RA may be driven by two major contributors: the loss of lean muscle mass (Matschke et al., 2010b) and a reduction in intrinsic muscle quality due to impaired muscle contractility (de Palma et al., 2000; Yamada et al., 2009).

Excitation-contraction (EC) coupling is the physiological process of converting a neuronal stimulus from the central nervous system to a mechanical response that leads to muscle contraction and consequently force production (Allen et al., 2008). Specifically, EC coupling occurs when depolarization of the sarcolemma results in increased sarcoplasmic reticulum (SR) Ca^{2+} release into the myoplasm (Allen et al., 2008), causing force generation when the myofibrillar proteins actin and myosin interact to form crossbridges. Impaired EC coupling may be the critical contributor to intrinsic muscle weakness in RA (Yamada et al., 2015). For instance, structural damage in the myofibrillar proteins and sarcotubular systems (de Palma et al., 2000) are commonly observed in muscle biopsies of RA patients with symptoms of muscle weakness (Russell and Hanna, 1988). Chronically elevated redox stress may underlie the pathology as nitrosative modifications of the myofibrillar protein observed in the muscle biopsies of RA patients as demonstrated within an animal model of RA (Yamada et al., 2015). Using the collagen-induced arthritis (CIA) mouse model that demonstrates similar pathological characteristics of human RA, Yamada et al. (2015) presented an apparent decrease in muscle force per cross-sectional area of the soleus muscle. Reduced force production was complemented with slower force development and slowed relaxation, a decreased maximal shortening velocity, and modifications in myofibrillar proteins induced by the highly reactive nitrogen species, peroxynitrite. The authors hypothesized that an increase in peroxynitrite-derived radical generation in rheumatoid muscle impaired cross-bridge cycling (Yamada et al., 2009). High levels of radicals, such as peroxynitrate and other reactive oxygen and nitrogen species (ROS/RNS), are associated with damage to muscle cellular components and contractile dysfunction in chronic diseases (Yamada et al., 2015). Despite an increased Ca^{2+} level during tetanic contractions, there was a decreased force per cross-sectional area in individual CIA muscle fibers, indicating weakness compared to control mice (Yamada et al., 2015). Overall, these studies demonstrated that contractile dysfunction is associated with decreased myofibrillar Ca^{2+} sensitivity, rather than an impaired excitability, SR Ca^{2+} uptake, or lower concentrations of cytosolic Ca^{2+} within animal models of RA (Yamada et al., 2009, 2015).

Decreased myofibrillar Ca^{2+} sensitivity indicates that muscles need a much higher concentration of Ca^{2+} released in order to function (i.e., produce the same level of force) at the same level as healthy muscle (Yamada et al., 2015). A potential consequence of the higher Ca^{2+} concentration for force generation is an increased energy cost of contraction due to elevated ATP consumption by the sarcoplasmic reticulum Ca^{2+}-ATPase to pump Ca^{2+} back into the sarcoplasmic reticulum; potentially exacerbating muscle fatigue. At the whole human level, the required release of additional Ca^{2+} to achieve the same force level as healthy individuals requires increased motor unit activation. The additional descending cortical drive to the motor unit pool potentially increases an RA patients' perception of effort required to achieve a given force level (Pageaux, 2016). Increased self-reported perception of effort can therefore have a significant effect on an individual's fatigue status, exercise intolerance, and lead to further complications in RA (Matschke et al., 2010b; Pageaux, 2016).

In summary, while animal data demonstrates that the major peripheral mediators of exercise-induced weakness are decreased myofibrillar Ca^{2+} sensitivity and increased intracellular Ca^{2+} concentration during muscle contraction, data from human muscle biopsies also indicate intrinsic contractile dysfunction and thus, decreased muscle strength in patients with RA (de Palma et al., 2000). Therefore, neuromuscular changes associated with RA are speculated to be involved with, and lead to, one of RA's most prominent symptoms: fatigue.

FATIGUE AND RA

Fatigue is a common symptom reported by patients with RA (Louati and Berenbaum, 2015). Approximately 40–80% of patients with RA experience fatigue, with 50% of individuals reporting severe fatigue (Nikolaus et al., 2013; Louati and Berenbaum, 2015). Medications used as treatment for RA, such as methotrexate, can induce or amplify perceived fatigue in patients with RA (Kluger et al., 2013), further complicating assessments of fatigue in RA patients. Clinically, a generally accepted definition of fatigue has yet to be defined, but some individuals have described it as "a state of exhaustion and decreased strength accompanied by a feeling of weariness, sleepiness and irritability, with a cognitive component" (Louati and Berenbaum, 2015). Fatigue is a valid outcome measure of RA, as well as a reliable differentiator of quality of life between individuals with RA who are doing poorly and those who are doing well (Balsamo et al., 2014). There is clear evidence demonstrating a common link between inflammation and fatigue, depression, and pain - the three most expressed symptoms associated with RA (**Figure 1**) (Louati and Berenbaum, 2015). Although each possesses complex mechanisms of action, it has been documented that cytokines are associated with all three domains (Louati and Berenbaum, 2015). Thus, the link between the three may potentially be inflammation associated with RA. Some studies have even demonstrated higher levels of IL-1 in the cerebrospinal fluid of individuals with RA compared to controls which correlated with their intensity of fatigue (Louati and Berenbaum, 2015). Furthermore, depressive symptoms and severity are exacerbated by increased levels of pro-inflammatory cytokines IL-1B, IL6, IL-18, TNF-α, and CRP (Slowik et al., 2017). Fibromyalgia, a condition characterized by chronic widespread pain is also common in RA and can lead to similar symptoms of RA such as depression and fatigue (Dhir et al., 2009), yet this specific condition is beyond the scope of this literature review. Because fatigue is often associated with psychological factors such as depression (Hewlett et al., 2010; Enoka and Duchateau, 2016), it can be important to separate whether fatigue is directly or indirectly related to disease progression in RA. Nonetheless, it cannot be ruled out that fatigue has a central origin as it has been shown that rest does not improve perceived symptoms of fatigue in chronic inflammatory diseases (Staud, 2012).

FATIGUE AND FATIGABILITY

Fatigue is distinguishable from other symptoms established in various inflammatory or neurological diseases, such as general

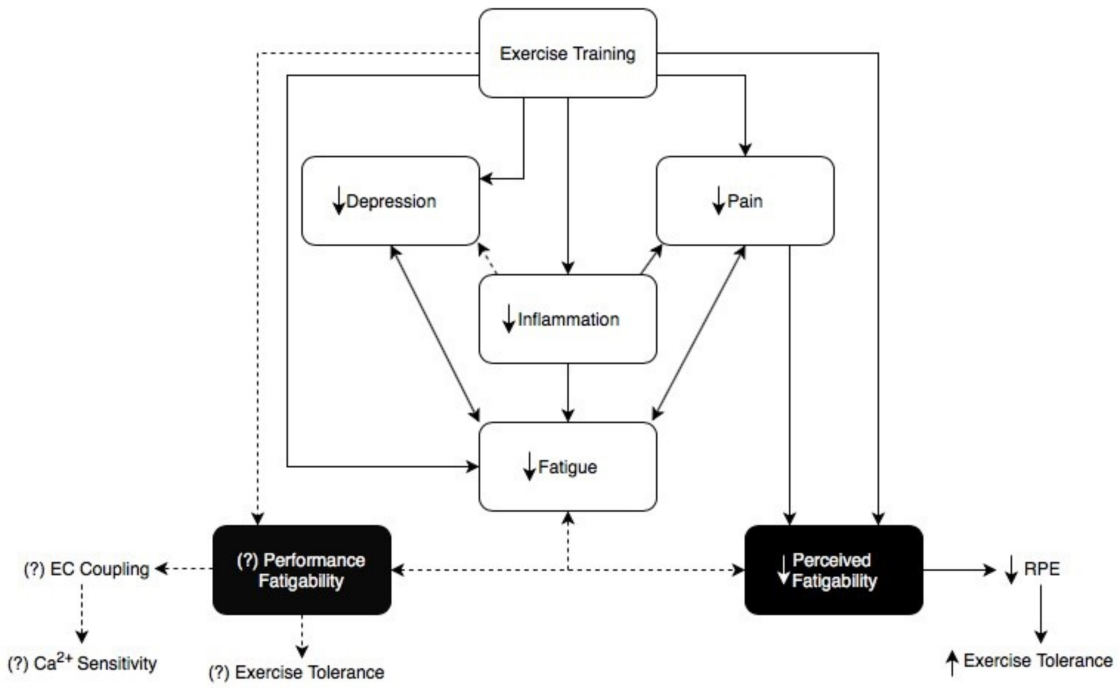

FIGURE 1 | This figure demonstrates the link between fatigue, depression, pain, and inflammation (Nikolaus et al., 2013; Louati and Berenbaum, 2015). Fatigue in RA can be subdivided into 'Perceived fatigability' and 'Performance fatigability', each with different underlying mechanisms (Enoka and Duchateau, 2016). Exercise training shows a speculative relationship between perceived and performance fatigability (Cooney et al., 2011; Veldhuijzen Van Zanten et al., 2015). This diagram explains that not only does exercise training reduce inflammation and alleviate symptoms in RA patients, it may also help to decrease performance and perceived fatigability which may ultimately act upon and reduce one another as well (Cooney et al., 2011; Veldhuijzen Van Zanten et al., 2015). We propose there is a distinct relationship between exercise training and its effects on performance and perceived fatigability relating back to the overall symptom of fatigue in this clinical population. Dotted lines represent the speculative relationship between exercise training and performance fatigability, as well as performance fatigability and perceived fatigability.

TABLE 1 | Definitions of the multiple subsets of fatigue.

Fatigue	"A state of exhaustion and decreased strength accompanied by a feeling of weariness, sleepiness and irritability, with a cognitive component" (Enoka and Duchateau, 2016)
Central fatigue	"Difficulty initiating or sustaining voluntary activities, leading to a progressive reduction in the activation of the muscle" (Gandevia, 2001; Staud, 2012)
Peripheral fatigue	"Fatigue produced by changes at or distal to the neuromuscular junction" (Gandevia, 2001)
Supraspinal fatigue	"A subset of central fatigue produced by failure to generate output from the motor cortex" (Gandevia, 2001)
Muscle fatigue	"A motor deficit, perception or a decline in [. . .] function, leading to a gradual decrease in the force capacity of muscle or the endpoint of a sustained activity" (Enoka and Duchateau, 2008)
Pathological fatigue	"Fatigue experienced as a symptom/outcome in acute or chronic diseases, such as RA, that often does not improve with rest" (Enoka and Duchateau, 2016)

malaise, depression, and apathy (Kluger et al., 2013). There have been multiple adjectives attached to the term "fatigue" including central, peripheral, supraspinal, muscle as defined in **Table 1**.

The terms "central" and "peripheral" indicate the most probable origin in the body that contributes to fatigue (Enoka and Duchateau, 2016). In some literature, central fatigue is described as "progressive reduction in voluntary activation of muscle during exercise" (Gandevia, 2001) where peripheral fatigue represents fatigue "caused by mechanisms distal to the neuromuscular junction" (Staud, 2012). Therefore, central fatigue is related to the failure of motivational and affective input, leading to a higher perception of effort and resulting in the sense of fatigue (Staud, 2012). Peripheral fatigue includes multiple neuromuscular changes affecting the contractility of muscles (Staud, 2012). The major mechanisms involved in peripheral fatigue include changes in activation of the muscle such as: impaired action potential propagation along the sarcolemma, reduced SR Ca^{2+} release and reuptake, decreased Ca^{2+} sensitivity of the myofibrils, and decreased number of force-generating crossbridges or force produced per crossbridge (Allen et al., 2008; Enoka and Duchateau, 2008). Peripheral fatigue arises from impaired EC coupling that leads to decreased force produced by the contracting muscle. In order to increase force production, there is a need for increased motor neuron pool activation via an increased cortical drive. Increased cortical drive can lead to a higher perception of effort, which in turn decreases exercise tolerance and contributes to fatigability. Therefore, both central and peripheral mechanisms of fatigue are not necessarily mutually exclusive (Gandevia, 2001; Pageaux, 2016).

There are key limitations to the central-peripheral fatigue continuum: (1) the belief that the mechanisms needed to maintain task performance while counteracting declining muscle force capacity are independent from those generating sensations of fatigue, and (2) during experimentation, almost all of the physiological processes in a task-dependent action, from the CNS to the muscle involved, can contribute to fatigue, implying that it would be very difficult to distinguish all the potential contributors to fatigue without a holistic perspective (Enoka and Duchateau, 2016). In order to move away from the central-peripheral dichotomy, a new taxonomy involving the term "fatigability" has been suggested (Kluger et al., 2013; Enoka and Duchateau, 2016). While the term fatigue describes a "state of exhaustion and decreased strength", the expression fatigability denotes "susceptibility to fatigue" (Nikolaus et al., 2013; Enoka and Duchateau, 2016). In other words, individuals who are less fatigable reach the same level of fatigue as others at a much greater demand (Enoka and Duchateau, 2016). Perceptions of fatigue, also referred to as the subjective sensations of fatigue, and fatigability are distinct and possibly independent, but establishing an association between the two is very important. "Perceptions of fatigue" and "performance fatigability" are subsections of fatigue that each contain further categories of factors related to fatigue. "Perceptions of fatigue" contain homeostatic and psychological factors, such as central regulation based on feedback or depression, whereas "performance fatigability" includes peripheral factors and central factors, similar to the mechanisms involved in peripheral, and central fatigue (Kluger et al., 2013; Enoka and Duchateau, 2016).

Further revisions to the taxonomy now include the current extent of conditions associated with fatigue. The concept of fatigue in this new taxonomy includes two attributes: performance fatigability and perceived fatigability. Performance fatigability regards "the decline in an objective measure of performance over a discrete period" where perceived fatigability includes "changes in sensations that regulate the integrity of the performer" (Enoka and Duchateau, 2016). A key feature of the taxonomy is that the degree of fatigue that limits both physical and cognitive function in individuals varies due to the many factors of performance and perceived fatigability within and between each category. Perceived fatigability still refers to homeostatic processes and psychological state, where performance fatigability refers to contractile function and muscle activation (Enoka and Duchateau, 2016). Perceived fatigability in an individual can be evaluated at both rest or during physical activity, where performance is evaluated through strenuous activity (Staud, 2012; Enoka and Duchateau, 2016).

Reporting fatigue should be focused on stating the primary outcome variable. Perceived fatigability can be measured through the use of subjective surveys to individually rate various dimensions of fatigue (Kluger et al., 2013; Enoka and Duchateau, 2016). Where performance fatigability can be measured through fatigue-inducing tasks, perceived fatigability should be measured though the individual's interpretation of their fatigue levels (Enoka and Duchateau, 2016). Assessments of performance fatigability focus on an outcome variable that can be evaluated throughout the duration of a given task (Enoka and Duchateau, 2016). The ability to complete physical tasks is quantified with clinically and laboratory-based methods testing endurance, strength, manual dexterity and locomotion. Such measures of fatigue include the completion time of specific tasks, the duration a fatigue-inducing task can be sustained, and the rate of change in variables associated with human performance (Enoka and Duchateau, 2016). Maximum voluntary isometric contraction (MVC) force, which indicates the greatest amount of tension a

muscle can generate or hold, can also be measured objectively through various laboratory techniques such as through time to task failure (Enoka and Duchateau, 2016). Walking endurance or time trials can be used when measuring the completion time of specific tasks. Results from laboratory studies testing human performance demonstrate the severity of fatigue an individual endures after or during completion; for instance, a shorter time to task failure would indicate increased fatigability in a patient compared to healthy controls who are less susceptible to fatigue and are able to sustain the activity for a longer period of time.

Throughout the literature, it is apparent that the use of subjective measures of fatigue (surveys and self-reports) are more common than objective measures in RA populations. There are twelve patient-reported outcome measures (PROMs) that have been most recently utilized to measure fatigue in RA (Hewlett et al., 2011). Of twelve fatigue scales reviewed within the literature, five were specific to RA. The five scales include Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire, Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales (severity, effect and coping), Functional Assessment Chronic Illness Therapy (Fatigue), Multi-Dimensional Assessment of Fatigue, and Multi-Dimensional Fatigue Inventory (Hewlett et al., 2011). Each PROM involves questions specific to fatigue and requires individuals to rank their level of fatigue on a scale – it could be their current fatigue levels, or fatigue levels over a certain amount of time (Hewlett et al., 2011; Nikolaus et al., 2013). Validity evidence for each PROM differs, as demonstrated in **Table 2**. Content validity refers to how well a test measures the symptom for which it is intended, construct validity refers to the degree to which a test measures what it claims to be measuring and criterion validity refers to the extent to which a measure is related to an outcome (Hewlett et al., 2011). Hewlett et al. noted that because fatigue is experienced as a multi-dimensional symptom with short-term or long-term duration, relying on PROMs alone can be difficult (Hewlett et al., 2011; Nikolaus et al., 2013). Specifically, it is the unpredictable multifactorial nature of fatigue in chronic inflammation that makes it difficult to evaluate fatigue using PROMs (Hewlett et al., 2011; **Table 2**).

Throughout this review, we advocate that fatigue should be assessed as a symptom, highlighting the need for subjective measures (Enoka and Duchateau, 2016). The more fatigue an individual experiences, the more difficult the task is perceived by the patient, which decreases motivation to continue or complete the task (Staud, 2012). In order to grasp an appreciation for self-reported fatigue, it may be necessary to complete both objective and subjective measures in clinical research in order to truly compare how both measures correspond to one another. This can determine if subjective measures used to document perceived fatigability truly correlate with objective measures of performance fatigability. Results from a recent study, indicated that neuromuscular fatigue during a 60 s isometric contraction, was weakly associated with RA patients' perceptions of fatigue (do Espírito Santo et al., 2017). It is important to note that performance fatigability is highly task-dependent (Enoka and Duchateau, 2016), thus it is not known whether perceptions of fatigue in this RA population better relate to dynamic fatiguing contractions such as those experienced during everyday life. This finding provides a proof of concept in linking perceived and performance fatigability in future clinical studies with the aim to fully capture the extent to which fatigue cognitively and physically impairs an RA patient's ability to function in everyday life (do Espírito Santo et al., 2017).

TRAINING STUDIES: EXERCISE AND PERCEIVED BARRIERS

There are various symptoms associated with RA that patients regard as their top priorities for treatment: less fatigue, less pain, hindering joint damage, ability to carry out activities of daily living, and improved mobility (Chauffier et al., 2011). Recent research indicates that exercise and physical activity can improve these disease-related symptoms as well as enhance mental health in RA patients (Veldhuijzen Van Zanten et al., 2015). The completion of both resistance training and endurance training in RA patients offers many benefits in skeletal muscle, bone, and joint health (Cooney et al., 2011). Patients with RA can benefit from the anabolic effects of exercise similarly to individuals without RA (Cooney et al., 2011). Progressive resistance training (PRT) has been demonstrated to increase muscle mass, strength, and function in RA patients, reducing and managing the risk of cachexia and sarcopenia (Masuko, 2014). PRT also improves bone mineral density, as well as benefits tendons and connective tissue (Cooney et al., 2011). Endurance training (ET) is also very important in increasing insulin sensitivity, improving body composition, and decreasing circulating CRP and IL-6 levels (Powers et al., 1999). Muscle antioxidant capacity is also increased following ET (Powers et al., 1999; Reeves et al., 2003) which may help counterbalance the chronically elevated redox stress in skeletal muscle of RA patients. The combination of both PRT and ET therefore helps to increase lean body mass, decrease body fat and improve disease activity in RA patients (Masuko, 2014). Importantly, both aerobic and resistance training also reduce the self-reported levels of fatigue in individuals with RA (Cooney et al., 2011; Cramp et al., 2013). Based on these studies and additional evidence brought forward by a systematic review regarding the effect of dynamic exercise programs on RA, it is evident that ET and PRT have positive effects on aerobic capacity and muscle strength, and should thus be recommended as a routine intervention for patients with RA (Hurkmans et al., 2009).

Even though exercise has been recommended as part of the management and treatment of RA and its co-morbidities, 71% of RA patients do not participate in regular physical activity (Veldhuijzen Van Zanten et al., 2015). Low physical activity levels indicate that many individuals with RA perceive various barriers when attempting exercise even if they are aware of the benefits. The primary barriers identified are disease-related, self-reported pain, and fatigue (Veldhuijzen Van Zanten et al., 2015). By overcoming perceived fatigability and motivating oneself to participate in physical activity, it is possible that performance fatigability can be reduced as well. Furthermore, by reducing performance fatigability, perceived fatigability is also potentially decreased, thus improving an individuals' perception

TABLE 2 | Patient-reported outcome measure scales developed with, evaluated in or specific to Rheumatoid Arthritis (Hewlett et al., 2011).

Scale	Content	Validity
Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire	Measures impact and severity of fatigue over the previous 7 days in rheumatoid arthritis	Content validity: strong Construct validity: strong Criterion validity: strong
Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales (severity, effect and coping)	Measures impact, coping and level of fatigue over the previous 7 days in rheumatoid arthritis patients	Content validity: strong Construct validity: strong Criterion validity: strong, moderate for coping
Functional Assessment Chronic Illness Therapy (Fatigue)	Measures fatigue levels in chronic illness over the previous 7 days	Content validity: moderate Construct validity: strong Criterion validity: strong
Multi-Dimensional Assessment of Fatigue	Measures severity, distress, timing and impact of fatigue over the previous 7 days	Content validity: moderate Construct validity: strong Criterion validity: strong
Multi-Dimensional Fatigue Inventory	Measures general, physical and mental fatigue as well as reduced motivation and activity	Content validity: moderate Construct validity: strong Criterion validity: moderate

that they are able to overcome various barriers (Veldhuijzen Van Zanten et al., 2015). In numerous training studies it has been documented that exercise can significantly reduce the sensation of fatigue (Cramp et al., 2013) as well as the pathogenesis of RA (Matschke et al., 2010b), which highlights the need for physical activity to be part of the treatment for managing symptoms in RA. A common misconception in individuals with RA is that intense exercise will further damage their joints (Cooney et al., 2011), yet, a recent meta-analysis reported that two of four studies investigating physical activity as an intervention for RA determined a statistically significant reduction in joint tenderness and swelling (Cramp et al., 2013). There is a clear need for clinicians and rehabilitation professionals to educate RA patients on the potential benefits of physical activity in alleviating and managing disease symptoms Halls et al. (2017). Although current literature suggests that among patients with RA, ET should be conducted at 60–85% of maximum heart rate (HR) for 30–60 min per week, and PRT should be conducted at 50–80% of the maximal voluntary contraction 2–3 times per week (Stenstrom and Minor, 2003), further research is still required to determine the optimal dose and types of exercise that can provide the best clinical outcomes for RA patients (Cooney et al., 2011; Veldhuijzen Van Zanten et al., 2015). Furthermore, future studies are needed to determine valid measurement methods of true baseline strength and fatigue as these factors will vary greatly between individuals due to perceived fatigability, pain, and disease status (Stenstrom and Minor, 2003).

FUTURE DIRECTIONS

There is still conflicting data within the literature regarding fatigue and the ways in which to evaluate fatigue within various populations. In order to make the literature on fatigue more coherent, we should move away from terms describing the origin of fatigue and instead focus on the terms "perceived fatigability" and "performance fatigability" as subsets of fatigue that are involved with both central and peripheral factors related to the symptom. Approaching the term fatigue as a symptom is necessary for the future foundation of measuring fatigue (Enoka and Duchateau, 2016). Self-reports are insufficient to measure performance fatigability, so instead we should focus on validated outcome measures of human performance in order to quantify performance fatigue levels (Enoka and Duchateau, 2016). The multifactorial and subjective nature of fatigue demonstrates the need for determining a multi-module approach to the evaluation of fatigue in healthy and rheumatoid populations (Hewlett et al., 2011).

SUMMARY

Overall, there is still confusion in the literature regarding fatigue, fatigability, and the best tools to measure fatigue, especially in RA patients. Fatigue is influenced by two domains: performance fatigability and perceived fatigability (Kluger et al., 2013; Enoka and Duchateau, 2016). Performance fatigability indicates the factors that lead to a measurable decline in performance over a specific period of time, such as contractile function and muscle activation, where perceived fatigability indicates the subjective state of the individual relating to psychological factors and deviation from homeostasis within the body (Enoka and Duchateau, 2016). Future studies should attempt to include both measures in order to correlate objective and subjective fatigue in their subjects/patients, as a limited number of clinical studies have included both in the past. Based on the latest evidence, it is apparent that evaluation of perceived fatigability would include the use of self-reports, PROMs, while evaluating performance fatigue would include clinical/laboratory assessments of outcome measures specific to human performance in order to gain accurate representation (Hewlett et al., 2011; Enoka and Duchateau, 2016; do Espírito Santo et al., 2017). There is a need for the development of fatigue measures specific to inflammatory diseases. However, the fluctuating nature of perceived fatigue in these populations, from

persistent fatigue to overwhelming events of fatigue, makes it difficult to gain accurate measures of the symptom (Hewlett et al., 2011). Further research is needed to address a multi-module approach to measuring fatigue in these populations in order to differentiate fatigue developed from the disease itself compared to normal physiological and aging processes, understand the concomitant nature of performance fatigability and perceived effort, as well, identify appropriate therapeutic interventions to minimize fatigue in patients with RA.

SEARCH METHODS

The following electronic databases were searched: PubMed database (1985 to present) and Cochrane Database of Systematic Reviews (2000 to present). In addition, we searched the reference lists of key articles, both human and animal studies, and review articles. We combined key words associated with the term 'fatigue' that were of relevance to our review (fatigability, rheumatoid arthritis, performance fatigability, perceived fatigability, and neuromuscular).

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the review and drafting the manuscript.

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Adjustments in Torque Steadiness During Fatiguing Contractions Are Inversely Correlated With IQ in Persons With Multiple Sclerosis

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Fatigue is one of the most debilitating symptoms of multiple sclerosis (MS), and the underlying mechanisms are poorly understood. When exposed to a physical or cognitive challenge, individuals with MS tend to exhibit greater declines in task performance (performance fatigability) and increased levels of self-reported fatigue (perceived fatigability), but these effects may be attenuated by greater intellectual capacity. The purpose of our study was to examine the influence of intelligence on fatigability in persons with MS. We hypothesized that greater intellectual capacity confers some protection against heightened levels of fatigue and fatigability associated with MS. Twelve adults with relapsing-remitting MS were compared with 12 control (CO) subjects who were matched for age, sex, and premorbid intellectual capacity. Performance fatigability was measured as the decline in maximal voluntary contraction (MVC) torque after 60 isometric contractions (10 s contraction at 25% MVC, 5 s rest) performed with the knee extensor muscles. Perceived fatigability was assessed with the modified fatigue impact scale (MFIS) questionnaire (trait fatigability) and the Borg rating of perceived exertion (RPE, state fatigability). Persons with MS reported greater MFIS scores (MS: 43 ± 14; CO: 11 ± 8, $P \leq 0.001$). Initial MVC torque for the knee extensors did not differ between the groups (MS: 112 ± 38 N·m; CO: 107 ± 44 N·m) and the decline (performance fatigability) was similar for both groups (MS: −16 ± 19 N·m; CO: −13 ± 16 N·m). RPE increased during the fatiguing contraction for both groups ($P < 0.001$) but was significantly greater in magnitude (main effect for group, $P = 0.03$) and increased more for the MS group (group × time interaction, $P = 0.05$). Torque steadiness declined during the fatiguing contractions (main effect for time, $P = 0.05$) and was less steady for the MS group (main effect for group, $P = 0.02$). Performance and full-4 IQ was correlated with the decline in torque steadiness for the MS group ($r = -0.63$, $P < 0.05$; $r = -0.64$, $P < 0.05$). Intellectual capacity was not associated with fatigability in persons with MS but was associated with adjustments in muscle activation during the fatiguing contractions.

Keywords: multiple sclerosis, fatigue, performance fatigability, perceived exertion, force steadiness, EMG, cognitive reserve

INTRODUCTION

Multiple sclerosis (MS) is a neurological disorder that compromises the integrity of signaling pathways in the central nervous system through chronic inflammatory responses and neurodegeneration (Trapp and Nave, 2008). Although the clinical progression of MS varies widely between individuals (Lublin and Reingold, 1996; Confavreux and Vukusic, 2006), one of the most common symptoms of the disease is a heightened level of fatigue (Fisk et al., 1994; Alvarenga-Filbo et al., 2015; Loy et al., 2017; Penner and Paul, 2017), the underlying mechanisms of which are poorly understood.

The word *fatigue* is commonly used throughout the literature to describe a wide variety of conditions, which leads to uncertainty in its intended meaning when it is not clearly defined. In an effort to remain consistent with more recent suggestions to adopt a unified taxonomy (Kluger et al., 2013; Enoka and Duchateau, 2016; Zijdewind et al., 2016), we define fatigue as a symptom that emerges in an individual due to adaptations in both perceived fatigability and performance fatigability. Perceived fatigability is assessed by self-report and reflects challenges to homeostasis and the psychological state of the individual. Trait levels of perceived fatigability refer to sensations reported by an individual over longer durations of time (days to weeks), whereas state levels indicate a momentary value. Performance fatigability is quantified as a decline in the ability to perform a given task due to adjustments in muscle activation and contractile capacity.

Symptoms of fatigue can severely limit activities of daily life and are often reported to have a more negative impact on quality of life than physical disability (Fisk et al., 1994; Amato et al., 2001; Janardhan and Bakshi, 2002; Alvarenga-Filbo et al., 2015). In addition to the debilitating effects of fatigue, MS often leads to various other cognitive and motor impairments. Cognitive impairments may include declines in processing speed, memory and executive function (Chiaravalloti and DeLuca, 2008), and motor impairments commonly include declines in mobility, strength, force steadiness, and performance fatigability (Koch et al., 2007; Dalgas et al., 2008; Hadjimichael et al., 2008). Some studies, however, have shown that possessing a higher premorbid intellectual capacity may confer protection against declines in cognitive function with progression of a neurological disease, an idea referred to as cognitive reserve. The concept of cognitive reserve posits that cognitive impairments develop more gradually as a neurological disease progresses in people with greater intellectual capacity (Stern, 2009). Persons with MS who have greater intellectual capacity, for example, can achieve comparable levels of performance on behavioral tasks with less modulation of cortical activity compared with those who have fewer years of education or lower vocabulary scores (Benedict et al., 2010; Sumowski et al., 2010).

Although current evidence on the relation between perceived fatigability and cognitive function appears equivocal (Morrow et al., 2009), persons with MS often report that fatigue interferes with cognitive functioning (Krupp et al., 1988; Monks, 1989) and that increases in fatigue occur after experiencing a cognitive challenge (Bailey et al., 2007; Tartaglia et al., 2008). Furthermore, a cognitive challenge worsens motor performance in individuals with MS more so than control subjects, and the increased cognitive demand is associated with elevated levels of perceived fatigability (Wolkorte et al., 2015). These findings suggest that intellectual capacity may be related to perceived and performance fatigability.

The purpose of our study was to examine the influence of intellectual capacity on perceived and performance fatigability in persons with MS. Intellectual capacity was measured by the Wechsler Abbreviated Scale of Intelligence. Given that intellectual capacity protects against MS-related declines in cognitive function (Sumowski et al., 2009a,b) and cerebral efficiency (Sumowski et al., 2010) and that fatigue is associated with greater levels of cortical activity (Enoka and Duchateau, 2016; Zijdewind et al., 2016; Loy et al., 2017; Severijns et al., 2017), we hypothesized that individuals with MS who had higher levels of intellectual capacity would experience lower levels of fatigue and fatigability.

MATERIALS AND METHODS

Twelve adults (39 ± 15 years, 1 man) with a diagnosis of relapsing-remitting MS and 12 control subjects (41 ± 14 years, 1 man) who were matched for age, sex, and intellectual capacity participated in the study after written informed consent was obtained. Participants with MS were included if they did not have a change in prescription medications (for ≥90 days), were able to walk ≥100 m unassisted, complained that fatigue interfered with their quality of life, and did not experience a relapsing episode within 90 days of participating in the study. None of the participants had a history of cardiovascular incidents, seizures, or traumatic brain injuries, and all participants were right-handed.

The experimental protocol was approved by the Institutional Review Board at the University of Colorado Boulder (protocol#: 12-0421) and conformed to the *Declaration of Helsinki*. The study involved one visit to the laboratory, which lasted ∼2 h. Intellectual capacity, executive function, walking performance, perceived fatigability, and performance fatigability were assessed during this visit.

Intellectual Capacity

Intellectual capacity was assessed with the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). The test provides a performance intelligence quotient (IQ) score derived from the following: the block design and matrix reasoning subtests, a verbal IQ score based on the vocabulary and similarities subtests, and a Full-4 scale that is a composite of the performance and verbal IQ scores. Verbal performance is resistant to declines caused by the progression of MS and was therefore used to estimate premorbid intellectual capacity (Lezak, 2004; Chiaravalloti and DeLuca, 2008; Sumowski et al., 2009a) and to match control participants with those in the MS group. The Behavior Rating Inventory of Executive Function (BRIEF) served as an additional measure of cognitive function by assessing difficulties in goal-directed behavior during activities of daily living (Roth et al., 2005).

Walking Performance

The 25-foot walk test was used to measure functional capacity of the lower extremities and was performed without the use of orthotic or other assistive devices. Participants were directed to one end of a 25-foot walkway, which was clearly marked with white lines at both ends. The instructions were to walk as quickly as possible, but safely, from one end to the other, and without slowing down until well past the end line. Measurements were made by one of the investigators using a digital stopwatch. The walk was performed a second time in the opposite direction, and the faster of the two times is reported.

Perceived Fatigability

Trait levels of fatigue experienced by participants were quantified using the Modified Fatigue Impact Scale (MFIS) questionnaire, which considers physical, cognitive, and social factors influencing perceived fatigability (Kos et al., 2006). Participants were asked to indicate how often fatigue has had an influence on 21 different situations over the 4 weeks immediately preceding the study. Additionally, participants were asked to report the state level of fatigue at seven instances during a series of fatiguing contractions using the modified Borg scale (6–20) (Borg et al., 1987).

Performance Fatigability

Participants performed 60 intermittent isometric contractions with the knee extensor muscles. After determining maximal voluntary contraction (MVC) torque, participants were asked to increase knee extensor torque to the target (25% MVC torque) displayed on the monitor (gain: 3% MVC force/cm) in front of them and to hold it as steady as possible for 10 s. The investigator verbally prompted the participant to begin each contraction and then to relax for 5 s. This procedure was repeated for 60 contractions. The protocol was performed with both the left and right legs in a randomized order with ∼ 20 min of rest between the two trials. MVC torque was measured before and after the 60 contractions. Performance fatigability was quantified as the change in MVC torque from before to after the intermittent isometric contractions. Rating of perceived exertion (RPE) was measured with the modified Borg scale (6–20) after every 10th contraction. The scale was anchored with six representing rest or no exertion, and 20 corresponding to the strongest possible effort.

Experimental Setup

Participants were seated in an upright position with hips and knees flexed to ∼1.57 rad. A strain gauge force transducer (JR3, Woodland, CA, United States) was positioned to contact the anterior aspect of the lower leg (∼8 cm above the ankle). The applied force was displayed on a monitor located at eye level ∼60 cm in front of the subject. The distance between the axis of rotation for the knee joint and the horizontal plane of the lower leg that contacted the center of the force transducer was measured and used to calculate torque about the knee joint. The upper body was secured to the chair using 5 cm wide nylon straps across the shoulders and lap in order to minimize movement during contractions.

Electromyographic (EMG) signals were recorded from the vastus lateralis muscle using Ag-AgCl surface electrodes (Covidien, Mansfield, MA, United States) arranged in a bipolar configuration. Three pairs of electrodes were placed over the vastus lateralis along a line between the anterior superior iliac spine and the lateral border of the patella in the presumed direction of the muscle fibers. Three reference electrodes were placed over the medial surface of the tibia. EMG signals were amplified (1000×), band-pass filtered (13–1000 Hz) (Coulbourn Instruments, Allentown, PA, United States), sampled at 2 kHz (Cambridge Electronic Design, Cambridge, England, United Kingdom), and stored on a computer (Dell, Plano, TX, United States).

Maximal Voluntary Contractions

Maximal voluntary contraction torque was measured before the 60 contractions to determine maximal knee extensor strength, to provide a reference value for calculating a target torque of 25% MVC, and to record peak EMG activity. MVC torque was measured again immediately after the 60 contractions to assess performance fatigability. MVCs were performed with the knee extensor muscles by gradually increasing torque from rest to maximum over ∼3 s and maintaining this torque for ∼3 s. The investigators provided strong verbal encouragement during each MVC, and the gain of the visual feedback was adjusted between trials. At least two trials were performed with ≥90 s of rest between consecutive trials. If peak torques were not within 5% of each other for the two trials, or if a participant indicated that one of the efforts was not maximal, additional MVCs were performed until these criteria were met. The greatest peak torque during these trials was used as the maximal value.

Data Analysis

Force and EMG data were digitized (Power 1401; Cambridge Electronic Design, Cambridge, England, United Kingdom) and stored on a computer for offline analysis using Spike2 data acquisition/analysis software (Cambridge Electronic Design, Cambridge, England, United Kingdom). Force signals were sampled at 1 kHz.

The maximal EMG amplitude during the MVC trial with the maximal torque was quantified as the root-mean-square (RMS) value during a 0.5 s interval that spanned the peak of the EMG. This value was used to normalize subsequent EMG recordings. EMG data recorded during the 60 contractions were quantified as the normalized RMS value during 8 s intervals for the first, 10th, 20th, 30th, 40th, 50th, and 60th contraction. Torque steadiness was quantified during the same 8-s intervals as the coefficient of variation for torque [% = (SD/mean) × 100; Galganski et al. (1993)].

Statistical Analysis

Dependent *t*-tests were used to compare dependent variables before and after the 60 contractions and independent *t*-tests were used to compare group differences of dependent variables and subject characteristics. Two-factor analysis of variance was used to examine changes in dependent variables measured across the 60 contractions (first contraction, and every tenth

contraction up to the 60th contraction) and differences between the two groups (MS and Control). Dependent variables measured during the fatigue protocol included EMG amplitude for the vastus lateralis muscle, knee extensor torque steadiness (the coefficient of variation for torque), and ratings of perceived exertion. One of the subjects in the MS group was unable to complete all 60 contractions, so data obtained during the last performed contraction were also used for the 50th and 60th contractions. Data collected on both legs were averaged for each participant as there were no significant differences between the left and right legs. Spearman's correlation coefficients were determined between all measures of physical and cognitive function. Correlations were performed separately for the two groups. A significance level for all statistical tests was set at $P \leq 0.05$. Data are presented as mean ± standard deviation (SD) in the text and as mean ± standard error (SE) in the figures.

RESULTS

By design, individuals with MS reported significantly greater levels of trait fatigue than the control (CO) group, as measured with the MFIS questionnaire (**Figure 1A**; MS: 43 ± 14; CO: 11 ± 8, $P \leq 0.001$). In contrast, there were no statistically significant differences between MS and CO groups for verbal IQ (**Table 1**; MS: 112 ± 13; CO: 114 ± 10), as the two groups were matched for this attribute. Performance IQ (MS: 119 ± 14; CO: 122 ± 11) and Full-4 IQ (MS: 118 ± 14; CO: 120 ± 10) also did not differ significantly between the two groups. The overall intellectual capacity of the MS group, therefore, was similar to that for the CO group, despite the MS participants having been diagnosed with the disease for 9.4 ± 6.4 years (range: 0.2–19 years) prior to participating in the study. However, a measure of executive function (BRIEF) was different between groups (MS: 122 ± 19; CO: 90 ± 17, $P \leq 0.001$), indicating lower executive function in the MS participants. Greater BRIEF scores were correlated with greater levels of trait fatigue (MFIS), but this relation was only significant ($P < 0.05$) for the CO group (**Table 2**).

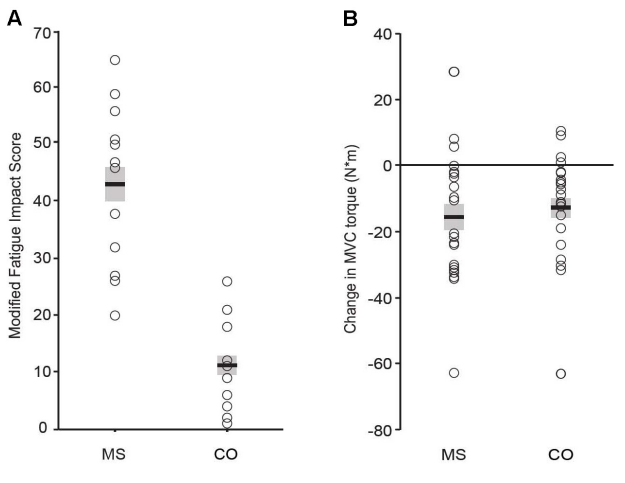

FIGURE 1 | Perceived trait fatigue **(A)**. Reported levels of fatigue (MFIS score) were greater for the MS group ($P = 0.001$). *Performance fatigability* **(B)**. Declines in MVC torque were significant ($P = 0.001$ for both groups) and did not differ between groups ($P = 0.74$).

There were no statistically significant group differences in either the 25-foot walk time (MS: 3.6 ± 0.4 s; CO: 3.3 ± 0.4 s) or knee extensor MVC torque prior to the 60 contractions (MS: 112 ± 38 N·m; 107 ± 44 N·m). Participants performed the 60 contractions with both legs separately due to the possibility of disease progression having an unequal effect on both sides of the body (Chung et al., 2008). However, changes in EMG, RPE, coefficient of variation for torque, and declines in MVC torque did not differ between left and right legs for either group of participants, so data for both legs were averaged for each participant. The two groups exhibited similar significant declines in MVC torque after the 60 contractions (**Figure 1B**; MS: −16 ± 19 N·m; CO: −13 ± 16 N·m).

Normalized EMG amplitude for vastus lateralis (MS: 38 ± 37% increase; CO: 31 ± 24% increase) increased, similarly, between groups ($P = 0.49$) during the 60 contractions (**Figure 2**; $P < 0.001$). Although the coefficient of variation for torque increased for both groups (MS: 66 ± 187% increase; CO: 40 ± 49% increase) during the 60 contractions (**Figure 3**; main effect for time, $P = 0.05$), the MS group was less steady (main effect for group, $P = 0.02$). Increases in coefficient of variation for torque were strongly correlated with increases in EMG amplitude for both MS ($r = 0.73$, $P \leq 0.001$) and CO ($r = 0.61$, $P \leq 0.05$) groups (**Table 2**). In addition, the increase in the coefficient of variation for torque during the 60 contractions observed for the MS group (start: 2.5 ± 1.6%; end: 3.9 ± 4.3%) was inversely correlated (**Table 2**) with two measures of intellectual capacity (Performance IQ: $r = -0.63$, $P \leq 0.05$; Full-4 IQ: $r = -0.64$, $P \leq 0.05$), but not verbal IQ.

Rating of perceived exertion increased for both groups during the 60 contractions (**Figure 4**; $P < 0.001$), but was significantly greater in magnitude (group effect, $P = 0.03$) and increased more for the MS group than the CO group (group × time interaction, $P = 0.05$). The MS group tended to exhibit a greater incidence of reaching maximal effort with 5 participants reaching a final RPE of 20 at the end of the 60 contractions and only one participant for the CO group ($\chi^2 = 3.6$, $P = 0.06$).

DISCUSSION

MS participants had greater trait levels of perceived fatigability (MFIS) and greater state levels of perceived fatigability (RPE) during the intermittent contractions, but similar levels of performance fatigability (decline in MVC force) compared with the control group. Contrary to our hypothesis, there was no association between intellectual capacity and either perceived or performance fatigability. Our main finding was that torque steadiness worsened at a greater rate in the MS group during the fatiguing contractions with the knee extensors and that the change in torque steadiness for the MS group was inversely related to intellectual capacity as measured by performance IQ

TABLE 1 | Subject characteristics.

	Multiple sclerosis (MS) *n* = 12, 1 man	Control (CO) *n* = 12, 1 man
Age (years)	39 ± 15	41 ± 14
Height (cm)	164 ± 5	169 ± 5
Body mass (kg)	58 ± 4	61 ± 8
MFIS	43 ± 14	11 ± 8†
WASI-Verbal	112 ± 13	114 ± 10
WASI-Performance	120 ± 14	122 ± 11
WASI-Full-4	118 ± 14	120 ± 10
BRIEF	122 ± 19	90 ± 17†
25-foot walk (s)	3.6 ± 0.4	3.3 ± 0.4
MVC torque (N·m)	112 ± 38	107 ± 44
MVC decline (N·m)	16 ± 19	13 ± 16

MFIS, Modified Fatigue Impact Scale; WASI, Wechsler Abbreviated Scale of Intelligence; BRIEF, Behavior Rating Inventory of Executive Function; MVC torque indicates the strength of the knee extensor muscle before the 60 isometric contractions, whereas MVC decline refers to the observed decrease in torque after the contractions. †*P ≤ 0.001 between MS and CO groups.*

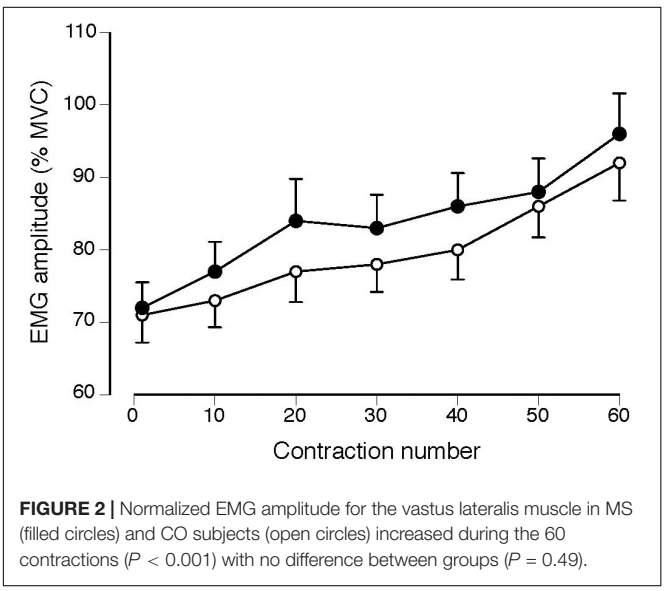

FIGURE 2 | Normalized EMG amplitude for the vastus lateralis muscle in MS (filled circles) and CO subjects (open circles) increased during the 60 contractions ($P < 0.001$) with no difference between groups ($P = 0.49$).

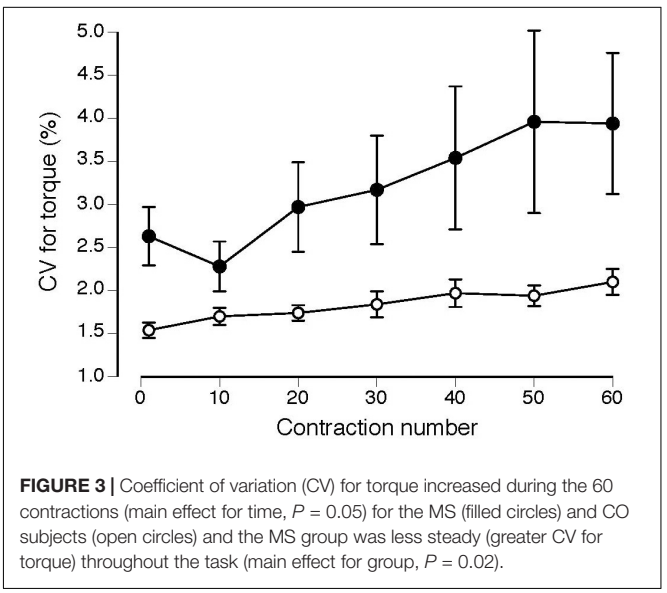

FIGURE 3 | Coefficient of variation (CV) for torque increased during the 60 contractions (main effect for time, $P = 0.05$) for the MS (filled circles) and CO subjects (open circles) and the MS group was less steady (greater CV for torque) throughout the task (main effect for group, $P = 0.02$).

and full-4 IQ, but not verbal IQ. There were no group differences for Performance IQ suggesting that cognitive function, as measured by performing the block design and matrix reasoning tests, was spared in this sample of MS participants. However, differences in performance IQ within the MS group were associated with a reduced ability to maintain a steady muscle contraction with the knee extensors. Further, MS participants had greater impairments in executive function as measured by the BRIEF score. These findings indicate that intellectual capacity as measured by verbal and performance IQ appear to be retained despite 9.4 ± 6.4 years (range: 0.2–19 years) of disease progression, however, executive function may be impaired earlier by MS.

Muscle Activation and Intelligence

Due to the association between the increase in perceived fatigability (RPE) and EMG amplitude during submaximal fatiguing contractions (Hunter et al., 2002; Rudroff et al., 2007), the more rapid increase in RPE for the MS group in the current study should have been accompanied by a quicker increase in EMG amplitude during the fatigue protocol. In contrast, the increase in EMG amplitude for the vastus lateralis muscle was similar for the two groups (**Figure 2**). However, normalized measures of EMG amplitude as recorded with bipolar electrodes are relatively insensitive to modest changes in the underlying motor unit activity (Mottram et al., 2005; Rudroff et al., 2013; Farina et al., 2014).

Nonetheless, the more rapid increase in the coefficient of variation for torque – a measure of torque steadiness – for the MS group suggests that the neural drive to the muscles differed between the two groups during the 60 isometric contractions. The synaptic inputs received by motor neurons arise from three sources: a control signal received by all motor neurons, independent noise, and common noise (Farina and Negro, 2015;

TABLE 2 | Correlation coefficients for pairs of variables are shown for both multiple sclerosis (MS) subjects and control (CO) subjects.

	Verbal IQ	Performance IQ	Full-4 IQ	BRIEF	ΔRPE	Δ MVC	Δ EMG	Δ CV for torque
MFIS	0.06/0.09	−0.36/0.12	−0.15/−0.05	0.33/0.60*	−0.27/−0.10	−0.22/0.45	0.24/0.41	0.10/0.19
Verbal IQ		0.74†/0.55	0.88‡/0.86†	−0.23/−0.09	−0.25/−0.12	0.04/0.49	0.11/−0.13	−0.49/0.02
Performance IQ			0.94‡/0.80†	−0.48/−0.20	−0.21/−0.27	0.15/0.06	−0.24/−0.31	−0.63*/−0.03
Full-4 IQ				−0.36/−0.14	−0.24/−0.19	0.13/0.34	−0.17/−0.11	−0.64*/0.12
BRIEF					0.30/0.43	0.17/0.41	0.34/0.46	0.57/0.57
Δ RPE						0.21/0.23	0.50/−0.01	0.56/0.20
Δ MVC							0.34/0.45	0.23/0.50
Δ EMG								0.73†/0.61*

*Spearman's rank correlations for each pair of variables are presented in the table as MS/CO. Changes in rating of perceived exertion (RPE), maximal voluntary contraction (MVC) torque, electromyography for vastus lateralis (EMG), and coefficient of variation for torque (CV for Torque) refer to differences (Δ) between initial and final measurements. *$P \leq 0.05$, †$P \leq 0.01$ and ‡$P \leq 0.001$.*

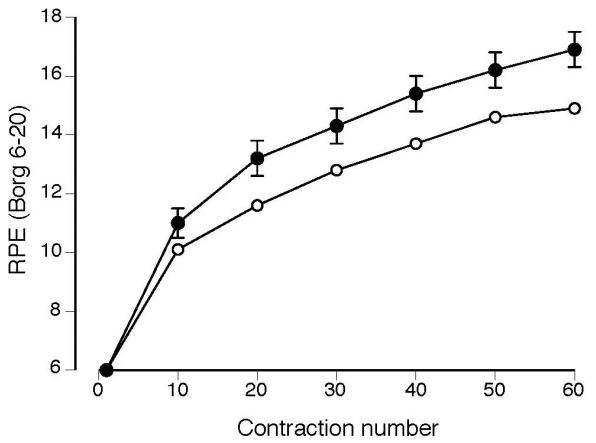

FIGURE 4 | Rating of perceived exertion (RPE) increased more for the MS group (filled circles) during the 60 isometric contractions (group × time interaction, $P = 0.05$) than for the control group (open circles). Values reported as mean ± SE.

Farina et al., 2016). Although the timing of the action potentials discharged by each motor neuron is relatively independent, the control signal to produce the required muscle force (neural drive to muscle) depends on the common synaptic input received by the motor neurons. Critically, there is a strong association between the estimated variance in the common synaptic input to motor neurons and the amplitude of the force fluctuations (force steadiness) during a steady submaximal contraction (Farina et al., 2016; Feeney et al., 2018; Thompson et al., 2018). Thus, the more rapid increase in the coefficient of variation for torque during the fatigue protocol for the MS participants in the current study suggests quantitative differences between the two groups in the variance in the control signal generated by the nervous system during this task.

Consistent with the interpretation of a significant role for motor unit activity in modulating motor function in persons with MS, Almuklass et al. (2018) found that some of the variance in the performance of walking tests by individuals with MS could be explained by the discharge characteristics of motor units during steady submaximal contractions. They found that 40% of the variance in a test of walking endurance (6-min test) and maximal gait speed (25-ft test) could be explained by predictor variables that included the mean interval between consecutive action potentials (interspike interval) for soleus and medial gastrocnemius during submaximal isometric contractions, the strength of the dorsiflexor muscles, and force steadiness of the plantar flexor muscles.

Our findings indicated a strong correlation between the worsening of torque steadiness during the 60 isometric contractions and intellectual capacity for the MS group, but not the control group. Studies that have examined the interactions between cognitive and motor function have shown that the ability to exert a steady force during a voluntary contraction is compromised when the individual is exposed to a cognitive challenge (Zijdewind et al., 2006), and that this effect is greater during fatiguing contractions (Lorist et al., 2002) and in older adults (Vanden Noven et al., 2014; Pereira et al., 2015). Similarly, D'Orio et al. (2012) found that measures of processing speed, executive function, memory and general intelligence were among the cognitive variables that were significantly associated with walking speed and fall frequency in persons with MS. General intelligence as measured by the WASI test was associated with walking speed ($r = -0.272$, $P = 0.017$) as well as frequency of falls ($r = -0.229$, $P = 0.043$). Although measures of intellectual capacity were not correlated with walking performance in our study and time to complete the 25-foot walk did not differ between the two groups, intellectual capacity was inversely correlated with a worsening of torque steadiness during the 60 isometric contractions for the MS group, which may indicate that changes in the neural control of leg muscles may precede declines in walking performance.

Fatigue and Fatigability

Despite greater trait and state levels of perceived fatigability, performance fatigability for the MS participants was not different from control participants. The groups had similar declines in knee extensor torque after the fatigue protocol and similar increases in EMG amplitude. Similarities between groups could not be explained by baseline differences in MVC torque or

mobility as measured by the 25-foot walk test. Steens et al. (2012a) reported similar observations when they compared the decrease in MVC force after a 2-min sustained maximal contraction with a hand muscle exhibited by 20 persons with relapsing-remitting MS and 20 age- and sex-matched control subjects. Based on a multiple-regression analysis to explain the variance in the trait level of fatigue (Fatigue Severity Scale, FSS) for the MS participants, they found that 45% of the variance in the FSS score could be explained by the measure of performance fatigability (decline in MVC force) and normalized muscle strength (MVC force). When a measure of depression (Hospital Anxiety and Depression Scale Questionnaire) was included in the analysis, the regression model explained 77% of variance in the trait level of fatigue (FSS score).

In another study, Steens et al. (2012b) compared the adjustments exhibited by persons with relapsing-remitting MS and control subjects during the 2 min sustained maximal contraction with a hand muscle. As in their other study (Steens et al., 2012a), performance fatigability (decline in MVC force) was similar for the two groups of participants. Nonetheless, there were significant differences between the two groups in the changes in the level of voluntary activation (twitch interpolation technique) and cortical activation as determined with functional MRI. Compared with the control subjects, the MS participants exhibited a more substantial and variable reduction in voluntary activation and less of an increase in cortical activation during the fatiguing contraction. A multiple-regression analysis indicated that control subjects who were stronger experienced greater performance fatigability, as reported in other studies (Hunter and Enoka, 2001; Keller-Ross et al., 2014), and that performance fatigability for the individuals with MS was less for those who could sustain greater levels of voluntary activation (Wolkorte et al., 2016).

Based on the results of Steens et al. (2012b), a greater increase in perceived fatigability (RPE) during the fatigue protocol in our study might be explained by a tendency for persons with MS to experience a greater reduction in voluntary activation during fatiguing contractions. Thus, it is necessary for these individuals to increase the levels of cortical activation to achieve the submaximal target torque during the fatigue protocol.

Limitations

Although our study enrolled relatively few participants with a heterogeneous disease status, one of its strengths was that the participants in the MS group reported greater levels of trait fatigue despite no significant group differences in intellectual capacity, strength, or walking speed, as such differences may have influenced measured levels of trait fatigue. Consequently, our findings may not generalize to a wider population of individuals with MS who have varying levels of disability. Also, we did not control the medications being taken by our participants to treat symptoms other than to ensure that they were on stable doses of medications.

CONCLUSION

Although our study found no statistically significant associations between the trait level of fatigue and measures of performance and perceived fatigability for the MS participants during a series of intermittent isometric contractions, intellectual capacity was associated with adjustments in torque steadiness during the fatiguing contraction. This finding substantiates further inquiry into the utility of the performance IQ score to detect changes in neuromuscular function that precede physical disability due to disease progression in persons with MS.

AUTHOR CONTRIBUTIONS

JG contributed to the conception of the study, participant recruitment and testing, data analysis and interpretation, and writing and approval of the manuscript. AR and BC contributed to participant recruitment and testing, data analysis, and writing and approval of the manuscript. KK and GC contributed to testing, data analysis, and approval of the manuscript. MB and JC contributed to conception of the study, participant recruitment, data interpretation, and approval of the manuscript. RE contributed to conception of the study, participant recruitment, data interpretation, and writing and approval of the manuscript.

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Self-Reported Fatigue After Mild Traumatic Brain Injury Is Not Associated With Performance Fatigability During a Sustained Maximal Contraction

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Patients with mild traumatic brain injury (mTBI) are frequently affected by fatigue. However, hardly any data is available on the fatigability of the motor system. We evaluated fatigue using the Fatigue Severity Scale (FSS) and Modified Fatigue Impact Scale (MFIS) questionnaires in 20 participants with mTBI (>3 months post injury; 8 females) and 20 age- and sex matched controls. Furthermore, index finger abduction force and electromyography of the first dorsal interosseous muscle of the right hand were measured during brief and sustained maximal voluntary contractions (MVC). Double pulse stimulation (100 Hz) was applied to the ulnar nerve to evoke doublet-forces before and after the sustained contraction. Seven superimposed twitches were evoked during the sustained MVC to quantify voluntary muscle activation. mTBI participants reported higher FSS scores (mTBI: 5.2 ± 0.8 *SD* vs. control: 2.8 ± 0.8 *SD*; $P < 0.01$). During the sustained MVC, force declined to similar levels in mTBI (30.0 ± 9.9% MVC) and control participants (32.7 ± 9.8% MVC, $P = 0.37$). The decline in doublet-forces after the sustained MVC (mTBI: to 37.2 ± 12.1 vs. control: to 41.4 ± 14.0% reference doublet, $P = 0.32$) and the superimposed twitches evoked during the sustained MVC (mTBI: median 9.3, range: 2.2–32.9 vs. control: median 10.3, range: 1.9–31.0% $doublet_{pre}$, $P = 0.34$) also did not differ between groups. Force decline was associated with decline in doublet-force ($R^2 = 0.50$, $P < 0.01$) for both groups. Including a measure of voluntary muscle activation resulted in more explained variance for mTBI participants only. No associations between self-reported fatigue and force decline or voluntary muscle activation were found in mTBI participants. However, the physical subdomain of the MFIS was associated with the decline in doublet-force after the sustained MVC ($R^2 = 0.23$, $P = 0.04$). These results indicate that after mTBI, increased levels of self-reported physical fatigue reflected increased fatigability due to changes in peripheral muscle properties, but not force decline or muscle activation. Additionally, muscle activation was more important to explain the decline in voluntary force (performance fatigability) after mTBI than in control participants.

Keywords: mTBI, motor task, force decline, voluntary muscle activation, interpolated twitch technique, first dorsal interosseous

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INTRODUCTION

Traumatic brain injury is a serious health problem and one of the most important causes of impairment in adults; most cases sustain a mild traumatic brain injury (mTBI; Cassidy et al., 2014; Levin and Diaz-Arrastia, 2015). Despite the fact that most patients recover from mTBI, 15–20% of patients have persistent symptoms (Cassidy et al., 2014; Levin and Diaz-Arrastia, 2015) and fatigue is among the most frequently occurring complaints (van der Naalt et al., 1999; Lundin et al., 2006; Lannsjö et al., 2009; Mollayeva et al., 2014). Fatigue is a disabling symptom because it impairs physical and social functioning, and it impedes return to work (van der Naalt et al., 1999, 2017; Stulemeijer et al., 2006; de Koning et al., 2017).

Nowadays, the term fatigue is most often reserved for the self-reported symptom which can be evaluated using questionnaires. According to the taxonomy proposed by Kluger and colleagues, fatigue is mediated by two attributes (Kluger et al., 2013). The first attribute, perceived fatigability, corresponds to changes in subjective sensations occurring at rest or in the context of task performance and derives from psychological and homeostatic factors (Enoka and Duchateau, 2016). The second attribute, performance fatigability, relates to impaired task performance and is defined as the decline in an objective measure of performance over a discrete period of time (e.g., a decline in voluntary force or power during sustained contractions; Enoka and Duchateau, 2016). Although perceived and performance fatigability are distinct qualities they can interact.

So far, most studies investigating fatigue following mTBI have focussed on the relationship between self-reported fatigue and cognitive task performance (Möller et al., 2014, 2017; Nordin et al., 2016; Wylie and Flashman, 2017). Although the impact of mTBI on cognitive parameters is prominent, few groups also report (long-lasting) impairments in motor parameters including: a small reduction in voluntary drive (Powers et al., 2014), inhibitory changes in the primary motor cortex (De Beaumont et al., 2009), and reduced walking speed in a dual-task condition (Yasen et al., 2017). However, no data is available on the fatigability of the motor system in mTBI.

Another neurological patient population suffering from fatigue is multiple sclerosis (MS). Previous studies by our lab showed that self-reported fatigue in persons with MS was associated with measures of performance fatigability during a sustained maximal contraction These studies provided the rationale and experimental framework to investigate fatigue following mTBI (Steens et al., 2012; Wolkorte et al., 2015a). Although differences in the pathophysiology of MS and mTBI are evident, the conditions have aspects in common including neuroinflammation and loss of white matter integrity (Compston and Coles, 2008; Andriessen et al., 2010; Johnson et al., 2013; Tremblay, 2014; Armstrong et al., 2016). Since white matter integrity is essential for maintaining optimal activation of motoneurons during voluntary muscle contractions, we expect that mTBI will result in reduced voluntary activation of muscle fibers and affect measures of performance fatigability.

Therefore, it was the aim of the present study to assess the neuromuscular factors contributing to performance fatigability after mTBI, and to appraise these findings in the context of the increased levels of self-reported fatigue that occur post-injury. We hypothesize that mTBI may impair voluntary drive, thereby reducing muscle activation and leading to increased performance fatigability. Also, that this change might partially explain the increased levels of self-reported fatigue following mTBI. Furthermore, by investigating fatigue and fatigability using the same paradigm that was previously used in MS, we hope to increase the understanding of fatigue in neurological populations.

MATERIALS AND METHODS

Study Population

Twenty-two patients with mTBI and 22 age- and sex-matched control participants were included. mTBI was defined by a Glasgow coma scale score between 13–15 on admission, with posttraumatic amnesia less than 24 h and/or loss of consciousness of less than 30 min. Inclusion criteria included persistent complaints of (self-reported) fatigue for more than 3 months post injury and adequate hand dexterity (to perform the motor tasks). Exclusion criteria included psychiatric disorder, neurologic disease (including previous TBI), and drug or alcohol abuse. Data from the control subjects were also used in an accompanying study (Sars et al., 2018). Experiments were designed in accordance with the declaration of Helsinki (World Medical Association, 2013) and approval of the experimental procedures was provided by the medical ethical board of the University Medical Center Groningen. Written informed consent was obtained from all participants before the experiment.

Questionnaires and Cognitive Testing

For the mTBI patients, self-reported fatigue was quantified using two questionnaires: the Fatigue Severity Scale (FSS; Krupp et al., 1989) and the Modified Fatigue Impact Scale (MFIS; Multiple Sclerosis Council for Clinical Practice Guidelines, 1998; Schiehser et al., 2015). Mood was evaluated using the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983). Cognitive impairment and attentional processing were assessed in mTBI participants using the written form of the Symbol Digit Modalities Test (SDMT; Smith, 1982) and the 3 s Paced Auditory Serial Addition Test (PASAT'3; Gronwall, 1977; McCauley et al., 2014), respectively. Handedness was evaluated using the Edinburgh inventory (Oldfield, 1971).

Force Recording

Index finger abduction force was measured using hand-held transducers (van Duinen et al., 2007; **Figure 1A**). Participants held the transducers with their index fingers extended. The horizontal bar of the transducer was aligned parallel to the index finger and the finger bracket was positioned over the proximal interphalangeal joint. The thumb was taped to digits III-IV to maintain this hand position throughout the experiment. Force signals was sampled at 500 Hz using a 1401 interface and recorded on a computer with Spike 2 software (version 7.12, Cambridge Electronic Design, Cambridge, United Kingdom).

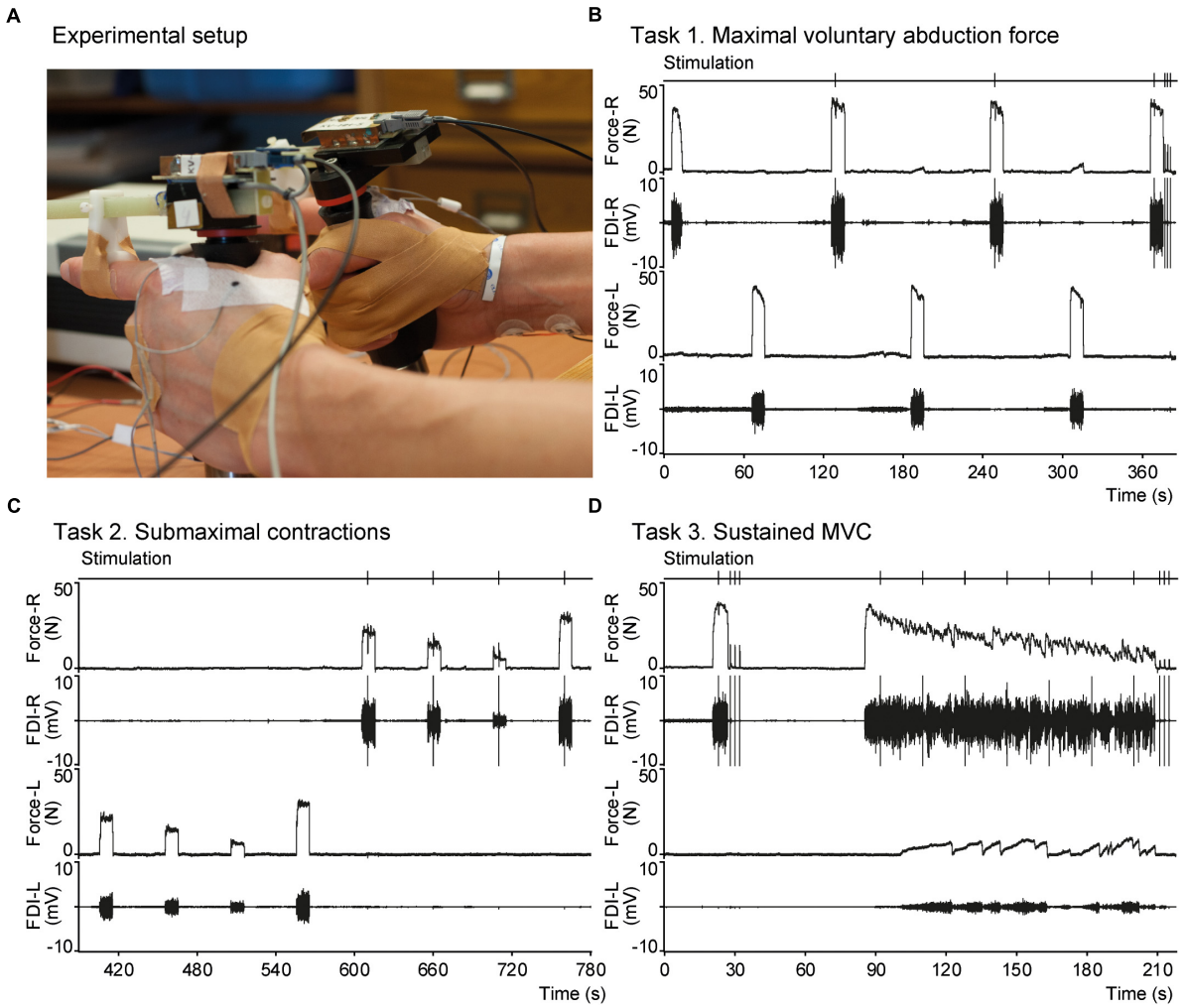

FIGURE 1 | Experimental setup and an example of raw data. **(A)** Photograph showing the hands a participant equipped with force transducers. The finger bracket is positioned over the proximal interphalangeal joint of the index fingers as can be seen for the left hand. Placement of EMG electrodes over the FDI can be seen for the left hand and electrodes used for electrical stimulation can be seen on the right wrist. **(B–D)** Panels showing raw data recorded in a male mTBI participant during tasks 1–3, respectively. From top to bottom each panel shows the time-points of electrical nerve stimulation, index finger abduction force of the right hand, EMG of the right FDI, force of the left hand, and EMG of the left FDI. MVC, maximal voluntary contraction; FDI, first dorsal interosseous.

Electromyography

Surface EMG was recorded from the first dorsal interosseous (FDI) of both hands using sintered silver/silver chloride electrodes (In Vivo Metric, Healdsburg, United States). After cleaning the skin with alcohol, one electrode was applied over the muscle belly of each muscle and the second electrode was applied over the adjacent metacarpophalangeal joint. A reference electrode was applied over the right wrist. EMG signals were amplified (200 V/V) using custom-made amplifiers, band-pass filtered (10–1000 Hz), and sampled (at 2000 Hz) using the same interface as the force signals.

Electrical Nerve Stimulation

Voluntary muscle activation of the right FDI was determined using the interpolated twitch technique (Merton, 1954; Behm et al., 1996; Gandevia, 2001). The ulnar nerve was electrically stimulated using a constant-current stimulator (pulse width 200 μs; DS7A, Digitimer, Welwyn Garden City, United Kingdom) via a pair of self-adhesive electrodes applied over the ulnar nerve close to right wrist. Stimulation intensity was set to ≥130% of the intensity required to evoke a maximal M-wave in the FDI (range: 39–100 mA). During the experimental tasks, forces were evoked using double pulses (10 ms interval) to improve the signal-to-noise ratio (Gandevia and McKenzie, 1988). The forces evoked at rest are referred to as doublet-force; to comply with previous literature, we use the term superimposed twitch (SIT) for the forces evoked during voluntary contractions.

Motor Tasks

Participants performed three isometric motor tasks in which they were asked to abduct their index finger. Participants were seated

behind a desk and could see their force production on a monitor in front of them during the tasks (see **Figure 1**).

Task 1 Maximal Voluntary Contraction (MVC)

Participants generated three maximal isometric index finger abductions (10 s) with the left hand and four with the right hand, alternating between hands. Contractions were followed by 50 s rest between subsequent contractions. A superimposed twitch was evoked during at least two maximal contractions with the right hand (∼3 s after the start of the contraction) and three doublet-forces were evoked at rest after the last contraction (2 s interval) to obtain potentiated doublet-forces.

Task 2 Submaximal Contractions

To determine differences in voluntary activation with a different method we also evoked superimposed twitches during submaximal contractions (De Serres and Enoka, 1998). Participants had to match their force level to a horizontal line indicating target force at 10, 30, 50, and 70% MVC. Three blocks were performed with each hand, alternating between the left and right hand (12 contractions per hand). Each contraction was sustained for 10 s with 40 s rest between contractions. A superimposed twitch was evoked during at least two sets of four contractions with the right hand.

Task 3 Sustained MVC

Participants generated a brief maximal index finger abduction for 6 s followed by 60 s rest. Next, participants generated a sustained MVC lasting 124 s. Superimposed twitches were evoked once during the brief MVC and at seven time points during the sustained MVC (18 s interval). Three doublet-forces (2 s interval) were evoked at rest after the brief MVC ($doublet_{pre}$) and after the sustained MVC ($doublet_{post}$).

Analysis

Questionnaire and cognitive test scores were calculated. PASAT scores below the 5th percentile of the normative scores (i.e., $<32/60$ for ≤ 12 years of education and $<35/60$ for >12 years of education) were indicative of impairment (Rao et al., 1991). SDMT scores were expressed as a *T*-score of the normative data matched for age and education (Smith, 1982). FSS scores were indicative of fatigue if a participants scored greater than the cut-off of 4.5 (Flachenecker et al., 2002), and greater than 29 in the case of MFIS total scores (Schiehser et al., 2015).

Force and EMG data were processed in Spike 2; EMG signals were transformed by calculating the root mean square (rms) over a moving window of 500 ms. Maximal force and rms-EMG were determined for the MVCs. The largest of the three potentiated doublet-forces evoked at rest was taken as the reference value and the superimposed twitches evoked during the maximal and submaximal contractions in task 1 and 2 were expressed as a percentage of this force.

During the sustained MVC, force and rms-EMG at the start and the end of the sustained contraction were average over 6 s and expressed as a percentage of maximal force and rms-EMG, respectively. Furthermore, force and rms-EMG during the sustained MVC were averaged over 2 s epochs (62 epochs in total, the 7 epochs which overlapped the electrical stimulation were excluded from statistical analysis), and normalized to maximal force and rms-EMG obtained during the MVC (task 1). The coefficient of variation (CV_{force}) for the right index finger abduction force was calculated by dividing the standard deviation during the 2 s epoch by the mean force. The superimposed twitches during the sustained MVC were linearly corrected for the decline in muscle force (due to factors within the muscle) using the following formula (Schillings et al., 2003):

$$\textit{Corrected SIT at time } t = \frac{SIT_t}{doublet_{pre} - (time_t/124s) \times (doublet_{pre} - doublet_{post})} \times 100\%$$

with t as the time of stimulation, and $doublet_{pre}$ and $doublet_{post}$ as the doublet-force prior to and after the sustained contraction, respectively.

Statistical Analysis

Statistical analysis was performed in R studio (R version 3.4.3). Normality was assessed graphically using quantile–quantile plots. Group comparisons of questionnaire scores and motor task parameters were performed by ANOVA with sex included as covariate in the analysis of motor parameters in order to better explain the remaining variance. Non-normally distributed data were transformed to obtain a normal distribution of the ANOVA residuals (Prescott, 2018). If transformation could not achieve a normal distribution of the model residuals, Mann–Whitney *U* tests were used. Values in the text are shown as mean (SD) for normally distributed data or median (range) for non-normally distributed data.

Multilevel modeling was used to analyze the superimposed twitches during the submaximal contractions (task 2). Pre-planned statistical models were used to describe the relationship between the size of the SITs and the force level at the time of stimulation. Next, group was added as a fixed effect to assess differences between mTBI and control participants, followed by sex.

To describe the changes over time, multilevel modeling was performed for the force, rms-EMG, and CV_{force} during the sustained MVC. Pre-planned statistical models were used to describe these time-related changes. We started with a simple model in which the intercept was allowed to vary randomly per participant. More complex models were constructed including time and the 2nd and 3rd degree polynomials of time as fixed effects, as well as random slopes for each of these variables per participant. After each step, statistical analysis determined whether the more complex model survived; the more complex model explained the data significantly better than the previous model if the Akaike information criterion (AIC) decreased by at least 2. For all parameters (force, rms-EMG, and CV_{force}) the models including (2nd and 3rd) polynomials of time and random intercepts and slopes explained significantly more variance. Therefore, in the results section we only describe whether the more complex models in which group, sex, and interactions were added explained (significantly) more variance than this

basic model. Next, group (mTBI) was added to the basic model as a fixed effect. Since sex and age can affect the time-related changes in force and EMG (Sars et al., 2018), we subsequently included these variables and their interactions to the model in a stepwise fashion. Model residuals were examined graphically for normality and heteroscedasticity (using quantile-quantile plots and heteroscedasticity plots) for all multilevel models. If required, the dependent variable was transformed to meet these criteria. Finally, robustness of the final models was tested by re-estimating the model on a trimmed dataset. This was done by first identifying the data points with scaled residuals greater than 2 for the corresponding model. These data points (model outliers) were then removed from the dataset and the model was re-estimated.

Associations between self-reported fatigue and the measures of performance and perceived fatigability were examined in mTBI participants. For this analysis, the MVC of the mTBI participants was expressed as a *Z*-score (calculated using the mean and standard deviation of MVCs in the control group, per sex). Associations were analyzed between force decline, voluntary muscle activation, and the change in doublet-force after the sustained MVC. Associations between two nominal variables were analyzed using Spearman's rank test (e.g., FSS and HADS scores). Linear regression was used for the associations between continuous variables and for multivariate analyses. Model residuals were examined for normal distribution using quantile-quantile plots.

RESULTS

One mTBI participant had problems performing stable MVCs and the SIT deviated more than three SD from the mean. Another mTBI participant did not perform the sustained contraction adequately and showed progressively increasing force during the first minute. These two participants were excluded from all analyses. To maintain balanced groups, the two matched control participants were also excluded. The mean age of the remaining mTBI participants was 40.1 years (range: 23–56, 8 females) and 41.1 years in controls (range: 21–59, 8 females). One mTBI participant stopped contracting during the sustained MVC after 84 s. The data up to this time point were included in the analysis, however, this participant was excluded from all analyses regarding associations of self-reported fatigue and performance fatigability (we also checked whether inclusion of this subject affected our conclusion). Demographics and injury characteristics of the mTBI participants are shown in **Table 1**.

Questionnaires

Participants with mTBI reported higher levels of fatigue and depression. The FSS scores were increased in mTBI compared to controls (5.2 ± 0.8 *SD* vs. 2.7 ± 0.8 *SD*, $P < 0.01$), and 15 out of the 20 mTBI participants scored greater than the cut-off of 4.5 indicative of fatigue (Flachenecker et al., 2002). The median MFIS score reported by the mTBI participants was 51 (range: 25–71); all but one participant scoring above the cut-off score of 29 for fatigue (Schiehser et al., 2015). Scores on the MFIS subdomains are shown in **Table 2**. Furthermore, scores on the depression domain of the HADS were higher in mTBI (median: 7, range: 2–14) than in control participants (median: 0, range: 0–2, $P < 0.01$).

Cognitive Tests

The median score on the PASAT'3 was 49.5/60 correct responses (range: 31–59). One mTBI participant scored below the 5th percentile cut-off (i.e., <32/60 correct responses for an individual with <12 years of education; Rao et al., 1991). The median score on the SDMT was 51.5 (range: 36–72). Data were expressed as a *T*-score, corrected for age and education. The mean *T*-score was 41.7 (range: 30–75; Smith, 1982). Four participants had *T*-scores below the normal range (≤40); one of these participants fell in the category 'very low' (*T*-score ≤ 30).

Baseline Measurements

Index finger abduction MVCs of the right hand did not differ between mTBI participants (40.5 ± 8.6 N) and controls (38.0 ± 11.2 N, $F_{1,37} = 0.97$, $P = 0.33$; with sex included as a covariate, see **Table 3**). Similar outcomes were observed for the left hand (**Table 3**).

The potentiated doublet-forces at rest were also not different between mTBI (12.9 ± 2.4 N) and controls (11.1 ± 3.6 N, $F_{1,37} = 3.91$, $P = 0.06$, with sex included as a covariate, **Table 3**). The superimposed twitches during the brief MVC were also

TABLE 1 | Demographics and injury characteristics of mTBI participants.

	mTBI (*n* = 20)
Sex	
Male	12
Female	8
Mean age (years)	40.1 (10.9)
GCS on admission	
13	5
14	13
15	2
Mechanism of injury	
Fall	4
Traffic accident	10
Sports injury	4
Violence	1
Occupational injury	1
Median time since injury (months)	5 (3–18)
Education level*	
4	5
5	4
6	10
7	1

*Data shown as n, mean (SD), or median (range). *Education level is provided on a Dutch 7-point scale (levels 5–7 refer to completion of different levels of higher education; for details see: Schaart et al., 2008). GCS, Glasgow Coma Scale.*

TABLE 2 | Questionnaire scores.

	Control (n = 20)	mTBI (n = 20)	P-value
FSS	2.8 (0.8)	5.2 (0.8)	<0.01*
MFIS	–	51 (25–71)	–
MFIS physical	–	19.5 (5–32)	–
MFIS cognitive	–	27 (16–35)	–
HADS depression	0 (0–2)	7 (2–14)	<0.01*
HADS anxiety	4 (0–7)	6 (4–12)	<0.01*
Edinburgh inventory	85 (50–100)	90 (−100–100)	0.93

*Data shown as mean (SD) or median (range). * Indicates statistically significant difference (P < 0.05). FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; HADS, Hospital Anxiety and Depression Scale.*

similar for the two groups (mTBI median: 3.9, range: 0.0–17.3 vs. control median: 2.8, range: 0.9–15.4% potentiated doublet-force, $F_{1,38} = 0.08$, $P = 0.78$; after logarithmic transformation. See **Figure 2A**).

Voluntary Muscle Activation During the Submaximal Contractions

The superimposed twitches during the submaximal contractions were modeled using a multilevel model. The size of the superimposed twitches could be explained by a model including background force as fixed factor ($\beta = -1.09$, $t = -42.18$, $P < 0.01$) as well as random intercepts and slopes for force per participant. The model did not show significant improvement after including group or sex as fixed-factors. Thus, the twitch becomes on average 10.9% smaller when the voluntary background force increases with 10% MVC but we found no differences in the evoked twitches between controls and mTBI (see **Figure 2B**).

Voluntary Force and rms-EMG During the Sustained MVC

During the sustained contraction the force during the first 6 s (control: 81.8 ± 7.7 vs. mTBI: 80.8 ± 8.9% MVC) and last 6 s (control: 32.7 ± 9.8 vs. mTBI: 30.0 ± 9.9% MVC) did not differ between groups (**Table 3**). A difference was observed, however, between males and females ($F_{1,36} = 7.57$, $P < 0.01$) indicating a larger force decline in male participants (**Table 3**).

Instead of only using the data obtained at start and the end of the sustained contraction, we modeled the time course of the force. Adding group or sex to the *basic model* (see section "Materials and Methods") did not result in a significant model improvement (group: Δ AIC = −1.9, sex: Δ AIC = −0.2). However, the model improved after including the interaction between sex and time (sex * time: $\beta = 4.968$, $t = -2.20$, $P = 0.03$; Δ AIC = −2.7). No interaction was observed for time * group. These results demonstrate that male participants showed a larger force decline over time, without a difference between mTBI and control participants (see **Figures 3A,B**).

The model explaining the variance of the rms-EMG of the right FDI did not improve after including group (Δ AIC = 2.0). However, the *basic model* improved significantly after including sex (Δ AIC = −2.6; sex: $\beta = 2.10$, $t = 2.28$, $P = 0.03$), indicating that rms-EMG was lower in male participants (see **Figures 3C,D**). Next, a significant interaction was found for sex * group, but including this interaction did not significantly improve the model ($t = -2.62$, $P = 0.01$; Δ AIC = −1.9).

Finally, the coefficient of variation of the force of the right hand (CV_{force}) was examined. To obtain a normal distribution of the residuals, CV_{force} was transformed using a power transformation ($\lambda = 0.1$). Including group, sex, and age in the *basic model* did not significantly improve the model. Thus,

TABLE 3 | Motor parameters.

		Control (n = 20)	mTBI (n = 20)	P-value	
				Group	Sex
Baseline parameters					
MVC right (N)	M	43.3 (10.7)	44.8 (7.6)	0.33	<0.01*
	F	30.0 (6.2)	34.0 (5.4)		
MVC left (N)	M	53.6 (13.0)	55.4 (9.0)	0.76	<0.01*
	F	40.6 (8.0)	40.3 (5.6)		
Reference doublet-force (N)	M	11.3 (4.3)	13.9 (2.3)	0.06	0.14
	F	10.8 (2.5)	11.5 (1.8)		
MVC superimposed twitch (%reference)		2.8 (0.9–15.4)	3.9 (0.0–17.3)	0.78	
Sustained MVC					
Force first 6 s (% MVC)		81.8 (7.7)	80.8 (8.9)	0.71	
Force last 6 s (% MVC)	M	30.7 (10.1)	25.2 (9.3)	0.37	<0.01*
	F	35.7 (9.2)	36.6 (6.7)		
Mean SIT (% reference; n = 7)		10.3 (1.9–31.0)	9.3 (2.2–32.9)	0.34	
$Doublet_{post}$ (% reference)	M	40.1 (16.3)	33.7 (11.8)	0.32	0.18
	F	43.4 (10.4)	42.1 (11.4)		

*Data shown as mean (SD) or median (range). P-values are shown for group only or for group and sex if sex was a significant covariate in the ANOVA. * Indicates statistically significant difference (P < 0.05). M, male; F, female; MVC, maximal voluntary contraction; SIT, superimposed twitch.*

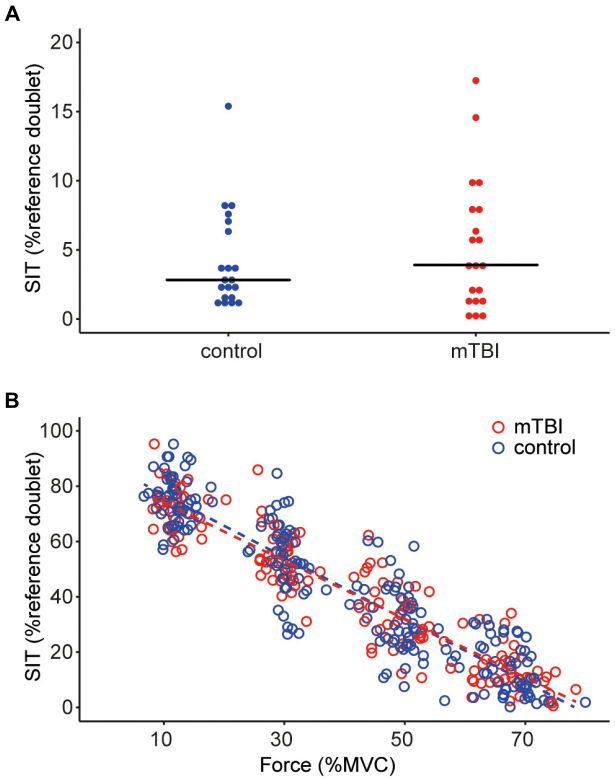

FIGURE 2 | (A) Dot plot showing the size of the superimposed twitches during the maximal voluntary contractions in task 1, values are rounded to the nearest 0.5%. The horizontal line indicates the median for the control participants (blue dots) and mTBI participants (red dots). **(B)** Superimposed twitches evoked during the submaximal contractions (at 10, 30, 50, and 70% MVC) in task 2. Control data is shown in blue, mTBI in red. A linear regression line is shown for both groups, but no significant differences were observed between control and mTBI participants. SIT, superimposed twitch.

CV_{force} increased over time but no differences were found between groups or sex.

During the sustained contraction the contralateral, non-target FDI also becomes (unintentionally) active (Zijdewind and Kernell, 2001). Both contralateral force and rms-EMG were log transformed to improve distribution of the residuals. Both parameters increased over time and were best fit by the *basic model*, but no differences were observed between groups or sex.

Because one participants stopped the sustained MVC after 84 s, the multilevel analyses were repeated without this participant. This did not affect the conclusion for any of the parameters.

Voluntary Muscle Activation During the Sustained Contraction

The time-course of the superimposed twitches before and during the sustained MVC) was modeled using a multilevel model. SITs were transformed by taking the square root. The model included time as fixed-factor (time: $\beta = 0.99$, $t = 4.31$, $P < 0.01$) and random intercept and slope for time per participant. The model indicates an increase in the size of the superimposed twitches over the course of the sustained contraction (i.e., a decrease in voluntary muscle activation), and no differences between mTBI and control participants (**Figure 4**). The mean of the seven superimposed twitches during the sustained MVC did not differ significantly between mTBI (median: 9.3 range: 2.2–32.9, $n = 19$) and control participants (median: 10.3, range: 1.9–31.0% $doublet_{pre}$, $F_{1,37} = 0.92$, $p = 0.34$; after square root transformation of the mean SIT).

Doublet-Forces After the Sustained Contraction

The doublet-force evoked after the sustained contraction declined in mTBI (to 37.2 ± 12.1% reference doublet-force, $n = 19$) and control participants (to 41.4 ± 14.0% reference doublet-force) but did not differ between groups ($F_{1,36} = 1.03$, $P = 0.32$; with sex included as a covariate).

Associations Between Self-Reported Fatigue and Measures of Fatigability

Since mTBI participants reported significantly higher FSS scores than control participants, we analyzed associations between these questionnaires with different measures of fatigability for the mTBI participants only.

In mTBI participants ($n = 20$), no significant relationship was observed between the FSS scores and the HADS depression scores ($P = 0.13$). MFIS scores were, however, significantly correlated with HADS depression scores (rho = 0.73, $P < 0.01$); the association between HADS was also observed for the physical subdomain of the MFIS (rho = 0.70, $P < 0.01$), as well as the cognitive subdomain (rho = 0.52, $P = 0.02$). FSS or MFIS scores did not show significant associations with the raw PASAT or SDMT scores.

Linear regression of FSS or MFIS with force decline and MVC *Z*-scores (conform Steens et al., 2012) did not produce a significant association (FSS: $P = 0.29$; MFIS: $P = 0.92$, $n = 19$). However, a significant negative association was observed between the MFIS physical subscale and the decline in doublet-force ($R^2 = 0.23$, $P = 0.04$, $n = 19$; **Figure 5**).

Associations With Force Decline

Force decline ($n = 39$) during the sustained contraction (i.e., force during last 6 s/first 6 s) was negatively associated with the MVC ($R^2 = 0.17$, $P < 0.01$) and positively associated with the decline in doublet-force ($R^2 = 0.50$, $P < 0.01$; **Figure 6**). Force decline was not associated with voluntary muscle activation during the sustained MVC (i.e., mean SIT; $P = 0.10$). Analyzing force decline for the mTBI ($n = 19$) and control groups ($n = 20$) separately, the decline in doublet-force was able to explain more variance in control ($R^2 = 0.53$, $P < 0.01$) than in mTBI participants ($R^2 = 0.45$, $P < 0.01$). However, in mTBI participants significantly more variance ($P = 0.03$) could be explained by including voluntary muscle activation (mean SIT) in the model together with the decline in doublet-force ($R^2 = 0.59$, $P < 0.01$;

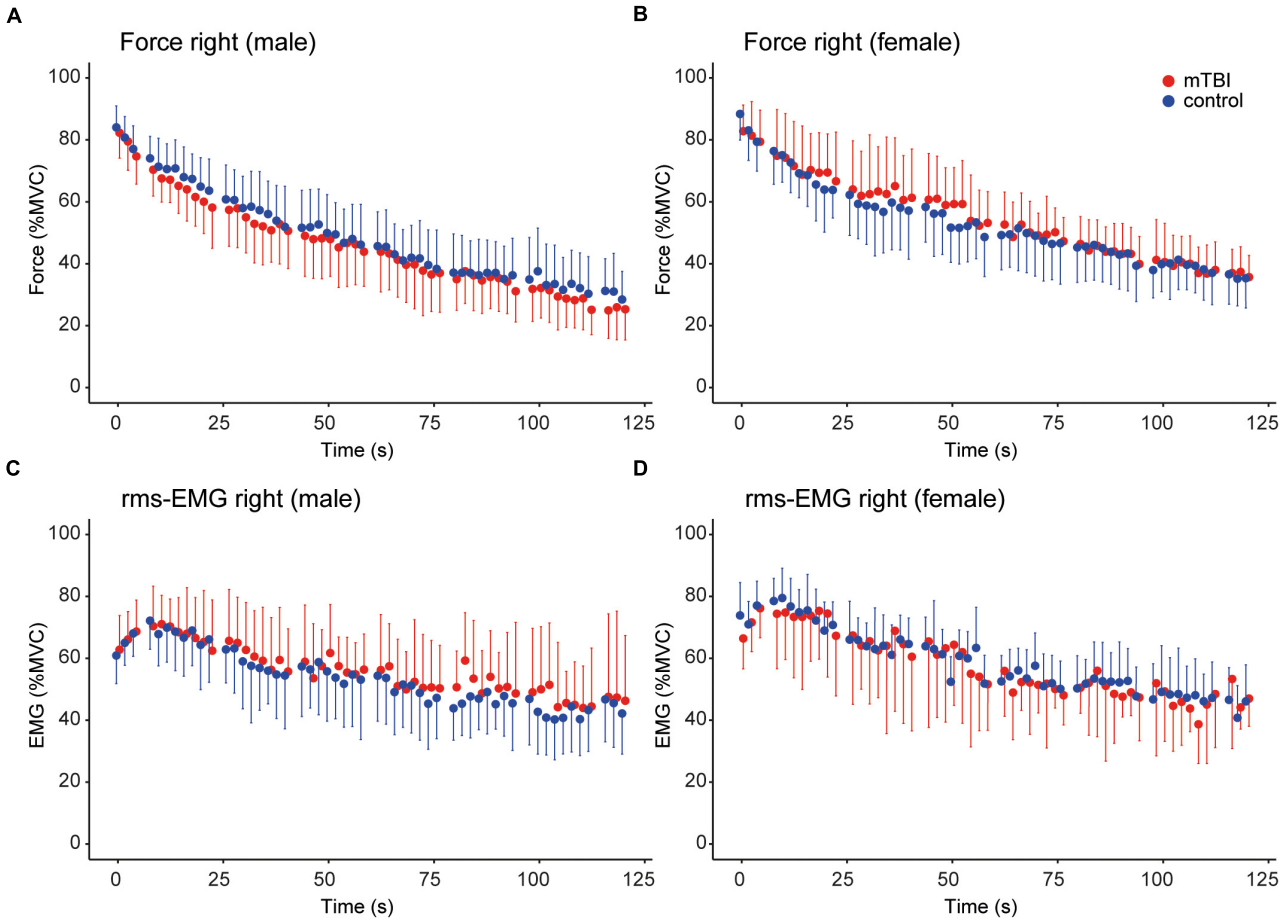

FIGURE 3 | Time course of the force and rms-EMG of the right hand during the sustained MVC. For all panels, control data (n = 20) is shown in blue and mTBI (n = 20) in red. **(A,B)** Force (averaged over 2 s epochs) during the sustained MVC in male and female participants. **(C,D)** Mean rms-EMG (averaged over 2 s epochs) in male and female participants. Error bars in **(A–D)** show the standard deviation.

mean SIT: $\beta = -4.03$, $P = 0.03$, $\text{doublet}_{\text{post}}$: $\beta = 0.73$, $P < 0.01$). Including the voluntary muscle activation was not able to improve the model in controls.

DISCUSSION

Consistent with literature (van der Naalt et al., 1999; Lundin et al., 2006; Stulemeijer et al., 2006; Lannsjö et al., 2009), participants with mTBI reported increased levels of fatigue and depression at more than 3 months post injury compared to control participants. No force or EMG differences were observed between groups during the sustained contraction reflecting similar levels of performance fatigability. Although individual differences in force decline could best be explained by changes in muscle properties (i.e., the decline in the doublet-force; see **Figure 6**), in mTBI participants the remaining variance could be explained by differences in voluntary muscle activation (i.e., mean SIT). Furthermore, (moderate) associations were found between scores on the physical subdomain of the MFIS questionnaire and the decline in doublet-force after the sustained contraction in mTBI participants.

Fatigue and Performance Fatigability After mTBI

As expected, participants with mTBI reported increased levels of fatigue at more than 3 months post injury (van der Naalt et al., 1999; Lundin et al., 2006; Stulemeijer et al., 2006; Lannsjö et al., 2009); indicated by both FSS and MFIS scores. However, contrary to our expectations, performance fatigability in mTBI participants did not differ from age- and sex-matched controls.

The injury mechanism of mTBI has been well described. Impact-acceleration forces cause axonal injury and white matter tracts of the anterior corona radiata and corpus callosum are among the regions which are frequently damaged (Armstrong et al., 2016). Axon demyelination, as well as neuroinflammation with microglial activation develop post-injury (Andriessen et al., 2010; Armstrong et al., 2016). A post-mortem study using tissue from moderate-severely injured patients found that inflammation can persist for several years post-injury

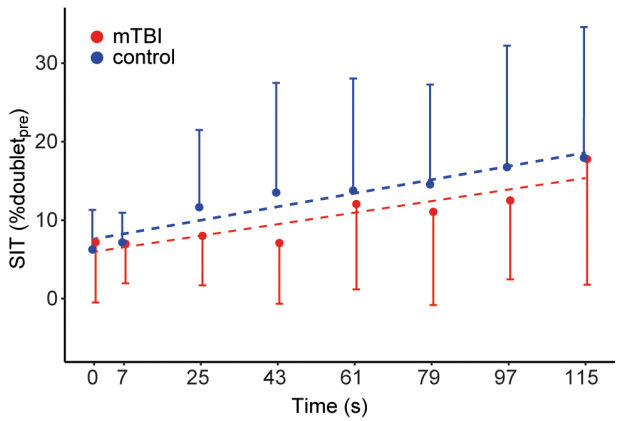

FIGURE 4 | Time course of the superimposed twitches during the sustained MVC. Dots show the mean size of the superimposed twitches evoked before (t = 0 s) and during the sustained MVC (t = 7–115 s). Control data (n = 20) is shown in blue and mTBI (n = 20) in red. Error bars indicate the standard deviation. Superimposed twitches were linearly corrected for the decline in muscle force and expressed as a percentage of the doublet$_{pre}$.

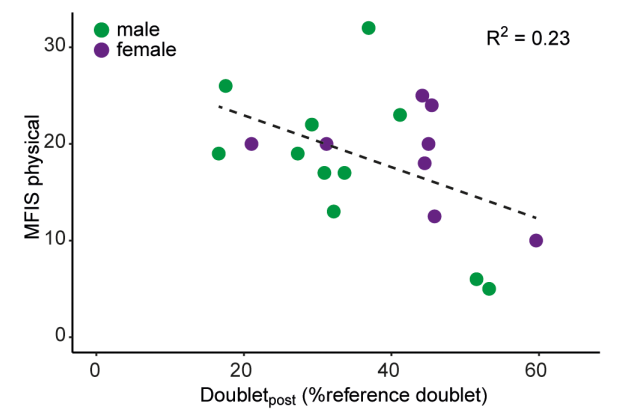

FIGURE 5 | Association between scores on the physical subdomain of the MFIS and the decline in the evoked doublet-force after the sustained MVC (i.e., doublet$_{post}$). Male mTBI participants (n = 11) are shown in green, female mTBI participants (n = 8) are shown in purple.

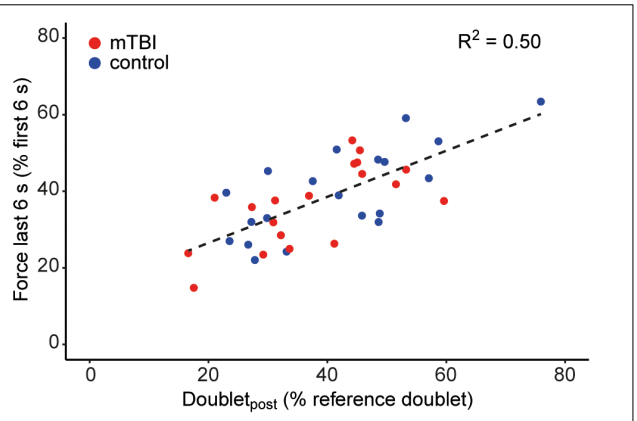

FIGURE 6 | Association between force decline during the sustained MVC and the evoked doublet-force after the sustained contraction (i.e., doublet$_{post}$) showing that participants with greater force decline also showed a greater decline in electrically evoked force. Control participants (n = 20) are shown in blue and mTBI (n = 19) in red.

(Johnson et al., 2013). These findings are complemented by imaging studies in mTBI patients which have shown structural white-matter changes in addition to functional changes such as disruption of networks (Inglese et al., 2005; Eierud et al., 2014).

Force decline during a sustained maximal contraction provides a measure of performance fatigability (Enoka and Duchateau, 2016). This decline in voluntary force may occur due to changes in peripheral muscle properties; i.e., factors at and distal to the neuromuscular junction (Allen et al., 2008). In addition, muscle fibers can become less optimally activated by the central nervous system (Gandevia, 2001). The interpolated twitch technique can be used to provide an estimation of the portion of the muscle that is not maximally activated (Behm et al., 1996). Since maximal activation of muscle fibers requires optimal activation of the motoneuron pool we expected that voluntary muscle activation could be compromised after mTBI as the result of damage to white matter tracts and myelin modification that evolves post-injury (Inglese et al., 2005; Armstrong et al., 2016). This is especially important for hand muscles which receive a relatively large portion of synchronized input from the corticospinal tract (Day et al., 1989; Lemon, 2008; Keen et al., 2012). In a previous study, a small decline in voluntary muscle activation of the FDI was observed in the early stage following concussion (Powers et al., 2014). However, we did not find differences in force decline nor in voluntary muscle activation between mTBI and control participants in the present study.

Besides the force decline and voluntary muscle activation of the right FDI, we analyzed two other parameters as indirect measures of performance during the sustained MVC. Firstly, the coefficient of variation of the force of the right hand (CV_{force}) was used as a measure of force steadiness. Secondly, the force and EMG of the contralateral (left) hand were recorded and analyzed. Both measures increase during fatiguing contractions (Lippold, 1981; Zijdewind and Kernell, 2001; Shinohara et al., 2003) and reflect increased effort. Neither parameter showed a difference between mTBI and control participants that could indicate increased effort in the mTBI group.

In both groups, individual differences in force decline during the sustained MVC were best explained by changes in peripheral muscle properties (i.e., the decline in doublet-force after the contraction; see **Figure 6**). However, only in the mTBI group could the variation in voluntary muscle activation (i.e., mean SIT during the sustained contraction) explain the remaining variance of the force decline. Although we were not able to objectify differences in performance between the groups, this may suggest that maintaining voluntary drive could be difficult after mTBI. This idea is further supported by the task performance of the two excluded participants and one mTBI participant who all had profound difficulties in performing the sustained contraction.

The rationale for investigating performance fatigability in the context of increased self-reported fatigue came from

previous findings in individuals with relapsing remitting MS (Steens et al., 2012; Wolkorte et al., 2015a). Although the severity of fatigue reported by mTBI participants was similar to the levels of fatigue in MS (Steens et al., 2012: FSS 5.3 ± 0.9 *SD*), associations between self-reported fatigue and reduced voluntary muscle activation or (normalized) force decline were not found in the present study. However, a (moderate) association between the physical subdomain of the MFIS and the decline in doublet-force after the sustained MVC was observed in mTBI participants. The associations between the decline in doublet-force with self-reported (physical) fatigue as well as with force decline underline the importance of peripheral muscle properties to explain variation in fatigue and performance fatigability in persons with mTBI.

Cognitive Impairment After mTBI

Cognitive impairment is a prominent complaint after mTBI (van der Naalt et al., 1999; Lundin et al., 2006; Lannsjö et al., 2009). In the present study we screened for cognitive impairment using the PASAT and SDMT. On both tests, performance of the mTBI participants was comparable to the reference population. It is possible that the 3 s PASAT task was not sensitive enough to capture subtle differences (Tombaugh, 2006), but also the SDMT showed low scores for only 20% of mTBI participants. Most of our mTBI participants (and controls) had completed a higher education program (see **Table 1**). Since higher education is known to attenuate changes in cognitive task performance due to TBI (Sumowski et al., 2013), it is possible that the relatively high level of education of our mTBI participants diminished the effects of the TBI on the cognitive (and perhaps also the motor) task.

Several studies have focused on the relationship between self-reported fatigue and performance during cognitive tasks; another example of performance fatigability (Ziino and Ponsford, 2006; Möller et al., 2014, 2017). For these tasks, also no associations between measures of self-reported fatigue and performance fatigability were observed.

Fatigue and Depression

It is known that fatigue and depression are often found in the same patients and that fatigue and depression scores are mostly well correlated (Kluger et al., 2013). In the present mTBI population we found increased values for both depression and fatigue scores. We found an association between the HADS depression scores and the MFIS scores, but not the FSS scores. Though, previous studies have also reported the association between HADS depression scores and FSS scores after mTBI (Norrie et al., 2010; Möller et al., 2014).

Force Measurements

Across all groups, the MVCs of the left hand were on average 20% larger than for the right hand. This difference has been reported before in our studies (e.g., Post et al., 2007) but not by other groups. Our force transducer is equipped with a full bridge strain gauge configuration and therefore records force independent of the position of the finger bracket (i.e., the connection between the index finger and the transducer; see **Figure 1A**; van Duinen et al., 2007). Furthermore, the force difference between the left and right hand remains present if the same force transducer is used for both hands. In other words, differences in the length of the index finger do not affect the force data and cannot explain the difference in force. In cadavers, we dissected three pairs of human hands to study the anatomical differences between the left and right FDI. No systematic differences were found between the left and right FDI for the mass, length, or cross sectional width; though the cross sectional width of the left FDI was larger in two pairs of specimens.

Limitations of the Study

The target muscle of the present study was the FDI, a small hand muscle. We chose this muscle because we wanted to be able to compare the present data with the data obtained in persons with MS (Steens et al., 2012). Furthermore, intrinsic hand muscles are more strongly dependent on synchronized corticospinal input compared to most other muscles (Keen et al., 2012). Therefore, we expected differences in voluntary muscle activation in this muscle. It is, however, possible that measures of performance fatigability would have shown larger differences in other larger muscle (groups).

Contrary to most research related to fatigue following mTBI, we used motor tasks to investigate performance fatigability. A general limitation of using cognitive tasks to measure time-related changes (i.e., performance fatigability) is that performance on these tasks is often affected by learning processes. Since cognitive and motor tasks share higher cortical processes as illustrated by the direct interaction between cognitive and motor task performance in both controls (Lorist et al., 2002; Wolkorte et al., 2014) and clinical populations (Howell et al., 2013; Sarajuuri et al., 2013; Wolkorte et al., 2015b; Yasen et al., 2017), we expected to find differences between mTBI patients and controls in our motor tasks. An advantage of motor tasks is the ability to quantify output (force) continuously throughout the task. Furthermore, by using the interpolated twitch technique (Merton, 1954; Allen et al., 1994; Behm et al., 1996) during a sustained maximal muscle contraction it is possible to discriminate between factors residing in the muscle and factors in the central nervous system which are responsible for force decline. Nevertheless, the present study only found minor differences in motor parameters between controls and the mTBI population. It is possible that our outcomes measures were not sensitive enough and that a combination of cognitive and motor task would require more attentional resources and therefore induce larger differences.

CONCLUSION

Fatigue is an important symptom after mTBI, but the underlying mechanisms remain poorly understood. Despite increased levels of self-reported fatigue, no differences were observed in force decline in persons with mTBI. Nevertheless, the present data indicate that changes in peripheral muscle properties could be important for understanding the mechanisms affecting perception of fatigue in persons with mTBI. These peripheral muscle properties together with changes in voluntary muscle

activation were able to explain most of the variation in force decline during the sustained maximal contraction. Besides relevance for improving our understanding of fatigue, these findings also indicate the importance of studying a combination of motor and cognitive parameters after mTBI.

AUTHOR CONTRIBUTIONS

IZ and JvdN designed the experiments. RP and IZ performed the experiments and analyzed the data. RP, IZ, and JvdN wrote the manuscript.

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MINI REVIEW
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Skeletal Muscle Fatigability in Heart Failure

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Evidence suggests that heart failure (HF) patients experience skeletal muscle fatigability in the lower extremity during single-limb tasks. The contribution of skeletal muscle fatigability to symptoms of exercise intolerance (perceived fatigue and dyspnea) is relatively unclear. Symptomatic or 'perceived' fatigue is defined by the sensations of exhaustion or tiredness that patients experience either at rest or while performing a motor task. Although factors that contribute to symptoms of fatigue in patients with HF are multifactorial; the skeletal muscle likely plays a major role. Skeletal muscle fatigability, as opposed to symptomatic fatigue, is an objective measure of a reduction in muscle force or power or reduced ability of the muscles to perform over time. Indeed, evidence suggests that patients with HF experience greater skeletal muscle fatigability which may contribute to a diminution in motor performance and the overall symptomatology that is hallmark of exercise intolerance in HF. This review will discuss (1) skeletal muscle fatigability in patients with HF, (2) the mechanisms contributing to locomotor skeletal muscle fatigability in HF and (3) the relationship of fatigability to symptoms of perceived fatigue and exercise intolerance in HF patients. Evidence suggests that cardiac dysfunction alone does not contribute to exercise intolerance. Therefore, mechanisms of skeletal muscle fatigability and their contribution to symptoms of fatigue and exercise intolerance, is an increasingly important consideration as we develop rehabilitative strategies for improving motor performance and functional capacity in patients with HF.

Keywords: heart failure, fatigue, fatigability, exercise intolerance, skeletal muscle

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INTRODUCTION

Heart failure (HF) is the inability of the heart to supply the periphery with adequate nutrients and oxygen. HF is either defined by the inability of the heart to pump blood adequately (HF with reduced ejection fraction, HFrEF) or the inability of the heart to fill adequately (HF with preserved ejection fraction, HFpEF) (Hunt et al., 2009). Although there are many causes of HF, the end result is a systemic illness that affects multiple organ systems, including skeletal muscle (Wilson, 1995). Exercise intolerance, low exercise capacity accompanied by symptoms of dyspnea and fatigue, is a hallmark of HF (Wilson and Ferraro, 1983; Wilson et al., 1984b; Piepoli et al., 1995; Wilson, 1995). Mechanisms of exercise intolerance in patients with HF are multi-factorial with several excellent reviews detailing the importance of skeletal muscle to exercise intolerance (Lipkin and Poole-Wilson, 1986; Wilson and Mancini, 1993; Poole et al., 2012, 2018; Hirai et al., 2015). Symptoms of exercise intolerance are commonly dissociated with measurements of resting cardiac

output, ejection fraction and left atrial pressure in HF (Franciosa et al., 1979; Higginbotham et al., 1983; Szlachcic et al., 1985; Lipkin and Poole-Wilson, 1986). However, the contribution of skeletal muscle fatigability and associated mechanisms to perceptions of fatigue and exercise intolerance are unknown and will be discussed in this review. Indeed, the purpose of this review is to provide an overview of skeletal muscle fatigability and discuss the extent to which fatigability contributes to symptoms of fatigue and exercise intolerance in patients with HF. Although both HFrEF and HFpEF likely exhibit skeletal muscle fatigability, the majority of the work in fatigability has been conducted in HFrEF and will therefore be the emphasis of this review. Further, the majority of the fatigability work in HF was performed in the 1980s and 1990s. These studies will be the focus of the discussion, with more recent work in muscle to delineate potential mechanisms of fatigability. In final, this review will highlight the critical need for further characterization and delineation of mechanisms of skeletal muscle fatigability in HF.

Symptomatic or 'perceived' fatigue is defined by the sensations of weariness, increasing sense of effort, mismatch between effort expended and actual performance or exhaustion (Kluger et al., 2013). Fatigue is measured subjectively, often times by a rating of perceived exertion scale (Borg, 1974; Borg et al., 1987) or merely by the presence of its existence in clinical populations. A clear distinction, however, needs to be made between perceived fatigue as described by patients and skeletal muscle fatigability (Kluger et al., 2013).

Fatigability, commonly called performance fatigability, is an objective measure of a *reversible,* reduction in muscle force or power or the reduced ability of the muscles to perform over time (Gandevia, 2001). Mechanisms of fatigability can occur upstream of the neuromuscular junction (central or neural mechanisms) and/or at or below the neuromuscular junction (peripheral mechanisms). Central mechanisms can include motivation, inhibition at the motor cortex or a reduction in drive to the motor neurons or inability to fully recruit motor units (Gandevia, 2001). Peripheral mechanisms include impairment at the neuromuscular junction, changes in blood flow, metabolism, contractile properties and calcium kinetics (Fitts, 1994, 2008; Kent-Braun et al., 2012). Mechanisms of greater fatigability in patients with HF are not clear, but clinically relevant, and likely to contribute to perceptions of fatigue and exercise intolerance. Although there is no consensus, there is evidence to suggest, that mechanisms of fatigability are likely a combination of deconditioning and the pathophysiology of HF (Buller et al., 1991; Piepoli et al., 1995; Piepoli and Coats, 2013).

ARE PATIENTS WITH HF MORE FATIGABLE?

Several studies suggest that patients with HF are more fatigable when compared with controls (**Figures 1**, **2**). **Figure 1** represents studies that measured the reduction in strength after various single-limb fatiguing interventions. **Figure 2** represents the studies that measured time to task failure or how long participants could hold a submaximal or maximal contraction, or in one case of isometric intermittent contractions, how many contractions the participants were able to perform (Minotti et al., 1992b). In both **Figures 1**, **2** the reduction in strength or time to failure for the HF participants was normalized to the CTL participants. For brevity, if studies sorted out differences in fatigability based on severity of HF according to the New York Heart Association (NYHA) classification scale (Weiss et al., 2017), this is discussed in the text but averaged for **Figure 2**. Fatigability and mechanisms that contribute to fatigability are known to be task dependent (Hunter, 2018) and may also be dependent on the muscle (Hunter et al., 2004; Senefeld et al., 2017). This means that fatigability for isometric (static or intermittent), dynamic tasks, maximal or submaximal may alter the performance of the muscle and the mechanisms that cause the muscle to fatigue are dependent on that task and may be different for each muscle. Although the literature in HF is sparse compared with healthy adults or aging literature, the majority of the studies demonstrate that patients with HF are considered more fatigable in that they experience a greater reduction in strength as well as a briefer time to failure when compared with control participants. Further, for the knee extensor and plantar flexor muscles, fatigability was greatest for patients with the most severe HF symptoms (Buller et al., 1991; Harrington et al., 1997; Weiss et al., 2017). This was not consistent, however, for the adductor pollicis muscle (Buller et al., 1991). Buller et al. (1991) observed that when the adductor pollicis was electrically stimulated, HF patients who identified as mild HF were more fatigable compared with controls. Surprisingly, however, patients that identified as severe HF were less fatigable then control participants (Buller et al., 1991 in **Figure 1**). Further, when blood flow was occluded to the adductor pollicis muscle during electrical stimulation, there was little difference between both mild and severe HF patients and control participants (Buller et al., 1991). The difference between lower and upper extremity fatigability in patients with HF is not completely understood but may be related to a greater deconditioning of the lower extremity muscles in patients with HF. However, this should be taken with caution as very few studies have measured skeletal muscle fatigability of the upper extremity in patients with HF and these studies have primarily used electrical stimulation vs. volitional fatiguing contractions (Buller et al., 1991).

MECHANISMS OF SKELETAL MUSCLE FATIGABILITY

Influence of Muscle Mass and Strength to Skeletal Muscle Fatigability

Skeletal muscle strength plays a major role in fatigability in healthy adults (Hunter and Enoka, 2001; Keller-Ross et al., 2014). During isometric tasks, individuals that have weaker muscles generally demonstrate a longer time to task failure or greater resistance to fatigue, which could be due to greater blood perfusion during the task and/or a greater proportion of type I (oxidative) muscle fibers (Hunter, 2009). Whether or not skeletal muscle strength is affected in patients with HF is equivocal in the

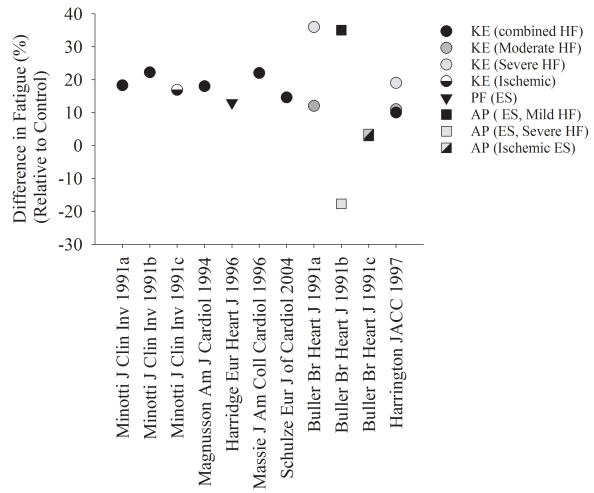

FIGURE 1 | Reduction in Strength after a fatiguing contraction in HF, relative to controls. Each symbol represents the reduction in strength after various fatiguing interventions, normalized to the control group in each respective study. The majority of studies demonstrate a greater fatigability in HF patients compared with controls. When studies used multiple protocols (Buller et al., 1991; Minotti et al., 1991), each protocol was indicated in its own column. CTL, control; HF, heart failure; KE, knee extensors; PF, plantar flexors; AP, adductor pollicis; ES, electrical stimulation.

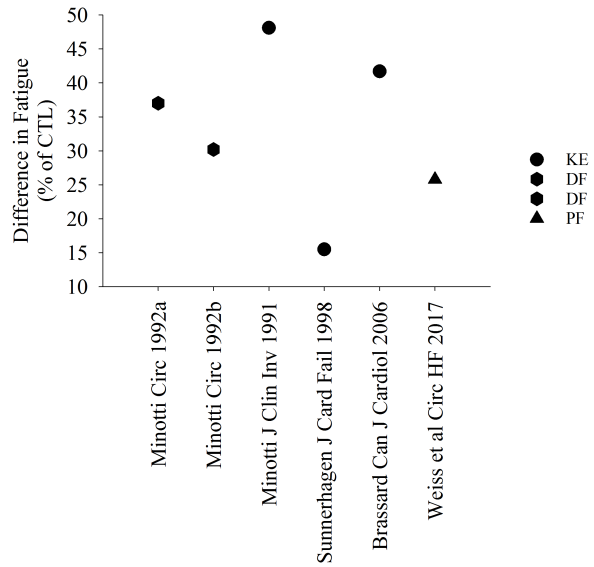

FIGURE 2 | Percent difference in time to task failure in patients with HF. Data in HF is represented as a relative value in comparison with controls. All studies demonstrated a briefer time to failure or greater fatigability in HF. DF, dorsiflexor muscles.

literature. Some studies suggest that skeletal muscle strength is relatively preserved in patients with HF (Minotti et al., 1992a; Harridge et al., 1996; Massie et al., 1996; Brassard et al., 2006), but others indicate strength is reduced (Buller et al., 1991; Magnusson et al., 1994; Sunnerhagen et al., 1998; Schulze et al., 2004). Of significance and similar to what we observe in the relationship

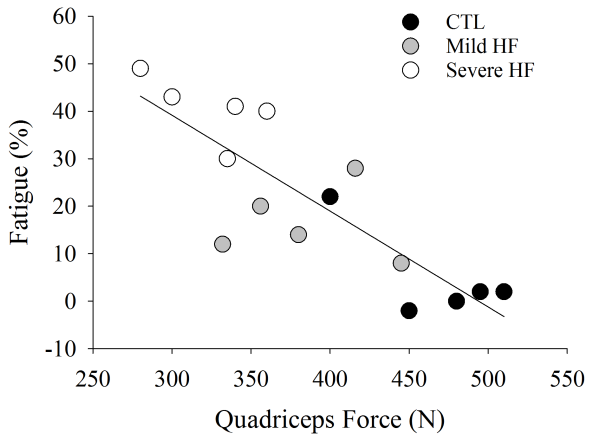

FIGURE 3 | Data extracted from Buller et al. (1991). Quadriceps force was strongly associated with fatigue (%) (r = 0.81, P < 0.001). Individuals who were weaker (severe HF patients) had the greatest fatigability (%).

between HF and fatigability, these latter studies observed that patients with the most severe HF exhibit the greatest deficits in strength (Buller et al., 1991). Indeed, patients with severe HF, also had the weakest knee extensor muscles and greater fatigability after intermittent isometric contractions at 40% of maximal voluntary contraction for 20 min (r = 0.81, $p \leq 0.01$, **Figure 3**). This is in contrast to what is observed in healthy adults when time to task failure is measured during isometric fatiguing contractions (Hunter, 2009). In the case of Buller et al. (1991), the stronger individuals (less severe HF and control participants) had greater strength and were less fatigable (less of a reduction in strength) than weaker individuals who also identified as having severe HF symptoms. To further illustrate the importance of strength to fatigability, patients with severe HF that exhibit cachexia (loss of muscle mass and body weight) have reduced skeletal muscle strength and experience greater reductions in maximal strength (21.1% ± 1.9) vs. non-cachectic HF patients (13.9 ± 1.6%) after a fatiguing intervention (Anker et al., 1997b).

Mechanisms contributing to a reduction in strength in patients with HF are likely linked to skeletal muscle atrophy. Several studies demonstrate a strong relationship between a reduction in strength and a loss of muscle mass (Buller et al., 1991; Minotti et al., 1993; Magnusson et al., 1994). The causes of muscle atrophy in patients with HF are likely multifactorial and include disuse, reduced blood flow, neural and hormonal factors and/or intrinsic skeletal muscle alterations (Wilson et al., 1984b; Mancini et al., 1992; Gosker et al., 2000; Miller et al., 2009, 2010). For example, metabolic abnormalities in HF affect various endocrine systems leading to an imbalance of catabolic and anabolic function which results in progressive catabolic state in advanced stages of disease (Mancini et al., 1992). The neurohumoral activation is accompanied by increased serum levels of pro-inflammatory cytokines (TNFα, IL-1β and IL-6) (Torre-Amione et al., 1996). Several studies indicate that systemic markers of pro-inflammatory cytokines contribute to muscle atrophy in patients with HF (Anker et al., 1997a; Hambrecht et al.,

2002). Collectively, these studies suggest that maintaining skeletal muscle mass and strength may be important for fatigue resistance in patients with HF. It remains to be determined, however, if and how reduced strength or muscle atrophy causes fatigability or if it is a coincidental and/or simultaneous occurrence with the change in fiber type composition (**Figure 4**) (Minotti et al., 1993).

Contribution of Neural Mechanisms to Skeletal Muscle Fatigability in HF

Central (neural) mechanisms of skeletal muscle fatigability is defined by a reduction in voluntary activation from contributions upstream of the neuromuscular junction (Gandevia, 2001). There are limited studies that have assessed neural mechanisms of fatigability in patients with HF, however, these studies suggest that neural mechanisms are likely not a major cause of fatigability. For example, Harridge et al. (1996) demonstrate a 30% greater fatigability in patients with HF, but this could not be attributed to poor neural drive. Minotti et al. (1992b), using a dynamic and sustained isometric contractions of the dorsiflexors, reported that neural drive was a limiting factor to force production during fatiguing exercise, but this limitation was similar in patients with HF and control participants (Minotti et al., 1992b). Further, a more recent study demonstrated that patients with HF had a similar reduction in skeletal muscle strength and voluntary activation (measured via transcranial magnetic stimulation) of the quadriceps muscle after a peak exercise test (Hopkinson et al., 2013). Alternatively, greater skeletal muscle fatigability was correlated with a reduction in electromyographic (EMG) activity of the knee extensor muscles during a maximal isometric fatiguing contraction (Schulze et al., 2004). The authors recognize this finding as a pronounced decrease in neuromuscular activity in HF, however, surface EMG does not only represent neural activation, but also represents changes distal to the neuromuscular junction (Farina et al., 2004). Collectively, although neural fatigue appears to contribute to skeletal muscle fatigability in HF, this does not appear to be different from those without HF and is not a major contribution to the greater fatigability observed in patients with HF.

Contribution of Peripheral Mechanisms to Skeletal Muscle Fatigability in HF

Mechanisms contributing to fatigability that occur at or distal to the neuromuscular junction (NMJ) are defined as peripheral. This includes; impairment of the NMJ to transmit the action potential along the sarcolemma and t-tubule, alterations to the contractile properties, muscle metabolism and blood flow and intrinsic changes to the skeletal muscle. The NMJ can be assessed by the compound muscle action potential or the M wave, which is the EMG response to maximal stimulation to the motor nerve or muscle. The M wave was found to be similar in HF and CTL participants during an intermittent isometric fatiguing contraction, suggesting that the integrity of the NMJ is well-preserved with fatigue in HF (Minotti et al., 1992b). As such, the majority of the evidence suggests that alterations peripheral of the NMJ are likely the cause of greater fatigability in HF.

Altered Contractile Properties and Muscle Metabolism in HF

Several studies suggest a loss in proportion of type I and type IIa fibers, a gain in type IIx fibers (Mancini et al., 1989; Sullivan et al., 1990; Harridge et al., 1996; Sunnerhagen et al., 1998) and a lower level of oxidative enzymes among HF patients than in controls (Sullivan et al., 1990; Drexler et al., 1992; Massie et al., 1996; Sunnerhagen et al., 1998). For example, a faster time to peak tension in the plantar flexor muscles and a faster ½ relaxation time in the knee extensor muscles was observed in HF with 54% and 45% greater fatigability in HF patients, respectively (Harridge et al., 1996). The faster ½ relaxation time in patients with HF suggests faster calcium kinetics and specifically calcium reuptake in the sarcolemma (Inghilleri et al., 1993). Further, Brassard et al. (2006) demonstrated that a 39% briefer endurance time in patients with HF was correlated with lower oxidative enzymes [citrate synthase (CS), 3-hydroxyacyl-CoA dehydrogenase (HADH)] and greater glycolytic enzymes [phosphofructokinase (PFK)]. This suggests that the greater fatigability in the vastus lateralis in patients with HF was likely due to lower oxidative capacity. These patients also had an elevated median frequency of surface EMG suggesting a greater reliance on type II fiber recruitment (Brassard et al., 2006). These findings confirmed results of greater oxidative capacity and lower glycolytic capacity found in earlier studies (Sullivan et al., 1990, 1991). As such, lactate production was found to be greater during submaximal exercise in patients with HF (Sullivan et al., 1990, 1991). Several studies that use phosphorus nuclear magnetic resonance (^{31}P NMR) demonstrate altered metabolism, such that a greater increase in the ratio of inorganic phosphate to phosphocreatine (Pi/PCr) was found during the higher intensity workloads in patients with HF (Wiener et al., 1986). Consistent with these findings, evidence suggests that HF patients demonstrate a reduced number of mitochondria and the mitochondria to be structurally altered in skeletal muscle of HF (Drexler et al., 1992; Hambrecht et al., 1995). This is likely due to the elevated sympathetic activity and release of neurohumoral factors, such as catecholamines or renin-angiotensin-aldosterone system (Palaniyandi et al., 2010). In summary, several lines of evidence suggest that HF muscles demonstrate a higher glycolytic and lower oxidative capacity during exercise which contributes to skeletal muscle fatigability in HF (**Figure 4**).

Critical power represents the highest *power* output sustained without loss of homeostasis (Jones et al., 2010) and subsequently the highest rate of oxidative metabolism that can be sustained without a progressively increasing contribution to energy turnover from substrate-level phosphorylation (anaerobic glycolysis) (Jones et al., 2010). While challenging to assess, it has been suggested that critical power is reduced in patients with HF, which likely contributes to a greater skeletal muscle fatigability (Jones et al., 2010) and therefore reduced tolerance to exercise (Poole et al., 2012).

Altered Blood Flow in Patients With HF

Several aspects of muscle blood flow control are disrupted in HF. A decrease in skeletal muscle perfusion during exercise is a powerful stimulus for early anaerobic metabolism

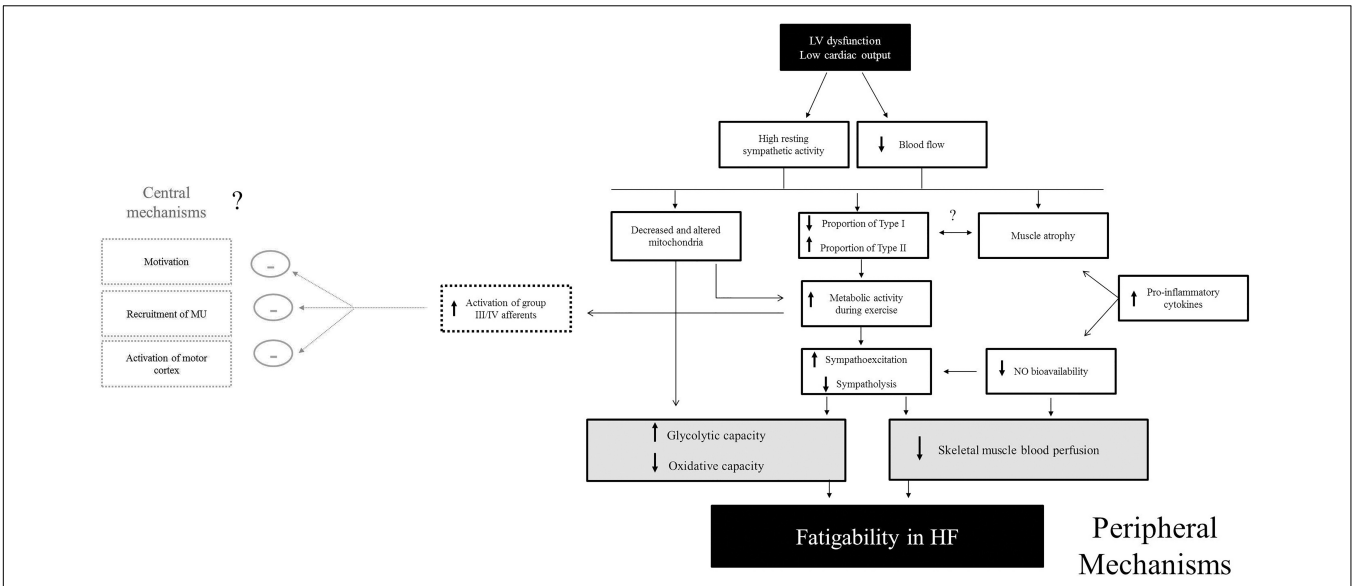

FIGURE 4 | Proposed mechanisms of fatigability in HF patients. Mechanisms contributing to muscle fatigability in HF are likely a cascade of events that may be initiated by high sympathetic activity and reduced cardiac output. This review indicates that peripheral factors likely play a large role in fatigability. In particular, skeletal muscle perfusion and altered muscle metabolism appear to be observed as major contributing factors (shown in gray). Although central factors have not yet been shown to contribute to fatigability in HF, more research needs to be conducted to directly measure neural mechanisms of fatigability in these patients. Because greater activation of skeletal muscle (group III/IV) afferents are known to inhibit motor activity (Garland and Kaufman, 1995), the possibility of greater inhibition of the central nervous system by exaggerated activity of group III/IV afferent (outlined in gray boxes) exists.

(Pernow et al., 1975; Walker et al., 1982) which has been demonstrated in HF (Zelis et al., 1974; Wilson et al., 1984a,b). Part of the blood flow discrepancy in HF may also be due to an intrinsic abnormality in limb vasodilatory capacity (Zelis et al., 1968), greater sympathetic activity (Notarius et al., 2001; Osman and Lee, 2015) greater impedance of the muscle pump from post capillary resistance (Zelis et al., 1974; McAllister et al., 1993; Shiotani et al., 2002); however, muscle fiber capillary density appears to be normal (Lipkin et al., 1988). Nitric oxide (NO) bioavailability is also compromised, which would constrain sympatholysis (the ability to oppose α-adrenergic vasoconstriction and shear stress-mediated vasodilation) (Thomas et al., 2001). Importantly, greater increases in pro-inflammatory cytokines such as TNF-α and IL-1β levels may also impact NO bioavailability (Batista et al., 2009) leading to greater vasoconstriction of blood flow to skeletal muscle (**Figure 4**).

Although no studies have investigated leg blood flow during fatiguing contractions, leg blood flow was shown to be impaired during knee extensor exercise at various workloads (Amann et al., 2014). This was likely due to greater skeletal muscle group III/IV afferent feedback, causing greater sympathoexcitation and reduced vasodilatory capacity at the site of the muscle (Amann et al., 2014). Other studies using maximal whole body exercise have also demonstrated impaired blood flow (Magnusson et al., 1997; Wilson et al., 1983, 1984a,b) which could in part, be due to competition of blood flow between locomotor and respiratory muscles (Olson et al., 2010). Measurement of blood flow during a smaller muscle exercise, such as with the forearm muscles suggests that blood flow is impaired in some studies (Zelis et al., 1974; Longhurst et al., 1976), but not others (Wiener et al., 1986; Magnusson et al., 1997). Differences in cardiac dysfunction and severity of HF likely account for the difference in findings.

Oxygen uptake (VO_2) kinetics is dependent on the capacity of oxygen delivery to the active muscle as well as oxygen utilization in the exercising muscle (Xu and Rhodes, 1999). VO_2 kinetics are impaired in patients with HF (Poole et al., 2012) which is likely due to a reduced cardiac output, greater metabolic production during exercise, greater sympathetic activity, ventilatory work and recruitment of glycolytic fibers (Xu and Rhodes, 1999). When exercise in HF is above lactate threshold during dynamic exercise, which is often at low VO_2 values, VO_2 cost becomes greater, which is likely attributed to a combination of fatigue-related processes necessitating additional fiber recruitment and metabolic processes occurring within already recruited fibers (Poole et al., 2012; Jones and Poole, 2013). Consequently, slowed VO_2 kinetics, although not yet been demonstrated during single limb fatiguing contractions, is likely contributing to greater fatigability in patients with HF.

During fatiguing contractions where force is maintained at > 60% of maximum, severe restriction of blood flow can occur (Sjøgaard et al., 1988). Importantly, it was demonstrated that during a maximal fatiguing contraction to 60% of the maximal voluntary contraction of the dorsiflexor muscles, patients with HF demonstrated accelerated fatigability (Minotti et al., 1992b), indicating that the greater fatigability was likely independent of blood flow. Further, when the muscle is made to be ischemic during dynamic knee extensor contractions, greater fatigability in patients with HF is observed (Minotti et al., 1991). Although

not directly measured during a fatiguing contraction, this would collectively suggest that a lack of blood flow to the larger muscles likely contributes to greater fatigability (**Figure 4**), but also likely depends on the severity of HF (i.e., circulatory function).

Fatigability, Perceived Fatigue and Exercise Tolerance in HF: Are They Related?

How skeletal muscle fatigability, often considered performance fatigability, relates to symptoms of fatigue and exercise intolerance in patients with HF is an important question, yet challenging to answer. Studies that measured fatigability, did not report symptoms of fatigue during the fatiguing tasks. However, a number of these studies also conducted a peak oxygen consumption test (VO_{2peak}) and perceived leg fatigue is measured during VO_{2peak} testing. Although the measurements of fatigability during single-limb tasks and whole-body VO_{2peak} testing are different, some mechanisms contributing to both may be similar (Longhurst et al., 1976; Wilson, 1995; Amann et al., 2014).

The importance of skeletal muscle fatigability to exercise intolerance is highlighted by earlier studies that demonstrated strong correlations between fatigability during dynamic isokinetic (90° and 180°/s velocities) contractions and VO_{2peak} (Minotti et al., 1991). Particularly at 90°/s, the reduction in strength was correlated with VO_{2peak} ($r = 0.90$, $r < 0.001$), such that those patients who had a greater reduction in strength after a dynamic fatiguing intervention also had the lowest VO_{2peak}. Massie et al. (1996) observed a comparable finding with a similar fatiguing protocol ($r = 0.57$, $p = 0.03$) (Massie et al., 1996). This is particularly significant in view of the lack of correlation between VO_{2peak} and any measure of cardiac function. As of importance, both the fatigue index and VO_{2peak} correlated with the average fast twitch fiber area (Massie et al., 1996). Further, during VO_{2peak} testing, perceptions of leg fatigue was the greatest limiting factor reported by HF patients and was related to lower leg blood flow, greater oxygen extraction and greater muscle metabolism in HF patients (Wilson et al., 1984b, 1985). Collectively, findings from these studies suggest two important concepts: (1) skeletal muscle fatigability is closely associated to exercise capacity, a major measure of exercise intolerance in patients with HF and (2) some of the mechanisms (changes in fiber type distribution, muscle metabolism and blood perfusion to the muscle) that likely cause skeletal muscle fatigability are also major contributors to exercise intolerance in HF.

CONCLUSION

Heart failure patients experience greater fatigability of the skeletal muscles, particularly in the lower extremity. Mechanisms contributing to the greater fatigability in patients with HF are likely due to alterations in skeletal muscle metabolism, resulting in greater glycolytic capacity and reduced oxidative capacity of the muscle and reduced blood perfusion to the muscle. A schematic of potential major contributors to performance fatigability during single-limb skeletal muscle contractions in HF is detailed in **Figure 4**. The abundance of work in fatigability in HF patients is from several decades ago and the majority of the mechanisms that may play a role have not been directly measured during fatiguing contractions in HF. As such, there are significant knowledge gaps in factors that contribute to fatigability in patients with HF, particularly the extent to which central or neural fatigability may play a role. Further, as some of the skeletal muscle changes have been observed in HFpEF, little is known in regards to mechanisms of fatigability in both HFrEF and HFpEF patients.

AUTHOR CONTRIBUTIONS

MK-R drafted, revised and approved the manuscript and agree to be accountable for all aspects of the work. ML revised and approved the manuscript and agree to be accountable for all aspects of the work. BJ revised and approved manuscript and agree to be accountable for all aspects of the work.

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Fatiguing Trunk Flexor Exercise Decreases Pain Sensitivity in Postpartum Women

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Background: Low back pain (LBP) is common in the general population and among postpartum women. Abdominal muscle exercise is often used to treat LBP, but it is unknown if fatiguing abdominal muscle exercise can produce exercise-induced hypoalgesia (EIH).

Objectives: To assess pressure pain thresholds (PPTs) at rest and following fatiguing trunk flexor exercise (EIH) in (1) nulligravid and postpartum women to evaluate the impact of pregnancy and childbirth and (2) nulligravid women and men to examine sex differences.

Methods: Seventy healthy adults (31 postpartum women, 23 nulligravid women, 16 men) participated. Postpartum and nulligravid women were tested twice (16–18 weeks apart) to identify changes in EIH with postpartum recovery. PPTs were measured at the nailbed and superior rectus abdominis before and after exercise to investigate systemic and local EIH, respectively. Rectus abdominis muscle thickness was assessed with ultrasound.

Results: Postpartum women reported lower PPTs than nulligravid women at the abdomen ($p < 0.05$) whereas postpartum women had lower PPTs at the nailbed during the first session only. Men reported higher nailbed PPTs ($p = 0.047$) and similar PPTs at the abdomen than women ($p = 0.294$). All groups demonstrated EIH at the abdomen ($p < 0.05$). Systemic EIH was absent in postpartum and nulligravid women ($p > 0.05$), while men demonstrated hyperalgesia. Local EIH was positively associated with muscle thickness for men and women, which was not significant at the second timepoint.

Limitations: Acute exercise response may not reflect changes that occur with exercise training.

Conclusion: Fatiguing trunk flexor exercise produced local EIH for all groups including postpartum and nulligravid women. Clinically, trunk exercises may be useful for acute pain relief for clinical populations that are characterized by pain and/or weakness in the abdominal region muscles in populations with abdominal pain syndromes.

Keywords: exercise-induced hypoalgesia, pregnancy, pressure pain thresholds, muscle thickness, sex differences

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INTRODUCTION

Approximately 30% of adults in the United States experience chronic pain, with the low back being the most commonly reported location (Johannes et al., 2010). Low back pain (LBP) has also been identified as the leading cause of years lived with disability globally (Vos et al., 2012), and women are more likely than men to experience chronic LBP that impacts activities of daily living (Chenot et al., 2008). In addition, LBP frequently occurs with pregnancy, with approximately 75% of pregnant women reporting low back and/or pelvic girdle pain (Wang et al., 2004; Wu et al., 2004). Roughly one out of four women with LBP during pregnancy will continue to have pain after childbirth (Albert et al., 2000; Robinson et al., 2010), and up to 20% of these women have pain that interferes with performance of activities of daily living 3 years after childbirth (Albert et al., 2001; Norén et al., 2002). Furthermore, prolonged pain can lead to central sensitization, which is an increased responsiveness of nociceptive neurons in the central nervous system (International Association for the Study of Pain), making early management of pain an important factor in the prevention of chronic pain syndromes and disability.

Several studies have identified impaired function of the abdominal muscles in individuals with back pain. Smidt et al. (1983) found that individuals with LBP demonstrated lower isometric and isokinetic trunk flexion torques and were more susceptible to muscle fatigue of the abdominals compared with individuals without LBP. Postpartum women have been shown to have lower isometric trunk flexion strength and increased fatigability of both the trunk flexor muscles and lumbopelvic stabilizing muscles up to 26 weeks postpartum as compared to women who have never been pregnant (Deering et al., 2018a,b), which may contribute to LBP in this population. In postpartum women, increased inter-recti distance, suggesting compromised fascial integrity, has also been associated with low back and pelvic pain (Parker and Millar, 2008). These findings suggest that dysfunction of the abdominal muscles may play a role in the etiology of LBP, with rehabilitation implications including the response to exercise.

Pain can also lead to fear avoidance behaviors leading to further reductions in physical activity levels and muscle weakness; perpetuating a cycle of weakness, instability, pain, and reduced movement (Gutke et al., 2011). In contrast, exercise has been shown to be a non-pharmacologic intervention to decrease pain sensitivity in healthy individuals and patient populations (Naugle et al., 2012). The reduction in pain perception following exercise is known as exercise-induced hypoalgesia (EIH). Pressure pain thresholds (PPTs), which are the minimum intensity of a stimulus that is perceived as painful, are frequently used to assess EIH; an increase in PPTs following exercise is indicative of EIH (Hoeger Bement et al., 2008; Naugle et al., 2012).

EIH can occur locally at the exercising muscle as well as systemically at more distal sites such as the nail bed. The magnitude of EIH is dependent upon both the intensity and duration of exercise (Hoeger Bement et al., 2008; Naugle et al., 2012); greater pain relief occurs with fatiguing contractions (Hoeger Bement et al., 2008). Emerging evidence also shows that women may experience greater EIH than men, although this may be due to differences in baseline (pre-exercise) pain (Koltyn et al., 2001; Lemley et al., 2016).

Because postpartum women are at high risk of LBP and have low strength and endurance of the abdominal muscles compared with nulligravid women (Deering et al., 2018a,b), and as abdominal muscle exercise is typically used in the treatment of LBP for both men and women (Richardson et al., 1999; Hodges, 2003; Bastiaenen et al., 2004; Koumantakis et al., 2005; Pennick, 2007; Vleeming et al., 2008; Liddle and Pennick, 2015), we evaluated PPTs before and after fatiguing exercise of the trunk flexor muscles in (1) postpartum and nulligravid women (controls) to examine the impact of pregnancy and childbirth on pain thresholds and EIH, and (2) healthy men and nulligravid women to examine potential sex differences in pain thresholds and EIH (Koltyn et al., 2001) following abdominal muscle exercise. Postpartum and nulligravid women were tested twice, during the initial (8–10 weeks) postpartum period and follow-up (24–26 weeks) postpartum period, to determine if pain perception and response to exercise changes with the length of the postpartum period. The initial testing time point (8–10 weeks postpartum) was chosen due to many women in the United States receiving only 6–8 weeks of maternity leave (Vahratian and Johnson, 2009). Women who delivered vaginally or via Cesarean delivery were included, as both delivery methods are associated with some degree of pain and inflammation, whether from perineal/pelvic floor muscle injury or pelvic joint trauma from vaginal birth or surgical pain from Cesarean delivery, which can activate nociceptors (Chimenti et al., 2018). We hypothesized that (1) postpartum women would report lower resting PPTs than nulligravid women, and that both groups would demonstrate an increase in PPTs following fatiguing exercise (EIH) and (2) women would report lower PPTs at rest than men, and that both men and women would demonstrate EIH.

MATERIALS AND METHODS

Seventy healthy adults participated in the study. To examine the impact of pregnancy and childbirth on pain perception and EIH in response to abdominal muscle exercise (protocol 1), 31 postpartum women and 22 nulligravid women participated. To examine potential sex differences (protocol 2), 16 men and 19 women participated. Eighteen women participated in both protocols. During protocol 1, postpartum women were tested twice at the initial postpartum period (between 8 and 10 weeks) and follow-up at 24–26 weeks postpartum. Nulligravid women were tested, similarly, at two timepoints, separated by 16–18 weeks to match the testing time points of the postpartum women.

For protocol 1, 27 women between 8 and 10 weeks postpartum (31.2 $\pm$ 5.2 years; Vaginal delivery n = 17, Cesarean delivery n = 10) and 14 nulligravid women (25.8 $\pm$ 5.3 years) completed the initial time point of testing. At the follow up time point (24–26 weeks postpartum), 26 postpartum women (31.4 $\pm$ 4.8 years; Vaginal delivery n = 15, Cesarean delivery n = 11) and 14 nulligravid women (25.8 $\pm$ 6.1 years) completed the protocol.

Twenty-two postpartum women (vaginal delivery n = 14, Cesarean delivery n = 8) and six nulligravid women completed both time points.

Protocol Overview

All participants completed two experimental sessions at each time point of testing. Thus, participants in protocol 1 completed four experimental sessions (initial and follow-up postpartum period), whereas participants in protocol 2 completed two experimental sessions. The two protocols were identical except for minor deviations as outlined in the methods. During session one for both protocols, participants were familiarized to the pressure algometer (AlgoMed) at the nailbed of the left middle finger, completed ultrasound imaging of the abdominal muscles, and measurements of height and weight. Participants from protocol one also underwent assessment of PPTs at the lower abdomen (see PPT section for details).

During session two for both protocols, participants completed multiple questionnaires (Physical Activity Questionnaire, Oswestry Disability Index, McGill Short Form Pain Questionnaire, Pain Catastrophizing Survey, and the Fear Avoidance Beliefs Questionnaire) and performed the fatiguing trunk flexor exercise protocol. PPTs were measured before and after the exercise protocol at the left superior rectus abdominis muscle (to assess EIH local to the exercising muscle) and nailbed (to assess systemic EIH). The study was approved by the Institutional Review Boards at Marquette University and the Medical College of Wisconsin, and the Office of Clinical Research and Innovative Care Compliance at Froedtert Hospital. All participants provided written informed consent prior to study enrollment.

Fatiguing Trunk Flexor Exercise

Participants performed an intermittent isometric fatiguing trunk flexion task while seated upright in the Biodex dynamometer (Biodex Medical, Shirley, NY, United States). Trunk flexion maximal voluntary contractions (MVC) were performed prior to initiating the exercise protocol to determine maximal strength. At least three MVCs were performed, with a minimum of 1 min of rest between contractions, until two contractions were within 5% of each other to ensure true MVCs were obtained. The highest MVC was used to calculate the exercise intensity. The exercise protocol involved performance of trunk flexion contractions at 50% of MVC for 6 s with 4 s rest between contractions and 1 MVC every minute and at task failure (Deering et al., 2017). Task failure was defined as submaximal torque less than the 50% MVC target line for 3 s of the 6 s contraction or MVC strength less than or equal to 50% of baseline MVC.

Pressure Pain Thresholds (PPTs)

PPTs were assessed using a computerized pressure algometer with a 1 cm^2 rubber tip (Medoc Ltd., Yishai, Israel). PPTs were performed, before and within 5 min after the trunk flexor fatiguing exercise protocol while reclined in the Biodex dynamometer, at the nailbed of the left middle finger and at the left upper rectus abdominis (5 cm above and 2 cm lateral to the umbilicus). Three trials were performed at each site with an inter-stimulus interval of 10 s at a rate of 10 kPa/s. Participants were instructed to press a timing device "as soon as pressure changes to pain." While testing the abdominal muscle site, participants received the same instructions with the added instruction to breathe normally and not to press their abdomen out against the algometer. Pain thresholds were recorded for all three trials and averaged. Change in PPT was quantified in absolute (post-exercise PPT minus pre-exercise PPT) and relative [(post-exercise PPT minus pre-exercise PPT)/pre-exercise PPT] values.

For protocol 1, PPTs were also performed at the lower abdomen (during first session). Postpartum women who underwent Cesarean delivery were tested at the midpoint of their surgical scar, and all women in this group did have a Pfannenstiel (transverse) incision. Postpartum women who experienced a vaginal delivery and nulligravid women were tested in the midline of the abdomen, where a Pfannenstiel incision would be performed (approximately two finger widths above the pubic symphysis) (Mathai and Hofmeyr, 2007). Three PPT trials were performed and averaged.

Ultrasound Imaging of the Abdominal Muscles

Muscle thickness measurements of the right rectus abdominis were recorded at 2.5 cm above the umbilicus with a GE vivid e ultrasound machine (GE Healthcare, Little Chalfont, United Kingdom; 8LRS transducer). The full width of the rectus abdominis was scanned and the measurement was taken in the region that visually appeared to be the thickest at end expiration (Teyhen et al., 2007; Deering et al., 2017, 2018a,b).

Questionnaires: Pain and Fear Avoidance

Pain assessments included McGill Short Form Pain Questionnaire (Melzack, 1987), Pain Catastrophizing Scale (Osman et al., 1997, 2000), and the Fear Avoidance Beliefs Questionnaire (Waddell et al., 1993). LBP related disability was assessed with the Oswestry Disability Index (Fairbank et al., 1980; Fairbank and Pynsent, 2000; Fairbank, 2014).

Physical Activity

Physical activity at the time of testing was quantified with triaxial accelerometers (ActiGraph) worn around the waist for 4 days, inclusive of 2 weekend days. Average minutes of moderate intensity physical activity per day was calculated with ActiLife software.

Participants also completed a Physical Activity Questionnaire to estimate physical activity, represented as metabolic equivalents per hour per week, over the previous 12 months (Kriska et al., 1990; Deering et al., 2017).

Statistical Analysis

Power analysis was conducted using G Power software, which indicated the need for 18 subjects per group to achieve 95% power with alpha level of 0.05. Independent t-tests compared subject characteristics and baseline PPTs between groups (postpartum and nulligravid) and sexes. Questionnaires with ordinal scales

were compared between groups and sexes using the Mann–Whitney *U*-test. Change in PPTs following the exercise protocol were analyzed with repeated measures analysis of variance (ANOVA) over time (pre-post exercise) with group (postpartum vs. nulligravid) or sex as a between-subject factor. Correlation analysis between change in PPTs (post-pre) at the rectus abdominis muscle and muscle thickness was conducted with Spearman's rho non-parametric correlation due to non-normal distribution of ultrasound data. Pearson correlation was used to explore the relationship between baseline pain and pain response to exercise at both the nailbed and the abdomen. Significance was identified at $p < 0.05$. Data is presented in the text and tables as means ± standard deviation (SD).

RESULTS

Protocol One: Postpartum and Nulligravid Women

Subject characteristics, including weight, body mass index (BMI), trunk flexor strength and fatigability, and physical activity levels are presented in **Table 1**.

Pfannenstiel Site PPTs (Experimental Session 1)

No difference was noted in Pfannenstiel site PPTs between women who had a vaginal delivery and women who had a Cesarean delivery at 8–10 weeks postpartum (127.4 ± 53.2 vs. 103.8 ± 44.7, respectively, $p = 0.251$) or 24–26 weeks postpartum (112.3 ± 52.7 vs. 110.3 ± 46.5, respectively, $p = 0.922$), so both groups were combined. At the initial time point (8–10 weeks postpartum), postpartum women were more sensitive to pain (i.e., lower PPTs) than nulligravid women at the pfannenstiel site ($p < 0.001$; **Table 2**). At the follow up timepoint (24–26 weeks postpartum), postpartum women continued to demonstrate heightened sensitivity to pain at the pfannenstiel site ($p = 0.001$; **Table 2**).

Baseline PPTs Prior to Fatiguing Trunk Flexor Exercise (Experimental Session 2)

There was no difference in baseline PPTs between women who had a vaginal delivery and women who had a Cesarean delivery at 8–10 weeks postpartum (NAILBED: 169.2 ± 87.5 vs. 221.1 ± 129.4, respectively, $p = 0.225$; SUPERIOR RECTUS ABDOMINIS: 117.2 ± 55.7 vs. 140.1 ± 74.1, respectively, $p = 0.371$) or 24–26 weeks postpartum (NAILBED: 157.9 ± 89.9 vs. 235.9 ± 114.3, respectively, $p = 0.063$; SUPERIOR RECTUS ABDOMINIS: 101.0 ± 41.2 vs. 134.5 ± 65.9, respectively, $p = 0.124$), so both groups were combined. At the initial timepoint, postpartum women had lower PPTs than nulligravid women at the nailbed ($p = 0.026$; **Table 2**) and the superior rectus abdominis site ($p = 0.031$; **Table 2**). By 26 weeks postpartum, there was no difference in baseline pain at the nailbed between postpartum and nulligravid women ($p = 0.326$; **Table 2**), but postpartum women continued to be more sensitive to pain at the superior rectus abdominis site ($p = 0.027$; **Table 2**) compared with the nulligravid women.

TABLE 1 | Subject characteristics: nulligravid and postpartum.

	Initial (8–10 weeks postpartum)		Follow up (24–26 weeks postpartum)	
	Nulligravid (*n* = 14)	**Postpartum (*n* = 27)**	**Nulligravid (*n* = 14)**	**Postpartum (*n* = 26)**
Age (years)	25.8 ± 5.3	31.2 ± 5.2*	25.8 ± 6.1	31.4 ± 4.8*
Height (cm)	166.9 ± 7.4	164.3 ± 4.6	166.1 ± 8.6	163.8 ± 4.8
Weight (kg)	63.8 ± 13.1	75.6 ± 12.8*	63.3 ± 8.0	70.7 ± 13.4*
BMI (kg/m^2)	22.8 ± 4.0	28.1 ± 4.8*	22.8 ± 2.2	26.7 ± 4.9*
McGill pain intensity (cm)	0.5 ± 1.1	0.3 ± 0.7	0.3 ± 0.7	0.9 ± 2.0
Oswestry (%)	1.1 ± 2.6	4.3 ± 5.4*	0.9 ± 1.9	5.0 ± 7.3
Fear Avoidance Beliefs Questionnaire (AU)	0.3 ± 0.6	7.7 ± 10.3*	0.5 ± 1.3	7.7 ± 12.3
Pain Catastrophizing Scale (AU)	9.9 ± 6.7	9.8 ± 9.1	6.1 ± 6.1	9.0 ± 9.4
Rectus abdominis muscle thickness (cm)	1.0 ± 0.2	0.8 ± 0.2*	1.0 ± 0.1	0.8 ± 0.1*
Trunk flexor MVC (Nm)	47.4 ± 26.8	27.6 ± 11.5*	44.5 ± 17.2	23.9 ± 10.2*
Trunk flexor time to task failure (s)	655.7 ± 336.3	191.8 ± 161.1*	623.6 ± 405.5	290.7 ± 169.7*
Self-reported physical activity over the previous 12 months ($MET*hr*week^{-1}$)	44.2 ± 29.0 (*n* = 13)	23.1 ± 19.7* (*n* = 25)	30.3 ± 21.6 (*n* = 14)	15.6 ± 17.9* (*n* = 23)
Average minutes/day of moderate physical activity (accelerometer)	47.7 ± 25.0 (*n* = 8)	19.3 ± 19.2* (*n* = 19)	29.3 ± 14.1 (*n* = 8)	16.4 ± 11.2* (*n* = 11)

**Indicates $p < 0.05$. cm, centimeters; kg, kilograms; m, meter; Nm, Newton meters; s, seconds; MET, Metabolic equivalents; hr, hour.*

TABLE 2 | Experimental pain perception.

	Initial (8–10 weeks postpartum)		Follow up (24–26 weeks postpartum)		Protocol 2 (sex differences)	
	Nulligravid (n = 14)	Postpartum (n = 27)	Nulligravid (n = 14)	Postpartum (n = 26)	Men (n = 16)	Women (n = 19)
Pfannenstiel site PPT (kPa)	191.5 ± 43.8	118.7 ± 50.7*	178.2 ± 51.5	111.5 ± 49.2*	*N/A*	*N/A*
Baseline nailbed PPT (kPa)	260.7 ± 69.6	188.4 ± 105.6*	226.1 ± 107.6	190.9 ± 106.3	317.8 ± 162.2	228.2 ± 90.1*
Baseline superior rectus abdominis PPT (kPa)	186.9 ± 84.4	125.7 ± 62.7*	171.9 ± 79.4	115.2 ± 54.5*	217.7 ± 110.4	181.5 ± 90.3
Absolute change in PPT at nailbed (kPa)	−2.6 ± 32.9	6.3 ± 42.3	−12.8 ± 31.5	−10.6 ± 37.4	−29.8 ± 46.4	4.5 ± 27.5*
Absolute change in PPT at superior rectus abdominis (kPa)	27.1 ± 47.0	13.4 ± 27.0	10.5 ± 35.3	16.7 ± 19.4	27.9 ± 39.8	19.7 ± 41.8
Relative change in PPT at nailbed (%)	−0.6 ± 13.0	2.6 ± 24.6	−5.6 ± 20.1	−1.8 ± 22.3	−7.9 ± 17.4	0.9 ± 18.7
Relative change in PPT at superior rectus abdominis (%)	18.7 ± 21.7	10.7 ± 19.4	7.3 ± 19.0	16.6 ± 19.9	16.4 ± 20.6	13.6 ± 20.6

**Indicates $p < 0.05$. PPT, Pressure Pain Threshold; kPa, kilopascals; N/A, Not Assessed.*

PPTs Before and After Fatiguing Trunk Flexor Exercise

At the initial timepoint, women who delivered vaginally and women who delivered via Cesarean section had similar pain responses to exercise at the nailbed (time p = 0.489; time × delivery type p = 0.917; delivery type p = 0.246) and the upper abdomen (time p = 0.019; time × delivery type p = 0.778; delivery type p = 0.382), so both delivery types were combined into one postpartum group. Nulligravid and postpartum women demonstrated an increase in PPT (i.e., local EIH) at the superior rectus abdominis following fatiguing trunk flexor exercise (time p = 0.001; time × group p = 0.241; **Figure 1C**). At the nailbed, postpartum women and nulligravid women demonstrated no change in PPT following exercise (time p = 0.780; time × group p = 0.498; **Figure 1A**). There were no differences in absolute or relative changes in PPTs after fatiguing exercise between postpartum and nulligravid women at the nailbed or superior rectus abdominis site at the initial or follow up timepoints ($p > 0.05$; **Table 2**).

At the second timepoint, no difference was noted in the pain response to exercise in women who delivered vaginally or via Cesarean section at the nailbed (time p = 0.106; time × delivery type p = 0.163; delivery type p = 0.089) or the upper abdomen (time $p < 0.001$; time × delivery type p = 0.650; delivery type p = 0.165), so both delivery types were combined into one postpartum group. Postpartum and nulligravid women had an increase in PPT at the superior rectus abdominis following fatiguing trunk flexor exercise (time p = 0.003; time × group p = 0.472; **Figure 1D**). At the nailbed, PPTs were unchanged following fatiguing trunk flexor exercise (time p = 0.054; time × group p = 0.854; **Figure 1B**).

Associations

At the initial timepoint, EIH (increase in PPTs following exercise) at the superior rectus abdominis site was positively correlated with thickness of the rectus abdominis muscle (r = 0.321, p = 0.026); women with thicker abdominal muscles experienced greater local EIH. At the second timepoint only, exercise-induced changes in PPT at the nailbed was associated with baseline PPT at the nailbed ($r = -0.396$, p = 0.025); women who demonstrated greater baseline PPT at the nailbed reported less EIH than women with lower baseline PPT. Baseline PPT at the superior rectus abdominis was not associated with EIH at the superior rectus abdominis ($r = -0.056$, p = 0.733).

Protocol Two: Men and Women

Subject characteristics, including weight, BMI, trunk flexor strength and fatigability, and physical activity levels are presented in **Table 3**.

Baseline PPTs Prior to Fatiguing Trunk Flexor Exercise

Men demonstrated higher PPTs than women at the nailbed prior to performance of fatiguing exercise (317.8 ± 162.2 kPa vs. 228.2 ± 90.1 kPa, respectively, p = 0.047). Pre-exercise PPTs at the superior rectus abdominis site were similar between men and women (217.7 ± 110.4 kPa vs. 181.5 ± 90.3 kPa, respectively, p = 0.294).

PPTs Before and After Fatiguing Trunk Flexor Exercise

At the rectus abdominis, men and women demonstrated a similar increase in PPTs (i.e., EIH) after fatiguing exercise (**Figure 2B**; time effect p = 0.002; time × sex p = 0.575; sex p = 0.248). At the nailbed, women demonstrated no change in PPTs following fatiguing exercise, while men demonstrated a small decrease in PPTs (hyperalgesia) (**Figure 2A**; time effect p = 0.054; time × sex p = 0.010).

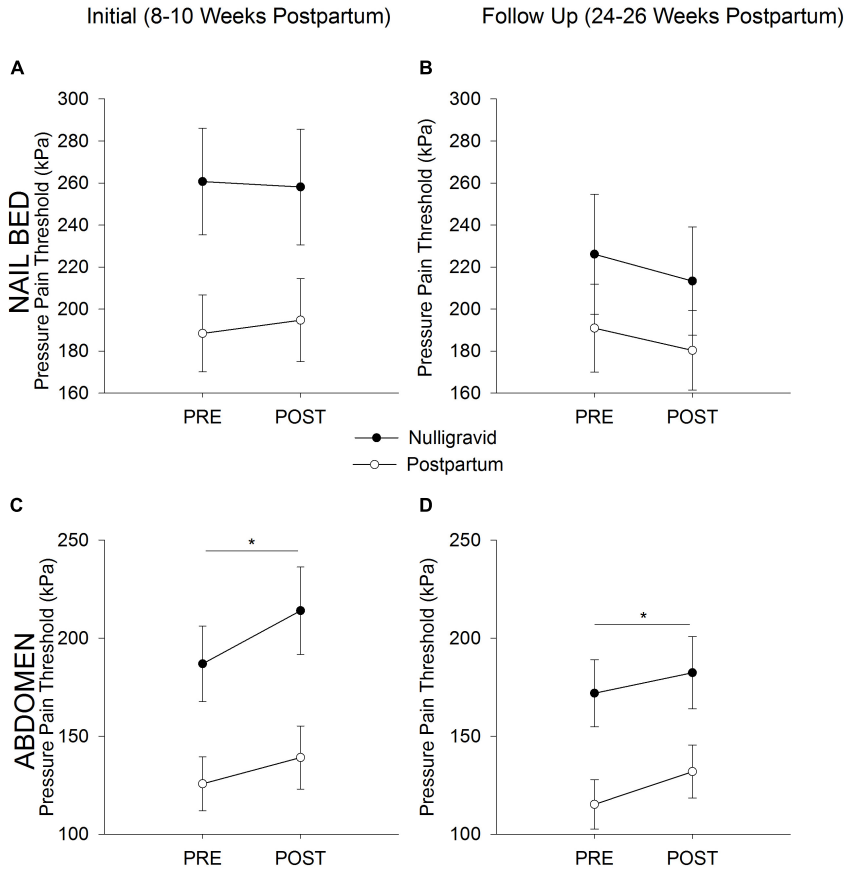

FIGURE 1 | Postpartum vs. Nulligravid PPTs. Pressure Pain Threshold before (Pre) and after (Post) Exercise in Nulligravid and Postpartum Women at the Nailbed **(A,B)** and Abdomen **(C,D)**. Neither postpartum nor nulligravid women demonstrated a change in PPT at the nailbed following fatiguing trunk flexor exercise at the initial **(A)** or follow-up **(B)** time points. Postpartum women had lower PPTs at the nailbed than nulligravid women at 8–10 weeks postpartum **(A)** but had similar PPTs as nulligravid women 24–26 weeks after childbirth **(B)** due to a decline in nulligravid PPTs from initial to follow up. Both postpartum and nulligravid women demonstrated EIH at the superior rectus abdominis site following fatiguing trunk flexor exercise at both the initial **(C)** and follow up **(D)** time points. Postpartum women had lower PPTs than nulligravid women at the abdomen at 8–10 weeks postpartum **(C)** and 24–26 weeks postpartum **(D)**. * indicates $p < 0.05$ (time effect).

Associations

EIH at the abdominal muscle site was positively correlated with rectus abdominis muscle thickness ($r_s = 0.462$, $p = 0.013$) such that thicker muscle was associated with greater EIH. Baseline PPTs at the nailbed were also associated with the change in PPT after exercise ($r = -0.443$, $p = 0.008$) such that those who had the greatest absolute change in PPT had lower baseline PPT. Furthermore, baseline PPTs at the abdomen were not associated with EIH at the abdomen ($r = -0.028$, $p = 0.872$).

DISCUSSION

The main and novel findings of this study are: (1) mode of delivery did not affect pain perception or the impact of exercise on pain perception; (2) postpartum women are more sensitive to pain than nulligravid women, especially at the abdomen; (3) EIH was experienced at the abdomen for all groups following fatiguing intermittent isometric exercise of the trunk flexor muscles; (4) men experienced slight hyperalgesia (decrease in PPTs) at the nailbed following trunk flexor fatiguing exercise; and (5) men and women with thicker abdominal muscles reported greater local EIH.

At the initial time point (8–10 weeks postpartum) in protocol 1, postpartum women had lower PPTs at all body sites tested (nailbed, lower abdomen, upper abdomen) than nulligravid women. In contrast, at 26 weeks postpartum, there was no statistical difference in PPTs at the nailbed between postpartum and nulligravid women. This lack of difference at 26 weeks postpartum was likely due to a decline in PPTs in the nulligravid group between the two testing time points because postpartum women demonstrated no change in PPTs between 8 weeks and 26 weeks postpartum. The heightened sensitivity to pain in the postpartum women, which persists at the abdomen almost 6 months after childbirth, highlights the need for assessment and management of pain throughout pregnancy and the postpartum period to avoid developing chronic pain syndromes (Albert et al., 2001; Norén et al., 2002; Phillips and Clauw, 2011). The increased pain sensitivity at the nailbed, and the lack of change in PPT at the nailbed at 26 weeks

TABLE 3 | Subject characteristics: men vs. nulligravid women.

	Men (n = 16)	Nulligravid women (n = 19)
Age (years)	24.1 ± 6.6	24.4 ± 4.9
Height (cm)	176.8 ± 7.4	167.1 ± 9.1*
Weight (kg)	72.7 ± 8.5	65.6 ± 12.2
BMI (kg/m^2)	23.0 ± 2.3	23.3 ± 3.7
McGill pain intensity (cm)	0.04 ± 0.2	0.4 ± 1.0
Oswestry (%)	2.1 ± 3.2	0.9 ± 2.0
Fear Avoidance Beliefs Questionnaire (AU)	1.9 ± 5.6	0.4 ± 0.8
Pain Catastrophizing Scale (AU)	8.1 ± 8.4	8.9 ± 7.7
Rectus abdominis muscle thickness (cm)	1.3 ± 0.4 (n = 13)	1.0 ± 0.2* (n = 15)
Trunk flexor MVC (Nm)	56.4 ± 23.2	50.4 ± 22.5
Trunk flexor time to task failure (s)	755.3 ± 458.4	647.2 ± 339.5
Self-reported physical activity over the previous 12 months (MET*hr*week^{-1})	59.2 ± 38.6 (n = 15)	43.2 ± 27.2 (n = 17)
Average minutes/day of moderate physical activity	42.0 ± 28.5 (n = 5)	37.8 ± 22.7 (n = 14)

**Indicates $p < 0.05$. cm, centimeters; kg, kilograms; m, meter; Nm, Newton meters; s, seconds; MET, Metabolic equivalents; hr, hour; AU, arbitrary units.*

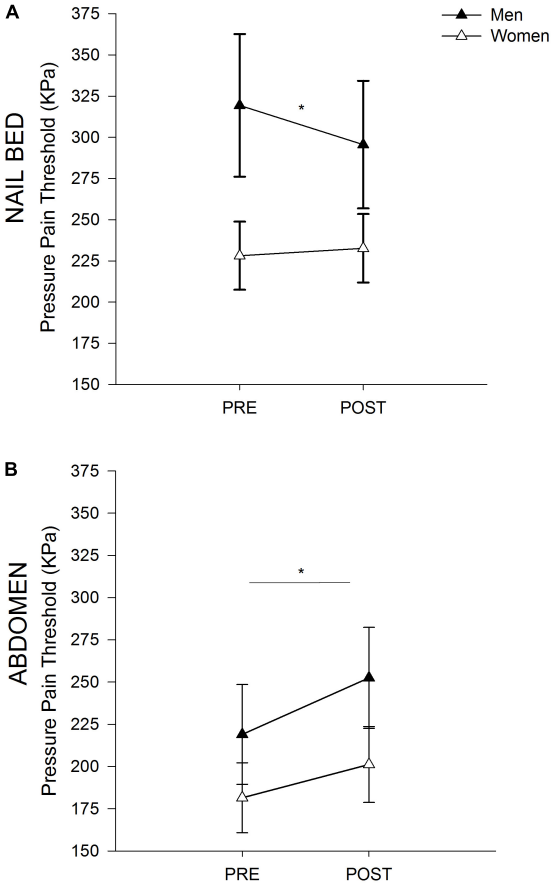

FIGURE 2 | Sex Differences in PPTs. Pressure Pain Threshold before and after Exercise in Men and Women at the Nailbed **(A)** and Abdomen **(B)**. **(A)** Women did not demonstrate a change in PPT at the nailbed following fatiguing trunk flexor exercise, while men demonstrated a decrease in PPT after exercise (hyperalgesia). Men had higher PPTs than women at the nailbed prior to exercise. **(B)** Both men and women demonstrated EIH at the superior rectus abdominis site following fatiguing trunk flexor exercise. Men and women had similar PPTs at the abdomen both before and after exercise. * indicates $p < 0.05$ (time effect).

postpartum suggests that central mechanisms may still be at play in the postpartum group (Staud, 2012). The prevalence of low back and pelvic girdle pain during pregnancy, which often receives minimal treatment, can contribute to central sensitization and the development of chronic pain. Further trauma experienced during labor and delivery (such as surgical intervention, perineal or pelvic floor muscle injury, pelvic joint trauma, etc) and the inflammatory processes which naturally occur as part of the healing process can also contribute to increased sensitization of nociceptors (Chimenti et al., 2018). Further research is needed to understand the role of central sensitization in postpartum women.

To our knowledge, this is the first study to show EIH following fatiguing trunk flexor exercises in any population. The decrease in pain sensitivity (increased PPTs at the abdominal site) following fatiguing trunk flexor exercise experienced by all groups in this study supports the use of abdominal muscle exercise for localized pain relief. This has important clinical considerations because of the prevalence of LBP as well as abdominal pain and incision site pain in postpartum women (Murray and Holdcroft, 1989; Waseem et al., 2011). Furthermore, postpartum women have demonstrated lower trunk flexor strength and lower endurance of both the trunk flexor and lumbopelvic stabilizing muscles compared with nulligravid women (Deering et al., 2018a,b). Thus, incorporating fatiguing exercise of the trunk flexor muscles is especially useful in this population to improve strength and fatigability of this muscle group and to manage pain.

Hypoalgesia was localized to the exercising muscle, which is similar to other studies that report greater EIH at the exercising muscle compared with distal sites (Kosek and Lundberg, 2003). Despite the local EIH effect that was similar between men and women, men reported systemic hyperalgesia (decrease in PPTs) at the nailbed following the trunk flexor exercise while women reported no change in PPTs. Interestingly, sex differences were also present in the baseline pain threshold at the nailbed with men reporting higher PPTs compared with women, and in both protocols baseline pain at the nailbed was associated with the change in PPTs at the nailbed following exercise. We have previously demonstrated similar associations between baseline pain and EIH (Hoeger Bement et al., 2011; Lemley et al., 2016). For example, in women with fibromyalgia, those with lower pain sensitivity (higher PPTs) measured at the finger reported hyperalgesia following exercise (Hoeger Bement et al., 2011). Thus, baseline pain is an important factor in the pain response following exercise; although there may be a critical threshold for

this association to occur and may be site specific. For example, the association occurred when baseline pain was measured at the finger or nailbed but not at the abdomen. Furthermore, there was no relation between baseline pain and EIH when baseline PPTs were relatively low (postpartum and nulligravid women) compared to the significant association when men reported higher baseline PPTs than nulligravid women.

Despite men reporting higher PPTs than women at the nailbed, the lack of a sex difference in PPTs at the abdominal site in this study is unique; men typically report higher PPTs compared with women as reviewed by Racine et al. (2012). The lack of a sex difference may be partially explained by the fact that women tend to have greater abdominal fat than men (Deering et al., 2017). Price et al. (2013) showed that higher pain thresholds occur in areas with excess subcutaneous fat.

Another novel finding of this study was that individuals with thicker abdominal muscles demonstrated greater EIH. Previously we have shown that regional lean mass predicts conditioned pain modulation (CPM) (Stolzman and Hoeger Bement, 2016); adolescents with greater lean mass have more efficient descending pain inhibition. We have also shown that CPM is positively associated with EIH (Lemley et al., 2015; Stolzman and Bement, 2016), and the two conditions likely have shared manifestations (Alsouhibani et al., 2018). Therefore, this study provides additional support regarding the importance of lean mass in producing pain relief following exercise potentially via descending pain inhibition.

In summary, fatiguing exercise of the abdominal muscles, using an intermittent isometric protocol, produced localized EIH in healthy postpartum women, nulligravid women, and men. This has important clinical implications because postpartum women demonstrated greater sensitivity to pain than nulligravid women at multiple body sites suggesting the development of central sensitization. There were also sex differences in pain perception at rest and following exercise. Prior to exercise, men reported less pain at the nailbed than women, and only men reported exercise-induced hyperalgesia at this site (distal from the exercising muscle). In both protocols, baseline pain sensitivity at the nailbed was associated with EIH. Thus, this study provides much needed clinical evidence showing that trunk flex exercises produce localized pain relief and the potential role of baseline pain in this response.

DATA AVAILABILITY

Raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

RD participated in study design, protocol development, procurement of funding, subject recruitment, data collection and analysis, and manuscript writing. TP participated in data collection and analysis and reviewed the manuscript prior to submission. MC participated in procurement of funding, subject recruitment, and manuscript review. SKH participated in study design, protocol development, procurement of funding, data analysis, and manuscript writing. MH participated in study design, protocol development, data analysis, and manuscript writing.

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frontiers in Physiology

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The Relationship Between Blood Flow and Motor Unit Firing Rates in Response to Fatiguing Exercise Post-stroke

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We quantified the relationship between the change in post-contraction blood flow with motor unit firing rates and metrics of fatigue during intermittent, sub-maximal fatiguing contractions of the knee extensor muscles after stroke. Ten chronic stroke survivors (>1-year post-stroke) and nine controls participated. Throughout fatiguing contractions, the discharge timings of individual motor units were identified by decomposition of high-density surface EMG signals. After five consecutive contractions, a blood flow measurement through the femoral artery was obtained using an ultrasound machine and probe designed for vascular measurements. There was a greater increase of motor unit firing rates from the beginning of the fatigue protocol to the end of the fatigue protocol for the control group compared to the stroke group (14.97 ± 3.78% vs. 1.99 ± 11.90%, $p = 0.023$). While blood flow increased with fatigue for both groups ($p = 0.003$), the magnitude of post-contraction blood flow was significantly greater for the control group compared to the stroke group ($p = 0.004$). We found that despite the lower magnitude of muscle perfusion through the femoral artery in the stroke group, blood flow has a greater impact on peripheral fatigue for the control group; however, we observed a significant correlation between change in blood flow and motor unit firing rate modulation ($r^2 = 0.654$, $p = 0.004$) during fatigue in the stroke group and not the control group ($r^2 = 0.024$, $p < 0.768$). Taken together, this data showed a disruption between motor unit firing rates and post-contraction blood flow in the stroke group, suggesting that there may be a disruption to common inputs to both the reticular system and the corticospinal tract. This study provides novel insights in the relationship between the hyperemic response to exercise and motor unit firing behavior for post-stroke force production and may provide new approaches for recovery by improving both blood flow and muscle activation simultaneously.

Keywords: stroke, blood flow, motor unit, fatigue, EMG

INTRODUCTION

In addition to baseline weakness, individuals with stroke can have decreased ability to generate on-going sub-maximal forces during activities, such as walking, that require repeated activation of muscles and this can limit function. For example, individuals with stroke have decreased walking endurance (Dean et al., 2001; Lloyd-Jones et al., 2009; Iosa et al., 2012), and have changes in walking kinematics and kinetics over short distances (Chen and Patten, 2008; Jonkers et al., 2009). In addition, slow walking speeds in people with stroke are associated with greater fatigability of lower limb muscles (Rybar et al., 2014). Despite the functional implications, mechanisms of neuromuscular fatigue (the acute, exercise-induced reduction in the ability to generate force) post-stroke are not well studied.

In healthy individuals and people with stroke, fatigability of muscles can be quantified as a reduction in maximal strength or power or the inability to maintain a submaximal force during ongoing contractions (Enoka and Duchateau, 2008). Fatigability of muscles can originate from factors which limit the nervous system's ability to excite muscle tissue (central fatigue) or from factors that interfere with muscle contractile properties (peripheral fatigue) (Gandevia, 2001; Enoka and Duchateau, 2008; Hunter, 2018). Central fatigue is often quantified through estimates of voluntary activation using the superimposed twitch technique (Allen et al., 1995; Gandevia et al., 1996; Shield and Zhou, 2004). In response to fatiguing contractions, central fatigue is shown as an increase in the amplitude of a superimposed twitch (SIT) force during a maximal effort contraction. At baseline (Horstman et al., 2008) and after fatigue (Knorr et al., 2011; Bowden et al., 2014), individuals with stroke have decreased ability to voluntarily activate musculature fully even with maximal efforts. Electrophysiological studies using transcranial magnetic stimulation have shown this may be due to a loss of excitatory descending drive most likely caused by the stroke-related lesions to the motor cortex (Foltys et al., 2003; Jang et al., 2017; Peters et al., 2017). Based on studies showing decreased excitability in descending motor pathways, it is not surprising that recent evidence suggests that in people with stroke, central fatigue is a more significant contributor to fatigability of the paretic leg muscles than for the non-paretic legs and healthy controls (Riley and Bilodeau, 2002; Hu et al., 2006; Klein et al., 2010; Knorr et al., 2011; Hyngstrom et al., 2012; Bowden et al., 2014; Rybar et al., 2014; Kuhnen et al., 2015; McManus et al., 2017). These studies attribute force generating deficits to baseline reductions in cortical commands, but they do not consider the impact of the build-up of metabolic by-products on muscle function that could contribute to increased fatigability of limb muscles.

Peripheral fatigue refers to fatigue that is due to reductions in muscle contractile function. For example, excessive accumulation of metabolic by-products that occurs with muscle contractions interferes with the excitation-contraction coupling (Kent-Braun et al., 2012). Accumulation of metabolic byproducts can result from inadequate perfusion of the muscle. Following stroke, this may impact contractile properties as blood flow to the muscles of the paretic leg is decreased at rest (Ivey et al., 2004; Billinger et al., 2009; Durand et al., 2015) and during brief, submaximal contractions (Durand et al., 2015) compared with healthy controls. Moreover, limitations in the hyperemic response to exercise is related to strength and other measures of function (Durand et al., 2015). In individuals with stroke, the contribution of inadequate blood flow to decreased muscle contractile properties and fatigability of limb muscles is not known. Inadequate muscle perfusion and accumulation of metabolites within the muscle can also affect neural activation of the muscle via activation of chemo-sensitive group III and IV afferent endings in the muscle (Matthews, 1972; Martin et al., 2008). Understanding the effect of blood perfusion to exercising muscles and motor unit firing is important because cooperation between the two systems may provide a method for recovery.

The association between blood flow and individual motor unit firing behavior during intermittent fatiguing contractions post-stroke has not been studied but may provide important insight for impaired force generation and task endurance in chronic stroke. The purpose of the study was to determine the relationship between the change in blood flow with metrics of fatigue and motor unit firing behavior in stroke and controls. We hypothesized that individuals with stroke would have a blunted hyperemic response to exercise accompanied decreased motor unit firing rates and this relationship would be different than controls.

MATERIALS AND METHODS

Participants

All participants gave informed consent before participation in this study, and the procedures were approved by the Medical College of Wisconsin Institutional Review Board (PRO190103). Ten participants with chronic, hemiparetic stroke (6 male, 4 female, 60 ± 6 years) and nine neurologically intact participants (6 male, 3 female, 63 ± 7 years) participated in the study. General inclusion criteria for stroke participants were: single, unilateral stroke (obtained through verbal communication from the physician and consistent with neurological physical examination); able to ambulate at least 30 feet (with or without an assistive device); ≥6 months post-stroke; at least 18 years old; and able to give informed consent. General exclusion criteria included for stroke participants were: brainstem stroke; any uncontrolled medical condition; contractures of any lower extremity joints; inability to follow 2–3 step commands; substance abuse; people unable to walk more than 10 feet without physical assistance; narrow angle glaucoma; chronic liver or kidney disorders; major psychiatric disorders; neurodegenerative disorders. **Table 1** reports the participants' characteristics.

Torque Measurements

Participants were seated upright on a Biodex System 3 (Biodex Medical Systems, Shirley, NY, United States) with the test leg hip and knee angles at 90 degrees of flexion. Isometric knee extension torque measurements were made using a JR3 E-series load cell (JR3, Inc., Woodland, CA, United States) mounted to the dynamometer spindle by means of a custom aluminum coupling. A quarter inch aluminum arm extended from the axis

TABLE 1 | Participant characteristics.

Participant characteristics		
	Control (*n* = 9)	**Stroke (*n* = 10)**
Sex, Male	6	6
Age (yr)	60 ± 6	63 ± 7
Height (cm)	173.2 ± 14.7	172.1 ± 11.7
Weight (kg)	80.3 ± 14.6	85.9 ± 19.7
Total body fat (%)	35.8 ± 6.5	39.8 ± 4.5
Lower limb muscle mass (kg)	13.0 ± 2.6	13.0 ± 2.6
Fugl-Meyer score	NA	23 ± 7
Physical activity (Met-h/week)	14 ± 7	13 ± 7

of the load cell to a bracket that secured either left or right ankle attachments. The ankle attachments were secured to the test leg two inches above the lateral malleolus. The torque was acquired by an EMG-USB2+ amplifier (256-channel regular plus 16-auxiliary channels, OT Bioelettronica, Turin, Italy), low-pass filtered at 500 Hz, sampled at 2048 Hz, and recorded using the OT Biolab software. The data was then zero phased, low-pass filtered at 15 Hz using a 4th order Butterworth filter prior to analysis.

Voluntary Activation and Resting Twitch Response

The knee extensor muscles were electrically stimulated using a constant current generator (DS7A, Digitimer, Welwyn, United Kingdom) that delivered a rectangular pulse of 100 μs duration over the quadriceps muscle group. The stimulation intensity (range 200 to 500 mA) was set at 20% above the level required to produce a maximal resting twitch amplitude that caused a supramaximal stimulation. The stimulation occurred at the peak torque (visually determined when the torque reached a steady plateau) of a maximum voluntary contraction (MVC) and is referred to as the "superimposed twitch." Once the knee extension torque returned to 0 Nm, a second stimulation was provided to elicit the resting twitch response. The maximal torque generated by the knee extensors in response to the electrical stimulation was acquired. The superimposed twitch was calculated as the magnitude of the increase provoked by the electrical stimulus during the MVC (i.e., peak of superimposed twitch minus the peak of the MVC contraction) (Allen et al., 1995). The resting twitch was the torque magnitude generated from the electrically evoked contraction of the relaxed muscle (i.e., the magnitude of the torque produced at rest). The voluntary activation was defined here as the completeness of motor unit recruitment and firing rate during a MVC and was calculated using an interpolated twitch technique (Shield and Zhou, 2004; Klass et al., 2007):

$$Voluntary\ Activation\ (\%) = \left(1 - \frac{superimposed\ twitch}{resting\ twitch}\right) * 100\%$$

Blood Flow Measurements

The participants rested upright in the Biodex seat for a minimum of 15 min prior to assessments of blood flow. Diameter, blood flow velocity, and volume of blood flow through the superficial femoral artery were obtained with a Doppler angle of insonation fixed at 60 degrees using a linear array 4.0–12.0 MHz transducer designed for vascular imaging and equipped to a Vivid e ultrasound machine (General Electric, Fairfield, CT, United States). Sonography makes it possible to estimate the volume blood flow $\left(\frac{mL}{min} = \left(\frac{cm^3}{min}\right) = velocity\left(\frac{cm}{min}\right) \times area(cm^2)\right)$ by careful measurement of the area, via the image, and the velocity distribution using the Doppler trace ($velocity = frequency \times wavelength$) (Walter et al., 1986). Blood flow measurements during the fatigue protocol were taken immediately after each fatigue cycle (1 cycle = 5 isometric contractions at 40% MVC held for 10s and separated by a 4 s rest, see **Figure 1**) while the participant remained seated upright and still for a 10 s video capture of the superficial femoral artery. The same portion of the artery was able to be visualized following all fatigue cycles because the participants were secured to the chair with a lap belt and the isometric contractions did not result in movement of the lower limb. Only measurements obtained during the first three complete cardiac cycles following each fatigue cycle were included for analysis because local blood flow is a tightly coupled metabolic demand. Blood flow measurements were normalized to lean muscle mass of the whole lower limb determined by the dual-energy absorptiometry (Lunar iDXA, General Electric, Fairfield, CT, United States) analysis. Normalized blood flow was not available for one of the control participants and one of the individuals with stroke because the participants declined body composition analysis.

Surface EMG Recordings

High-density surface electromyograms (HDsEMG) were obtained using a 64 channel 2-D electrode array with 8 mm interelectrode distance (ELSCH064NM2 – 13 rows, 5 columns, OT Bioelettronica, Turin, Italy). A double-sided adhesive sticker designed for and compatible with the array was placed over the array. The holes within the adhesive sticker were filled with a conductive electrode paste (Ten20, Weaver and Company, Aurora, CO, United States). The participant's skin was sterilized with an alcohol swab and rubbed to remove superficial dead skin. The array was placed over the belly of the vastus lateralis, midway between the patella and the greater trochanter. A reference electrode was placed over the ipsilateral lateral malleolus. Signals for each channel were differentially amplified between 1000 and 5000 V/V (participant dependent) and band-pass filtered (10–500 Hz) using the EMG-USB2+ amplifier. The signals were sampled at 2048 Hz, A/D converted to 12 bits, and acquired using the OT Biolab software throughout the duration of the fatigue protocol.

Prior to analysis, a 2nd order bandpass filter (10–500 Hz) and a notch filter (60 Hz) were applied to each channel of the HDsEMG array. The EMG root mean square (RMS) for each channel was calculated for the five consecutive, 10 s isometric contraction $\left(RMS = \sqrt{\frac{1}{N}\sum_{n=1}^{N} x_n^2},\ n = data\ point,\ N = total\ data\ points\right)$ for the first and last cycle of the fatigue protocol (described below **Figure 1**). For a spectral descriptor, the mean frequency of the EMG was also calculated: $f_{mean} = \frac{\int_0^{\frac{f_s}{2}} f\ S(f)df}{\int_0^{\frac{f_s}{2}} S(f)df}$, where S($f$) is the power spectral density (PSD) of the signal and f_s is the sampling

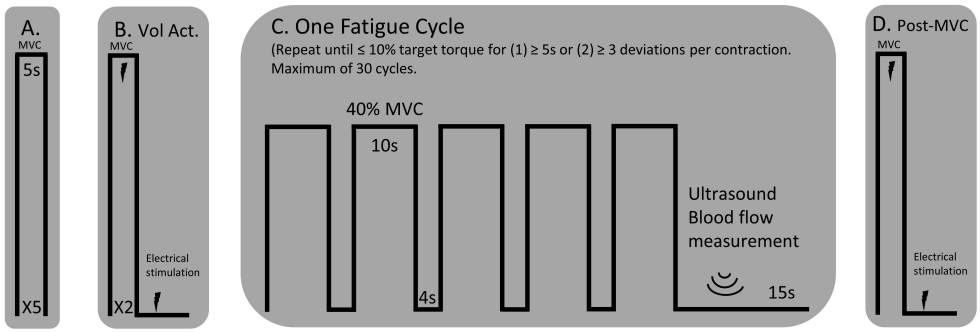

FIGURE 1 | Experimental Protocol. **(A)** MVCs of the knee extensor muscles with a 1-min rest between trials. **(B)** An interpolated twitch procedure was performed for a measure of voluntary activation and resting twitch torque. **(C)** A single cycle for the fatigue protocol consisted of five consecutive 10 s isometric contractions, separated by a 4 s rest, at 40% MVC. A blood flow measurement was performed over the femoral artery of the test leg using an ultrasound machine. The fatigue cycle was repeated until the participant could not hold the isometric contraction within 10% of the target torque for more than three deviations per isometric contraction or for greater than five consecutive seconds. **(D)** A post-MVC including the interpolated twitch procedure was performed immediately after the final blood flow measurement.

frequency. The EMG signal, $x(t)$, has a Fourier transform, $X(f)$, and a PSD $[S(f) = |X(f)|^2/N]$. The RMS and mean frequency values of all channels were averaged together for each fatigue cycle to provide an average RMS and mean frequency of the entire high-density surface array.

Motor Unit Decomposition

The 63 differentially amplified sEMG channels were visually examined to exclude channels that did not show EMG activity. The remaining channels were decomposed to attain instances of single motor unit action potentials by implementing a multichannel convolutive blind source separation algorithm described and validated by Negro et al (Negro et al., 2016). In summary, the decomposition algorithm discriminates between individual motor unit action potentials from multi-unit signals. This and similar approaches have been extensively validated in previous studies (Holobar and Zazul, 2007; Holobar Minetto et al., 2010; Martinez-Valdes et al., 2017; Chen et al., 2018). The motor unit spike trains are estimated from the deconvolved sources using a peak detection algorithm and K-means classification. To provide a normalized index of reliability similar to the pulse to noise ratio, a silhouette measure (SIL) was computed on each estimated source, and the source was considered of acceptable quality if SIL was greater than 0.85. SIL provides a measure of the quality of the extracted motor unit spike trains based on the relative amplitude of the deconvolved spikes compared to the baseline noise. Motor units were identified by applying the decomposition algorithm separately to the first and last cycles of the fatigue protocol. Under the assumption that motor unit action potential shape may change with endurance, motor units were not matched between the first and last cycles; however, under the assumption of stable motor unit action potential properties, this configuration provided the possibility to identify reliably the same motor units within the same fatigue cycle (Martinez-Valdes et al., 2017).

Before calculating the discharge rates of the inter-spike intervals (ISI), abnormally long (>250 ms, 4 Hz) or short (<20 ms, 50 Hz) ISI values were excluded. The instantaneous firing rates of individual motor units were calculated as the inverse of the inter-spike interval (Hz, pulses per second, $\frac{1}{ISI}$). The motor unit action potential instances were time-locked with the torque trace. The mean firing rates were determined as the average firing rates during all five 10 s holds at 40% MVC for one fatigue cycle (i.e., First and Last Cycles, see **Figures 1**, **2**). Therefore, the firing rate of the first fatigue cycle consists of the average firing rate for the first five contractions of the fatigue protocol, and the firing rate of the last fatigue cycle consists of the average firing rate for the last five contractions of the fatigue protocol.

Body Composition and Clinical Measurements

Anthropomorphic measurements were performed by a licensed bio nutritionist. Body composition analysis was conducted using an iDXA (GE Lunar Medical System, Madison, WI, United States) to determine the estimated visceral fat percentage, total lower limb mass, lean muscle mass of the limbs, and percent fat composition of each limb. A Lower Extremity Fugl-Meyer (assessment of motor impairment) was performed by a licensed physical therapist.

Experimental Protocol

The paretic leg of stroke survivors and the right leg of the control participants was tested. **Figure 1** illustrates the timeline of the experimental protocol, and **Figure 2** illustrates single participant examples for a control and an individual with stroke. Participants began by performing at least five baseline isometric maximum voluntary contractions (MVC) of the knee extensor muscles with 1 min of rest between trials. Visual feedback and verbal cueing were provided to the participant. The peak torque of all the trials was used as the MVC. Voluntary activation and resting twitch measures were made following the final MVC trial. A rest period of at least 5 min was provided following the final voluntary activation trial. Participants then performed the fatigue protocol. One cycle of the fatigue protocol consisted of five consecutive isometric contractions at 40% MVC and each contraction lasted

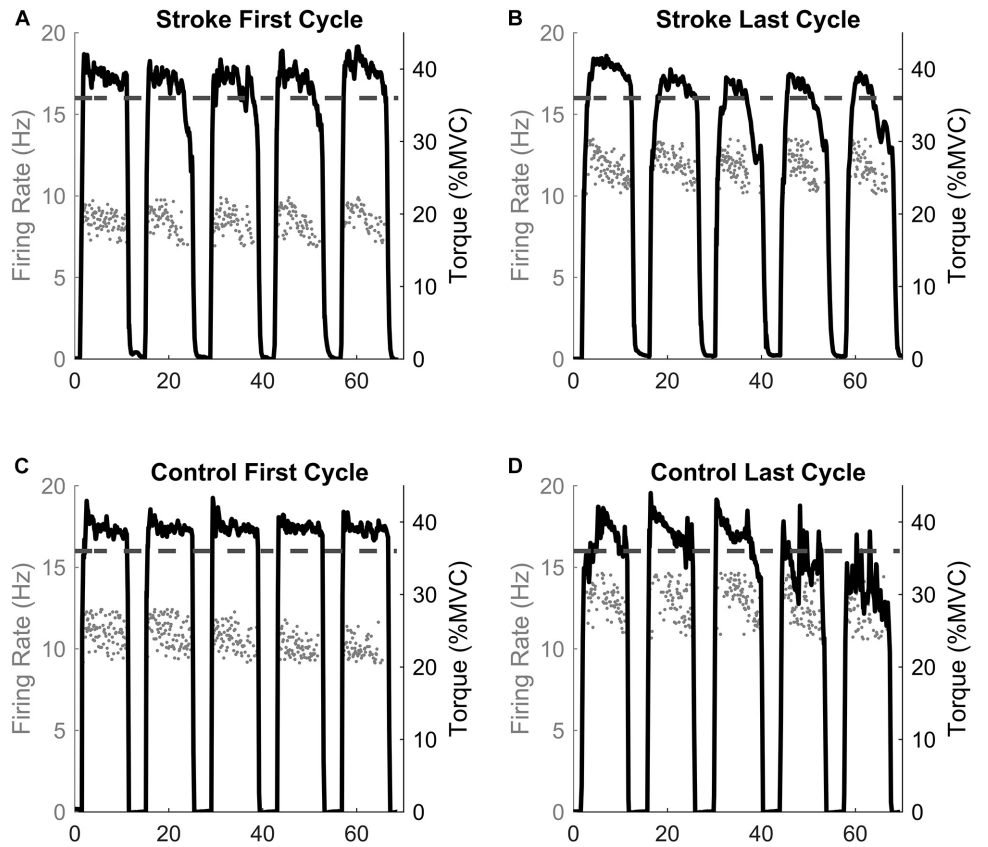

FIGURE 2 | Single participant example. The motor unit firing instantaneous discharges (gray dots) and the corresponding torque generated for the first and last fatigue cycles for the stroke **(A,B)** and control **(C,D)** participants. The dashed line represents the point of task failure if the torque was not maintained above that value. Note the inability to maintain the torque above the task failure line in the last cycle compared to the first cycle.

for 10 s with a 4 s rest provided between each contraction. Visual feedback of the torque trace and target torque was provided using a custom written LabVIEW (National Instruments, Austin, TX, United States) program. Immediately after each fatigue cycle, a measurement of blood flow was taken. An additional 15 s of rest was applied after each cycle to allow ample time for the vascular measurements. A participant repeated the fatigue protocol until the individual was unable to hold the torque trace within 10% of the target torque for 5 s continuously or until the participant had at least three deviations of greater than 10% of the target torque within a 10 s contraction. Final vascular, voluntary activation, and resting twitch measurements were made immediately (within 10 s) following task failure. Surface EMG using the high-density electrode array was recorded throughout the duration of the fatigue protocol.

Statistical Analysis

Data processing was performed in Matlab R2017b (Mathworks, Natick, MA, United States), and statistical tests were performed using IBM SPSS Statistics 24 (IBM, Armonk, NY, United States). Data are reported as the mean ± standard deviation. For one of the control participants and one of the individuals with stroke, body composition analysis was declined; therefore, those participants could not have blood flow normalized to lean muscle mass and were not included in that part of the analysis. The motor units for three control participants did not fulfill the SIL criteria (SIL $>$ 0.85); therefore, only the motor units from six control participants were considered.

Separate repeated measures, mixed model ANOVAs were performed to detect statistical differences between the tested GROUP (stroke, control) and fatigue CYCLE (first and last) in: (1) normalized blood flow; (2) absolute blood flow; (3) motor unit firing rates by participant mean; (3) voluntary activation; (4) resting twitch amplitude; (5) mean EMG RMS; and (6) EMG mean frequency. The between group variable was GROUP. CYCLE was the within group comparison. A multifactorial ANOVA was used to compare the individual motor unit firing rates (main factors: 1) CYCLE (first and last fatigue cycles), and GROUP (Stroke, Control). A repeated measures ANOVA was not used for the individual motor units because detection of the same motor units at the first and last fatigue cycles could not be determined. A Bonferroni correction was used in all *post hoc* testing.

Separate one-way analysis of variances (ANOVAs) were used to test for relative change $\left[\Delta = \left(\frac{variable_{\text{lastcycle}}}{variable_{\text{firstcycle}}} - 1\right) * 100\%\right]$ in: (1) mean MVC; (2) mean EMG RMS; (3) EMG mean frequency;

(4) motor unit firing rate by participant average; (5) mean blood flow (6) voluntary activation; and (7) resting twitch torque. A one-way ANOVA was also used to test for differences in task duration in terms of number of fatigue cycles completed.

Using the least squares estimates method for linear regression models, coefficient of determinations and model parameters were calculated for the following correlations: (1) Δ blood flow and task duration; (2) Δ blood flow and Δ MVC; (3) Δ blood flow and Δ motor unit firing rate; (4) absolute blood flow and MVC torque. ANOVAs were performed to test the significance of the correlations using the F-statistic. A runs test for detecting randomness was used to determine whether the linear regression fits the data. The linear regression models were included if the residuals showed a random, non-systematic pattern.

RESULTS

MVC Torque and Task Duration Measurements

At baseline, controls had a greater knee extension MVC compared to individuals with stroke (129.8 ± 53.2 Nm vs. 76.4 ± 29.4 Nm, $p = 0.003$). The relative decline in MVC was similar for both groups (−39.8 ± 10.1% vs. −34.3 ± 12.6%, $p = 0.311$). There was no difference in the number of fatigue protocol cycles completed (11.9 ± 10.2 cycles vs. 15.7 ± 8.2 cycles, $p = 0.383$).

Voluntary Activation

A significant interaction effect was observed in the voluntary activation measurement between the control and stroke groups [$F(1,17) = 24.9$, $p < 0.001$] as the individuals with stroke had a larger decrease in the voluntary activation from the first cycle to the last cycle of the fatigue protocol (93.6 ± 4.5% to 75.4 ± 10.5, $p < 0.001$) (**Figure 3A**). There was no significant difference in voluntary activation of the control participants (97.4 ± 2.4% to 95.6 ± 4.5%, $p = 0.465$) with fatigue. A main effect of fatigue cycle was observed, $F(1,17) = 37.0$, $p < 0.001$, as there was a decrease in voluntary activation with fatigue. There was also a main effect of group $F(1,17) = 24.8$, $p < 0.001$, where voluntary activation in the stroke group was less than controls. Finally, the stroke group had a greater decrease in the relative change in voluntary activation compared to the controls ($p < 0.001$) (**Figure 3B**). In summary, the individuals with stroke had a greater decrease in voluntary activation with the fatigue protocol, as well as a lower baseline voluntary activation.

Resting Twitch Torque

A significant interaction effect was observed in the resting twitch torque between the control and stroke limbs [$F(1,17) = 7.4$, $p = 0.015$] as there was a greater decline in resting twitch torque response in controls (41.5 ± 17.2 Nm to 18.6 ± 11.1 Nm, $p < 0.001$) compared to individuals with stroke (33.8 ± 17.2 Nm to 22.7 ± 13.0 Nm, $p = 0.002$) (**Figure 4A**). There was also a main effect of cycle [$F(1,17) = 61.3$, $p < 0.001$] but not a main effect of group [$F(1,17) = 0.8$, $p = 0.785$]. Relative change in resting twitch torque showed a significantly greater decrease for the control group compared to the stroke group ($p = 0.005$) (**Figure 4B**). In summary, the control participants had a greater decrease in muscle contractile properties (resting twitch torque) in response to the fatigue protocol.

Femoral Artery Blood Flow

There was a significant main effect of normalized blood flow with fatigue cycle [$F(1,15) = 24.4$, $p < 0.001$] as blood flow increased in both groups with fatigue (**Figure 5A**). There was also a significant main effect of group [$F(1,15) = 40.1$, $p < 0.001$] as blood flow through the femoral artery was greater for the control leg compared to the paretic leg. No significant interaction effect (group*cycle) was observed [$F(1,15) = 1.7$, $p = 0.207$]. Overall,

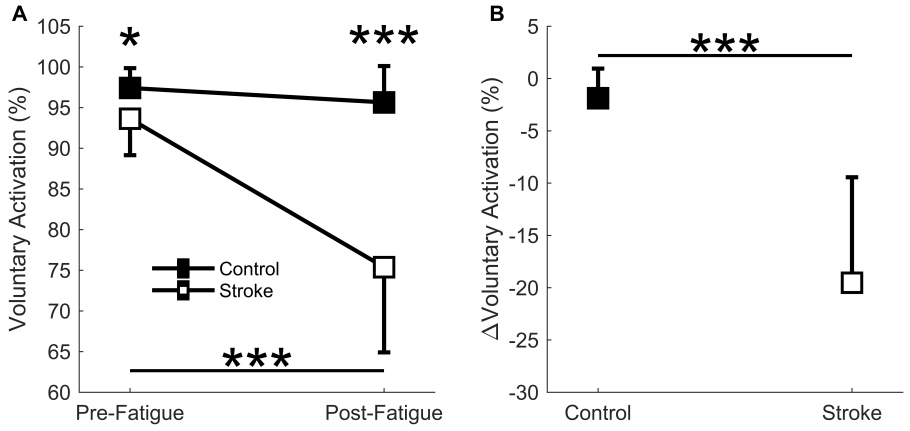

FIGURE 3 | Voluntary activation. Voluntary activation assessed using the twitch interpolation technique comparing the first and last cycle **(A)** and the relative change before and after the fatigue protocol **(B)**. A significant interaction effect ($p < 0001$) was observed as individuals with stroke significantly decrease voluntary activation with fatigue. Voluntary activation was significantly lower for the stroke participants at pre-fatigue ($p < 0.05$) and post-fatigue ($p < 0.001$), and significantly decreased with fatigue for the stroke participants ($p < 0.001$) but not the controls **(A)**. A significantly greater normalized decrease in voluntary activation was observed for the stroke participants ($p < 0.001$) compared to controls **(B)**. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

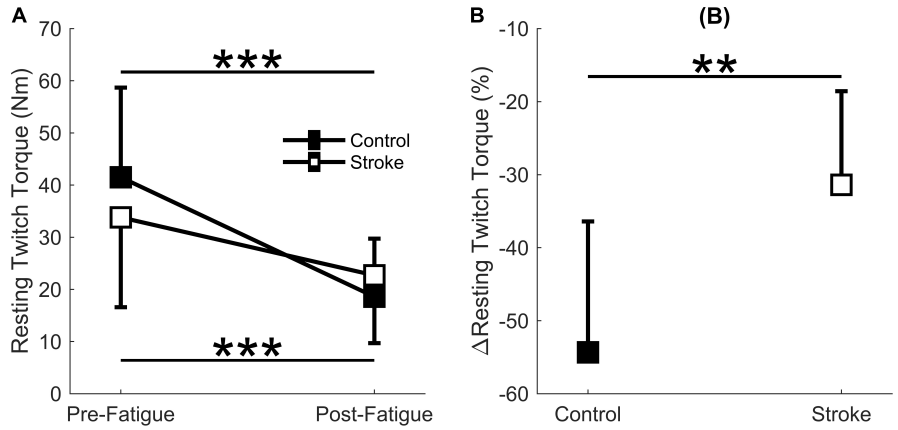

FIGURE 4 | Resting twitch torque. Resting twitch torque amplitude elicited from electrical stimulation to the rectus femoris comparing the first and last cycle **(A)** and the relative change before and after the fatigue protocol **(B)**. A significant interaction effect ($p = 0.015$) was observed as control participants significantly decreased resting twitch amplitude with fatigue. Resting twitch torque significantly decreased for both the stroke participants ($p < 0.001$) and controls ($p < 0.001$) **(A)**. Controls had a significantly greater normalized decrease ($p < 0.01$) in resting twitch torque compared to the stroke participants **(B)**. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

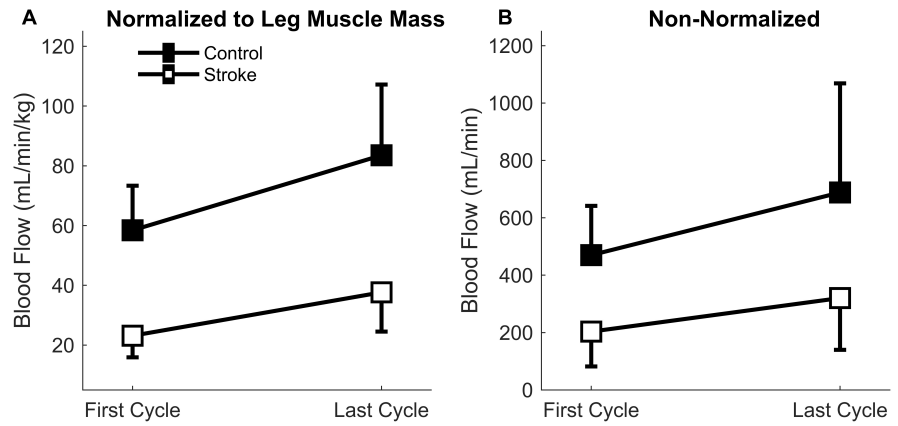

FIGURE 5 | Blood Flow through the femoral artery. Blood flow normalized to leg muscle mass **(A)** and absolute magnitude **(B)** comparing the first and last cycles. Main effects of limb and fatigue cycler were observed in both cases as both groups significantly increased blood flow with fatigue and the control participants had a greater magnitude of blood flow than the individuals with stroke.

lower levels of normalized blood flow were observed in the stroke group, but blood flow increased with fatigue regardless of group.

Because the normalized blood flow only applied to 17 of the participants (one control and one individual with stroke did not partake in body composition analysis), the absolute magnitude (non-normalized) was also calculated so that all participants were included (**Figure 5B**). Similar results were obtained for the absolute blood flow through the femoral artery in comparison to the normalized blood flow. A significant main effect of fatigue cycle [$F(1,17) = 11.6$, $p = 0.003$] and group [$F(1,17) = 11.4$, $p = 0.004$] was observed. There was no interaction effect [$F(1,17) = 1.060$, $p = 0.318$]. The data shows that regardless of group there was an increase in blood flow, but the blood flow response magnitude was greater for controls.

Regression analysis showed that changes in blood flow significantly correlated with task duration for the control group [$r^2 = 0.6$, $F(1,7) = 9.4$, $p = 0.018$, $\beta = 0.141$] as greater increases in blood flow related to longer task duration (**Figure 6**). Blood flow and task duration did not correlate for the stroke group [$r^2 = 0.010$, $F(1,8) = 0.079$, $p = 0.786$, $\beta = 0.031$]. Blood flow after the first fatigue cycle and MVC torque generation significantly correlated together for both control [$r^2 = 0.51$, $F(1,7) = 7.170$, $p = 0.030$, $\beta = 2.300$] and stroke participants [$r^2 = 0.78$, $F(1,8) = 28.6$, $p < 0.001$, $\beta = 3.375$] (**Figure 7**), showing that stronger individuals produced larger post-contraction blood flow responses. Changes in blood flow were not significantly correlated with changes in MVC torque generation for stroke [$r^2 = 0.003$, $F(1,8) = 0.020$, $p = 0.890$, $\beta = -0.020$] or control groups [$r^2 = 0.03$, $F(1,7) = 0.257$, $p = 0.628$, $\beta = 0.034$].

Motor Unit Firing Rates

A total of 186 motor units for the control leg (102 First Cycle, 84 Last Cycle), and 145 motor units for the participants with stroke (86 First Cycle, 59 Last Cycle) were accepted for data processing

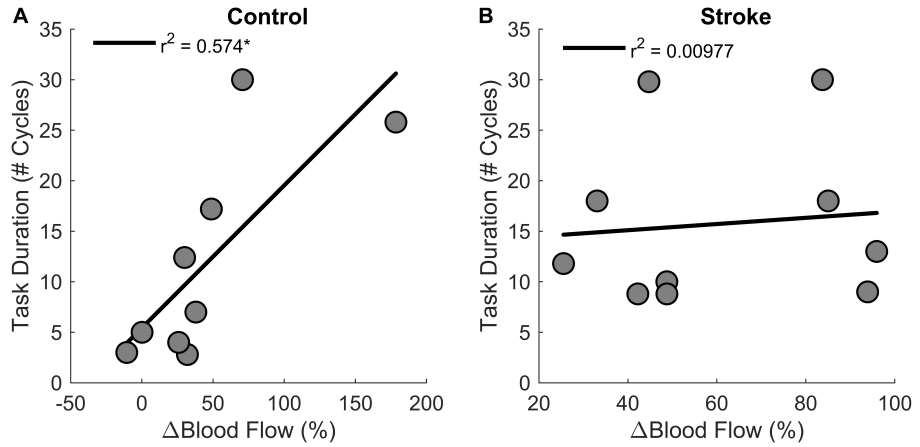

FIGURE 6 | Changes in blood flow and task duration. Changes in blood flow significantly correlated with task duration for the control group ($p = 0.018$) **(A)** but not the stroke group ($p = 0.786$) **(B)**.

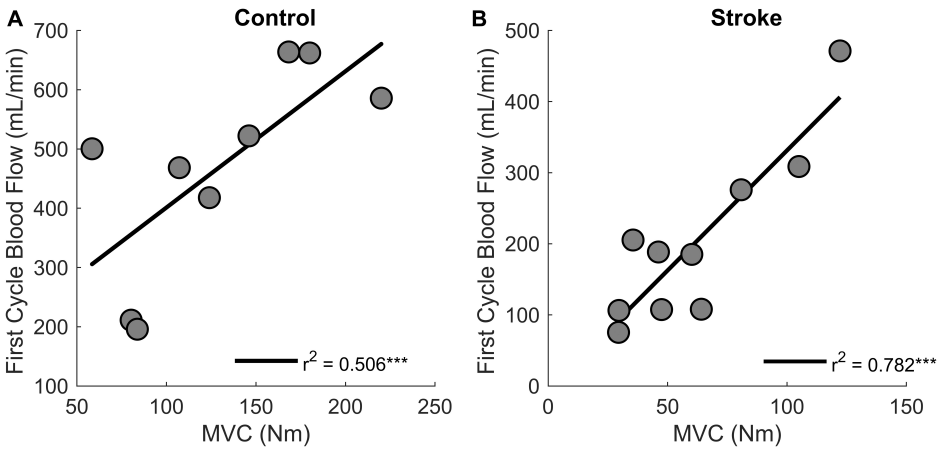

FIGURE 7 | MVC and blood flow after the first cycle. Higher magnitudes of blood flow were observed for stronger individuals in both control ($p = 0.030$) **(A)** and stroke groups ($p < 0.001$) **(B)**.

(totaling 331 motor units). When comparing the mean motor unit firing rates for the individual participants, a significant interaction effect occurred (group*cycle) [$F(1,14) = 10.3$, $p = 0.006$] as there was a greater increase in firing rates for the controls as compared to stroke (**Figure 8A**). Main effects of group [$F(1,14) = 10.9$, $p = 0.005$] and cycle [$F(1,14) = 13.5$, $p = 0.003$] were also observed. The mean firing rates of the individual motor units for each group and cycle were: control = 13.3 ± 3.0 Hz; stroke = 10.5 ± 2.7 Hz; first cycle = 11.5 ± 3.2 Hz; last cycle = 12.8 ± 3.1 Hz. Comparisons of the mean motor unit firing rate for the first fatigue cycle showed control motor unit firing rates were significantly greater ($p = 0.039$) than the participants with stroke. The relative change in firing rate (**Figure 8B**) was greater for control participants (15.0 ± 3.8%) compared to the individuals with stroke (2.0 ± 11.9%) [$F(1,14) = 6.6$, $p = 0.023$]. In summary, the control leg had higher motor unit firing rates and greater motor unit discharge adaptation with fatigue compared to the individuals with stroke.

EMG Root Mean Square (RMS)

There was a significant interaction effect (cycle*group) observed [$F(1,17) = 10.5$, $p = 0.005$] as there was a greater increase in the RMS magnitude in the control participants (435.3 ± 302.3 μV to 551.9 ± 353.9 μV) as compared to individuals with stroke (244.4 ± 161.1 μV to 279.45 ± 161.1 μV). A main effect of fatigue cycle [$F(1,17) = 36.4$, $p < 0.001$] was observed, but there was not a main effect of group [$F(1,17) = 3.9$, $p = 0.065$]. The relative increase in EMG RMS was greater in the controls compared to individuals with stroke (32.4 ± 17.7% vs. 16.0 ± 9.4%), $F(1,17) = 6.6$, $p = 0.020$. In summary, the magnitude and relative change in RMS was greater for the control participants compared to the participants with stroke.

EMG Mean Frequency

There was a main effect of fatigue cycle [$F(1,17) = 45.6$, $p = 0.016$] as the mean EMG frequency decreased (73.3 ± 14.8 Hz to 67.1 ± 14.6 Hz) from the first cycle to last cycle. There was not a

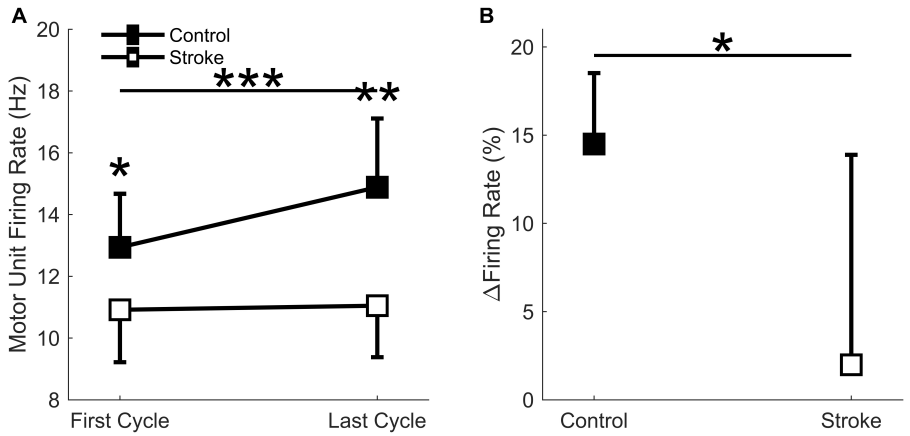

FIGURE 8 | Motor unit firing rate. A significant interaction effect was observed ($p = 0.006$) as the control participants significantly increased motor unit firing rates with fatigue cycle. Stroke participants had significantly lower firing rates at the first ($p < 0.05$) and last ($p < 0.01$) fatigue cycles, and only the control group significantly increased firing rates with fatigue ($p < 0.001$) **(A)**. Control participants had a significantly greater increase in normalized firing rates compared to the stroke group ($p < 0.05$) **(B)**. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

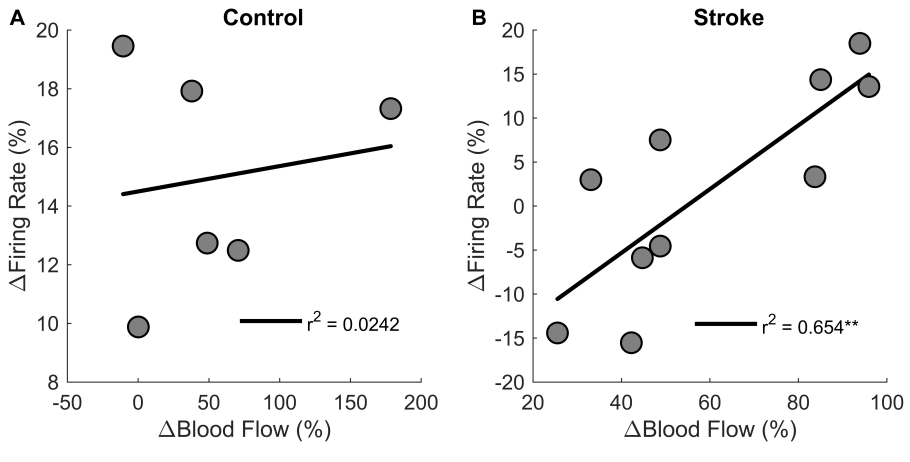

FIGURE 9 | Changes in motor unit firing rates and blood flow. Change in motor unit firing rate correlated with changes in blood flow from the first fatigue cycle to the last fatigue cycle for the participants with stroke ($p < 0.01$) **(B)** but not for controls **(A)**.

main effect of group [$F(1,17) = 0.3$, $p = 0.573$], but the interaction effect (cycle*group) approached significance [$F(1,17) = 4.3$, $p = 0.054$]. There was a significantly greater relative decrease in EMG mean frequency in controls compared to individuals with stroke ($-14.9 \pm 11.9\%$ vs. $-1.14 \pm 15.6\%$), [$F(1,17) = 14.5$, $p = 0.048$]. In summary, the decrease in relative change and magnitude in mean EMG frequency was greater for the control than stroke participants.

Correlations of Relative Changes in Blood Flow and Motor Unit Firing Rates

Correlations were performed to test if changes in motor unit firing rates correlated with changes in blood flow from the first fatigue cycle to the last fatigue cycle (**Figure 9**). There was a positive correlation between change in blood flow and change in motor unit firing rates [$r^2 = 0.6$, $F(1,8) = 15.1$, $p = 0.004$, $\beta = 0.362$] for the individuals with stroke, but not for the control group [$r^2 = 0.00242$, $F(1,4) = 0.1$, $p = 0.768$, $\beta = 0.009$]. In summary, changes in blood flow had a significant positive correlation with changes in firing rate for the participants with stroke but not for controls, showing that motor unit firing rates correlated with blood flow only for the individuals with stroke.

DISCUSSION

To understand the role of muscle perfusion during fatiguing contractions after a stroke and the effect on motor unit activity, we compared the hyperemic response of healthy controls to individuals with stroke and associated this with differences in motor unit firing rates. The novel findings in this study were: (1) the net magnitude of the blood flow through the femoral artery was blunted for people with stroke compared to healthy controls during intermittent, fatiguing contractions

(**Figure 5**); (2) greater increases in blood flow related to longer task duration for the control group but not the stroke group (**Figure 6**); and (3) changes in motor unit firing rates correlated with changes in blood flow for people with stroke (**Figure 9**). The individuals with stroke had a lower magnitude of blood flow through the femoral artery, but this did not have a lesser impact on peripheral metrics, such as resting twitch torque, than the controls; furthermore, the positive correlation among changes in motor unit firing rates and blood flow suggests a connection between muscle perfusion and neural inputs to the motoneuron. The differences seen in metrics of fatigue between controls and stroke are likely due to different mechanisms of fatigue for each group. Despite a decreased hyperemic response in the stroke group, blood flow appears to have a greater impact on peripheral fatigue and task duration for the control group. Factors which impact central fatigue such as associations between corticospinal and corticoreticular systems and inhibitory spinal reflex pathways may have a greater influence on blood flood and motor unit firing rates for the stroke group compared to the control group. Potential mechanisms and motor implications are discussed below.

Post-stroke Differences in Hyperemia

Post-contraction hyperemia was greater for controls compared to participants with stroke (**Figure 5**). In addition, greater torque production resulted in greater hyperemia for both control and stroke groups (**Figure 7**). As was previously shown, an increased blood flow response in the paretic leg positively correlated with limb strength (Durand et al., 2015). Stronger individuals typically have a greater blood flow response, likely because of strength-associated differences in the intramuscular pressure and mechanical compression of the vessels (Barnes, 1980; Hunter et al., 2009; Durand et al., 2015). Therefore, it is likely that differences in blood flow magnitude are partially due to strength differences between and within the control and stroke groups.

It is also possible that autonomic dysregulation contributed to the blunted magnitude of the blood flow response in the individuals with stroke. After a stroke, a simultaneous decrease in parasympathetic activity and increase in sympathetic activity has been observed during Ewing's battery assessment and during continuous monitoring of heart rate variability, blood pressure, and respiration (Dütsch et al., 2007; Xiong et al., 2014). This may increase peripheral vasoconstriction, lowering the blood flow magnitude in the stroke group compared to the control group.

Post-stroke Blood Flow Deficits Do Not Relate to Metrics of Peripheral Fatigue or Task Duration

Healthy individuals and people with stroke had similar relative declines in MVC torque and similar time to task failure, indicating that both groups reached a similar degree of neuromuscular fatigue at task failure; however, differences in the degree of central fatigue for the stroke group compared to the degree of peripheral fatigue for the control group showed different mechanisms of fatigue. The differences in central and peripheral fatigue, as well as differences in target torque, may explain why control participants did not have longer task duration compared to the stroke participants as we expected. The control group had greater fatigue within the muscle fibers (peripheral fatigue) as indicated by larger decreases in resting twitch torque (**Figure 4**) and greater compression of the EMG spectrum compared to the stroke group (De Luca, 1984; Merletti et al., 1990; Riley and Bilodeau, 2002; Knorr et al., 2011). Individuals with stroke, however, showed greater decreases in voluntary activation (**Figure 3**), less increase in EMG RMS, and less motor unit rate modulation (**Figure 8**) compared to the controls. These metrics indicate some combination of decreases from descending motor command and excitatory afferent inputs, as well as increases from inhibitory afferent inputs, to the motoneuron (Gandevia, 2001; Riley and Bilodeau, 2002; Knorr et al., 2011; Bowden et al., 2014; McManus et al., 2017). We also observed that greater increases in blood flow correlated with longer task duration only for the control group (**Figure 6**). Thus, the differences in metrics of central and peripheral fatigue may explain why blood flow did not have a greater disturbance to muscle contractile properties for the participants with stroke.

Controls had a much greater reduction in metrics of peripheral fatigue. Although blood flow increased for both groups, changes in blood flow related to task duration only for the control group. The accumulation of metabolic byproducts, such as extracellular K^+/Ca^{2+} from a slowed sarcoplasmic reticulum uptake and H^+ from lactic acid (Fitts, 2011; Kent-Braun et al., 2012), decreases muscle contractile properties and conduction velocity (Tesch et al., 1983; Kupa et al., 1995). This was reflected in lower post-fatigue twitch amplitudes (Kent-Braun et al., 2012) (**Figure 4**) and compression of the EMG power spectrum (De Luca, 1984) for the control group but not the stroke group. This aligned with previous fatigue studies that involved sustained contractions; however, those studies did not associate these metrics with metabolite accumulation and perfusion (McComas et al., 1973; Riley and Bilodeau, 2002; Fimland et al., 2011; Knorr et al., 2011; Bowden et al., 2014; McManus et al., 2017). We were able to study the effects of blood flow on muscle fiber properties because the intermittent task (as opposed to a sustained task) involves a perfusion-dependent mechanism – greater perfusion results in reduced metabolic accumulation (Sadamoto et al., 1983). This was evident for the controls as participants with greater blood flow had longer task duration (**Figure 6**). The differing effects of blood flow on metrics of peripheral fatigue and task duration suggest that the influence of post-contraction hyperemia was not the same for controls and participants with stroke.

It appears the individuals with stroke were inhibited by central fatigue before blood flow was a factor in muscle force generation. One might expect the greater perfusion to result in a greater clearance of metabolites (Sadamoto et al., 1983) and greater fatigue resistance; however, blood flow did not correlate with task duration for the stroke participants (**Figure 6B**). Like previous studies, voluntary activation was significantly reduced at task failure (**Figure 3**; Newham et al., 1995; Riley and Bilodeau, 2002; Knorr et al., 2011; Bowden et al., 2014). The decreased voluntary activation assumes a decreased neural drive to the muscle (Allen et al., 1995; Shield and Zhou, 2004). This is likely

facilitated by a loss of excitatory drive from the descending motor pathways after the stroke lesion (Murase et al., 2004; Jang et al., 2017). The reduced voluntary activation not only reflects a reduction in the integrity of the corticospinal tract, but also explains a portion of the post-stroke impairments in the firing rate magnitude and rate modulation (**Figure 8**) manifested in the reduced EMG (Gemperline et al., 1995). It is likely that the effects of deficient blood flow on muscle fiber properties and task duration were not observed because of the dominant central factors contributing to neuromuscular fatigue.

Motor Unit Firing Rates Correlated With Blood Flow Changes After Stroke

We saw that changes in blood flow correlated with motor unit firing rate modulation in the stroke group. Contrary to this study, previous studies observed either no change or decreases in motor unit firing rates with fatigue during sustained fatiguing contractions for both healthy individuals and individuals with stroke (Garland et al., 1994; Adam and De Luca, 2005; Mettler and Griffin, 2016; McManus et al., 2017); however, It has also been observed that motor unit firing rates increased with fatiguing contractions (Contessa et al., 2016). This study differed because motor unit firing rates were observed during intermittent contractions rather than sustained contractions. Motor unit firing rates increased in all control participants with fatigue; however, motor unit firing rates decreased in magnitude in 4/10 stroke participants. These four individuals also had lower changes in blood flow compared to those with greater rate modulation (**Figure 9B**). A possible explanation for the positive correlations observed for the stroke group but not the control group may be that the stroke lesion disrupted the common drive to the corticospinal and corticoreticular tracts (Buford and Davidson, 2004; Herbert et al., 2015; Brownstone and Chopek, 2018). Because corticoreticular projections originate from common areas as the corticospinal projections (primarily from the primary motor cortex and premotor cortical areas), disruptions of these common areas after a stroke likely have implications on autonomic control of blood flow from the reticular system and activation of the motoneuron pools through the corticospinal system. In animal models with decerebration or ischemic cortical lesions, inhibitory inputs from corticobulbar pathways to the reticular formation are lost, causing a greater relative increase in reticulospinal influence and a concurrent relative decrease in corticospinal influence (Hounsgaard et al., 1988; Herbert et al., 2015). This is thought to be the case in human stroke as there is evidence of increased activity in the reticulospinal pathways, possibly from the disinhibition of the reticular formation, and a loss of corticospinal input (Foltys et al., 2003; Kline et al., 2007; McPherson et al., 2008, 2018; Murphy et al., 2015; Jang et al., 2017). The decreased post-contraction blood flow through the femoral artery in this study may indicate increased autonomic drive, possibly caused by a disinhibited reticular drive providing an excessive sympathetic outflow. The reticular system is known to modulate autonomic outflow and is a source for the vasoconstrictor norepinephrine (Nette et al., 2006; Schwarz et al., 2015). The positive correlation between the hyperemic response and motor unit firing rate modulation is likely a result of the damage to these common pathways – controls and individuals with stroke that had less damage to these common pathways likely had greater modulation of motor unit firing rates and voluntary activation, as well as greater inhibition to the sympathetic outflow from the reticular formation.

An alternative explanation for the positive correlation between blood flow and motor unit modulation (**Figure 9B**) is that the decreased blood flow for the individuals with stroke may have an inhibitory effect on the motoneuron pool. Motor unit firing rates may be associated with blood flow because metabolic accumulation activates group III/IV afferent pathways, and these pathways are known to have an inhibitory effect on the motoneuron pool during fatiguing exercise (Kaufman et al., 1983; Amann et al., 2008; Amann, 2012; Taylor et al., 2016). The inhibitory effects of ischemia on motor unit output may also be enhanced because these pathways may be hyper-excitable after a stroke (Hidler and Schmit, 2004; Li, 2017). Recently, we showed a greater decrease in paretic motor unit firing rates during a sub-maximal contractions with a transient (5 min) bout of whole limb ischemia as compared to controls (Murphy et al., 2018). Therefore, the lack of motor unit modulation and inability to significantly increase EMG RMS may partly be due to enhanced inhibitory afferent input from group III/IV pathways. Though it is possible these afferents were activated in the control group, central factors were not significantly affected before peripheral fatigue was a factor. Enhanced group III/IV pathways may also explain why changes in motor unit firing rates significantly correlated with changes in blood flow for the stroke group but not the control group. Thus, it is plausible that the stroke-related deficiencies in the peripheral blood flow to the exercising muscle and a change in the excitability of the group III/IV afferent pathways may enhance the inhibitory response to ischemia, restricting motor unit firing rates and modulation.

Implications for Motor Performance

Results from this study have important implications for motor performance and motor recovery post-stroke. The intermittent contractions, as opposed to sustained, showed the effects of perfusion on motor performance after a stroke. This provides insight into functional motor performance because many activities of daily living, such as walking, consist of intermittent contractions. Currently, stroke rehabilitation strategies consider cardiovascular fitness and limb strength as separate issues. This study shows the importance of considering the cooperation between the corticoreticular and corticospinal tracts in force generation after stroke. We showed that individuals with stroke that have greater post-contraction blood flow also have greater strength (**Figure 7**) and greater motor unit modulation (**Figure 9**). It seems logical that improving the hyperemic response to exercise would help improve fatigue resistance, but the data from this study would suggest that neural issues are the limiting factor to force generation during fatiguing exercise. It appears that improving neural function should remain the primary focus for rehabilitation strategies; furthermore, the evidence of increased reticulospinal influence together with the

loss of corticospinal influence suggests that these two systems may be an undeveloped method for recovery. The loss of common pathways between the reticular system and spinal motoneurons may explain the systemic loss of both blood flow and motor unit rate modulation in some of the stroke participants. It is also possible that as neural function improves, perfusion to the muscle becomes more important. It has been shown that the hyperemic response to non-fatiguing muscle contractions has a positive relationship to limb function (Durand et al., 2015). Taken together, this data allows us to speculate that improving the neural contributions to the hyperemic response of limb muscles to exercise and motor unit rate modulation could optimize motor recovery in people with stroke.

ETHICS STATEMENT

All participants gave informed consent before participation in this study, and the procedures were approved by the Medical College of Wisconsin Institutional Review Board (PRO190103).

AUTHOR CONTRIBUTIONS

All authors contributed to the study design, interpretation of data, approved to the final version of the manuscript to be published, and agreed to be accountable for all aspects of the work. SM and MD collected and processed the data.

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Effects of Ankle Muscle Fatigue and Visual Behavior on Postural Sway in Young Adults

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Ankle muscle fatigue has been shown to increase body sway. In addition, body sway in quiet upright standing is reduced when saccadic eye movements are performed. The purpose of this study was to investigate the effects of visual information manipulation on postural control during ankle muscle fatigue in young adults. Twenty young adults performed: (1) two 60-s trials in quiet bipedal standing with eyes open, eyes closed, and while performing saccadic eye movements; (2) maximum voluntary isometric contractions in a leg press device, custom-made to test ankle plantar flexion force; (3) a calf raise exercise on top of a step to induce ankle muscle fatigue; and (4) a repetition of items 1 and 2. Postural sway parameters were compared with two-way ANOVAs (vision condition × fatigue; $p < 0.05$). Ankle muscle fatigue increased anterior-posterior and medial-lateral displacement and RMS of sway, as well as sway area. Saccadic eye movements reduced anterior-posterior displacement and RMS of sway and area of sway compared to eyes open and eyes closed conditions. Both saccadic eye movements and eyes closed increased the frequency of AP sway compared to the eyes open condition. Finally, anterior-posterior displacement, anterior-posterior RMS, and both anterior-posterior and medial-lateral sway frequency were affected by an interaction of fatigue and vision condition. Without muscle fatigue, closing the eyes increased anterior-posterior displacement and RMS of sway, compared to eyes open, while during muscle fatigue closing the eyes closed reduced anterior-posterior displacement and had no significant effect on anterior-posterior RMS. In conclusion, body sway was increased after induction of ankle muscle fatigue. Saccadic eye movements consistently reduced postural sway in fatigued and unfatigued conditions. Surprisingly, closing the eyes increased sway in the unfatigued condition but reduced sway in the fatigued condition.

Keywords: fatigue, posture, vision, saccadic eye movements, human movement, sensorial integration

INTRODUCTION

Postural control is essential for the performance of daily activities. Postural oscillations (postural sway) need to be controlled because they may interfere with performance and large oscillations could even contribute to the loss of balance. Recent studies showed that saccadic eye movements can positively affect postural control (Rodrigues et al., 2013, 2015; Bonnet and Baudry, 2016a). When saccadic movements are performed during standing, postural sway is reduced to allow accurate gaze shifts, which is an indication of functional integration of posture and gaze control (Stoffregen et al., 2006). This integration is attained by afferent (minimizing the changes of the projected image on the retina) and efferent (attenuating postural sway in an attempt to connect pre- and post-saccadic views of the scene) mechanisms (Guerraz and Bronstein, 2008). The reduction of postural sway has practical implications for performance in standing tasks (Zemková and Hamar, 2014).

Previous studies have conclusively shown that ankle (calf) muscle fatigue increases postural sway (Vuillerme et al., 2001, 2006; Boyas et al., 2011, 2013). The effects of ankle muscle fatigue on postural control have been explained by impairments of somatosensory input (Gribble and Hertel, 2004b), such as decreased position sense acuity (Björklund et al., 2000) and reduced neural transmission (Qu et al., 2009). As muscle fatigue directly affects somatosensory information (Gribble and Hertel, 2004a,b), this may be discarded by the postural control system at a central level during muscle fatigue, causing increased reliance on visual information (Vuillerme et al., 2001, 2006; Ledin et al., 2004). Previous studies have shown that visual information may compensate for the destabilizing effects of ankle muscle fatigue during quiet standing (Vuillerme et al., 2001, 2006; Ledin et al., 2004; Boyas et al., 2011, 2013). On the other hand, the evidence on the negative effects of the absence of vision on postural control (greater postural sway) during ankle muscle fatigue is inconclusive (Corbeil et al., 2003). Saccadic eye movement may serve as a strategy to increase postural stability under ankle muscle fatigue. Understanding whether saccadic eye movements provide a short-term solution for improving postural control under ankle muscle fatigue can contribute to developing strategies to combat balance impairments.

Assuming that (1) the ankle muscle fatigue increases postural sway due to impaired proprioception, (2) vision can reduce the increase in postural sway with ankle muscle fatigue, and (3) postural sway in quiet upright standing is reduced when saccadic eye movements are performed, the purpose of the present study was to investigate the effects of visual information manipulation (eyes closed, eyes open with fixed target, and eyes open with saccadic eye movements) on postural sway during ankle (calf) muscle fatigue in young adults. We hypothesized that the effects of saccadic eye movements and eye closed are stronger in the fatigued than in the unfatigued condition. Specifically, saccadic eye movements will alleviate the effects of ankle muscle fatigue, reducing postural sway compared to a condition with eyes open with a fixed gaze direction, while closing the eyes will increase postural sway compared to a condition with eyes open with a fixed gaze direction under ankle muscle fatigue. In addition to parameters reflecting the magnitude of sway, we analyzed the frequency content of the sway signals, as this may provide some insight into motor strategies used.

MATERIALS AND METHODS

Participants

Twenty young male adults (1.74 ± 0.06 m: 1.60–1.86 m; 75.97 ± 12.91 kg: 58.70–108.90 kg; 24 ± 3 years old: 20–30 years old) participated in this study. Exclusion criteria were the use of drugs that interfere with postural control (e.g., cardiovascular medication, antidepressants, benzodiazepines, opioids, and diuretics), self-report of musculoskeletal and/or neuromuscular impairments in the previous 6 months, and impairments in visual acuity not corrected by lenses. This study was carried out in accordance with the recommendations of Helsinki declaration, Ethics Committee on Human Research of the São Paulo State University, Bauru. The protocol was approved by the Ethics Committee on Human Research of the São Paulo State University, Bauru (CAAE: #48439015.0.0000.5398). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Experimental Protocol

The participants were instructed not to perform any strenuous physical activity in 48 h before the evaluation. They performed a warm-up with walking and stretching of 5 min before the start of the experimental protocol. In addition, they performed a series of familiarization trials (three or four trials) in the leg press instrument before the maximum voluntary isometric contractions (MVICs).

The following sequence of tasks was performed: (1) postural control protocol; (2) MVIC protocol; (3) ankle muscle fatigue protocol; (4) postural control protocol; and (5) MVIC protocol. No rest period was allowed between trials, and testing was started as soon as possible after the fatigue protocol, and the time between the fatigue protocol and the postural control trials (<6 min) was expected not to allow fatigue recovery (Barbieri et al., 2016).

Postural Control Protocol

The participants were tested in quiet bipedal (side-by-side) standing, barefoot, on a single force plate [AccuGait, Advanced Mechanical Technologies Inc. (AMTI), Boston, MA, USA], 50 cm × 50 cm, collecting data at a sample rate of 200 samples/s. They placed their feet side-by-side and shoulder-width apart, and the position of their feet was reproduced in all subsequent trials, by drawing their foot contours on a paper sheet fixed to the force plate. Two 60-s trials, before and during ankle muscle fatigue, of the following postural control conditions were performed: (1) eyes open (EO): quiet standing with gaze fixation on a stationary target positioned in front of the participant; (2) eyes closed (EC): quiet standing with closed eyes; and (3) saccadic eye movements (SE): quiet standing, performing saccades directed to a target appearing

on one side of a monitor, then disappearing and reappearing simultaneously on the opposite side of the monitor once per 2 s. The monitor was positioned 1 m away from the participant's eyes. The target was a red dot, 2 cm in diameter, on a white background with a subtended visual angle of approximately 1.15°. The total distance (19.5 cm) between right and left targets comprised a visual angle of 11° to avoid head movements (Rodrigues et al., 2015). Stimuli were generated by Flash Mx software (Macromedia) and presented on an LCD monitor (37.5 cm × 30 cm, LG, Faltron L1952H, 50/60 Hz, 0.8A). The order of the trials was randomized for each participant. For all trials, the participants were instructed to stand quietly in an upright position. In addition, in the EO and SE, the participants were instructed to keep their gaze on the target. An experienced researcher ensured that the participants remained quiet and complied with gaze instructions.

The center of pressure (CoP) was determined from the ground reaction forces by means of moment-of-force equilibrium calculations. The first 10 s of each recording were ignored to avoid potential disturbances resulting from delayed stabilization after the participant stepped onto the force plate. The data were filtered with a fourth-order low-pass Butterworth filter with a cut-off frequency of 5 Hz. Total displacement and root mean square (RMS), expressing CoP movement, were calculated for the anterior-posterior (AP) and medial-lateral (ML) directions, separately. In addition, the sway area (area of an ellipse containing 95% of the CoP data) and finally the median frequency of sway were calculated (Duarte and Freitas, 2010). The last parameter was calculated by employing spectral analysis of the position time series, separately for both movement directions.

Gaze behavior was recorded with a mobile eye tracker (Mobile Eyes-5 glasses, ASL, Bedford, MA, USA) during EO and SE. The data acquisition rate was 60 samples/s. The eye tracker system was calibrated using the nine-point calibration method. Calibration was also checked periodically between trials. Gaze fixation was defined as the stabilization of gaze (when two times points of gaze standard deviation—95% confidence interval—were less than one degree of visual horizontal and vertical angles) over 99 ms (Rodrigues et al., 2016; Gotardi et al., 2019; Santinelli et al., 2019). We analyzed the following parameters: number of fixations, mean duration of fixations, normalized total duration of fixations (the sum of fixations divided by the duration of the trial), and the area of fixation displacement (area of an ellipse that contained 85% of the horizontal and vertical fixation position data; Rodrigues et al., 2016). The area of fixation displacement for SE was analyzed separately for the right and left targets.

Maximum Voluntary Isometric Contraction Protocol

The MVIC was performed in a leg press device, custom-made to test ankle plantar flexion. A load cell with a precision of 0.1 kgf was used in combination with a signal amplifier (CSA/ZL-100Kgf, MK Control, São Paulo, Brazil) to collect force data. The force data were acquired using Labview software (National Instruments Inc., Austin, TX, USA) at a rate of 1,000 samples/s. The participants were seated in a backward inclined chair, with the hip joints flexed 90°, knee joints fully extended, and the feet in a neutral position with only the distal half of the feet contacting the load cell. The position of the feet on the device was marked to maintain the same position over the trials. The joint angles were determined by a mechanical goniometer. The participants were firmly secured with straps fastening legs and shoulders. The participants performed the task with both legs, with the instruction to produce maximum force as fast as possible without flexing the knee joint. Total contraction duration was 5 s. Participants performed two attempts before and after the ankle muscle fatigue protocol, with 2 min rest between attempts. The participants were verbally encouraged to perform the muscle contractions. The MVIC was determined as the mean of the peak values in the two attempts before and after the muscle fatigue protocol.

Ankle Muscle Fatigue Protocol

Muscle fatigue was induced by a calf raise exercise performed standing on top of a step (**Figure 1**; Barbieri et al., 2013). The speed of the exercise was controlled by a metronome at 30 beats/min. Initially, the participants performed some practice trials. The instruction was to repeatedly perform plantar flexion and dorsiflexion of the ankle over the complete range of motion at the frequency of movement indicated by the metronome. Participants were allowed to touch the back of a chair with their hands to ensure balance. The fatigue protocol was stopped when participants indicated to be unable to continue, or when

FIGURE 1 | Schematic representation of the ankle muscle fatigue protocol.

they reduced the range of ankle plantar flexion compared to the beginning of the protocol, or when they no longer performed at the desired movement frequency after encouragement. To rate the level of fatigue, a 20-point Borg scale (Borg, 1982) was filled in by the participants before and immediately after the muscle fatigue protocol. The endurance time during the fatigue protocol was recorded.

Statistical Analysis

The dependent variables were statistically analyzed with SPSS 15.0 for Windows ($\alpha < 0.05$). The data were normally distributed and verified by the Shapiro--Wilk test. The body sway parameters were compared through two-way ANOVAs (fatigue: before and after the muscle fatigue protocol; vision: EO, EC, and SE) with repeated measures for both factors. Tukey's *post hoc* tests were used to find differences among levels. The MVIC parameter and gaze parameters (separately for EO and SE) were analyzed with a Student's *t* test for repeated measurements, to assess the effect of fatigue. Partial η^2 was reported to express effect size and interpreted as small ($\eta^2 > 0.01$), medium ($\eta^2 > 0.06$), or large ($\eta^2 > 0.14$; Cohen, 1988).

RESULTS

Maximum Voluntary Isometric Contraction and Fatigue Protocol

The ankle muscle fatigue protocol lasted on average 270 s (±188 s – range: 94–955 s). The individuals reported a Borg score of 18 (±2–range: 15–20) after the fatigue protocol. In addition, the MVIC was reduced by 7% (range: 3–15%; $t_{19} = 2.25$, $p < 0.032$; before the fatigue protocol: 809 ± 231 N; after the fatigue protocol: 754 ± 188 N).

Postural Sway

The mean values, standard deviations, *p*'*s*, and effect sizes of CoP parameters in EO, EC, and SE before and after the muscle fatigue protocol are presented in **Table 1**. Main effects of fatigue on all parameters expressing amplitude of sway were found. In addition, vision conditions (main effects of vision condition) affected all AP amplitude parameters and frequency of sway in both directions. Finally, AP displacement, AP RMS, and both AP and ML sway frequency were affected by an interaction of fatigue and vision condition. In the next paragraph, we first present the significant fatigue and vision condition interaction effects and subsequently the significant main effects of fatigue and vision condition.

ANOVAs indicated interaction effects between fatigue and vision condition (**Figure 2**) on AP displacement ($F_{2,32} = 3.93$) and RMS ($F_{2,32} = 3.33$) of sway. *Post hoc* tests indicated that SE reduced AP displacement and RMS in the fatigued condition ($p = 0.005$ and $p = 0.003$, respectively) and in the unfatigued condition ($p = 0.006$ and $p = 0.006$, respectively), compared to the EO fixed gaze condition. Without muscle fatigue, closing the eyes increased AP displacement and RMS of sway ($p = 0.041$ and $p = 0.050$, respectively), compared to

TABLE 1 | Mean values and standard deviations of the center of pressure parameters and gaze parameters according to conditions before and after the fatigue protocol.

		Unfatigued condition			Fatigued condition			*p*		
		Eyes open	Saccadic eye movements	Eyes closed	Eyes open	Saccadic eye movements	Eyes closed	Fatigue	Condition	Interaction
Body sway parameters	AP displacement (cm)	305.32 ± 100.38	233.09 ± 82.65	347.89 ± 112.36	448.49 ± 169.80	311.89 ± 133.01	378.30 ± 100.44	**0.001** (0.46)	**0.001** (0.44)	**0.036** (0.17)
	ML displacement (cm)	111.89 ± 24.12	111.42 ± 20.79	111.95 ± 17.63	131.85 ± 22.39	125.92 ± 32.10	127.25 ± 27.84	**0.002** (0.41)	0.750	0.687
	AP RMS	0.38 ± 0.11	0.28 ± 0.09	0.43 ± 0.13	0.56 ± 0.21	0.39 ± 0.15	0.49 ± 0.13	**0.001** (0.48)	**0.001** (0.45)	**0.047** (0.15)
	ML RMS	0.14 ± 0.03	0.15 ± 0.04	0.14 ± 0.02	0.16 ± 0.02	0.16 ± 0.04	0.17 ± 0.04	**0.006** (0.33)	0.777	0.606
	Area (cm^2)	1.04 ± 0.42	0.78 ± 0.33	1.09 ± 0.35	1.72 ± 0.84	1.27 ± 0.68	1.57 ± 0.60	**0.001** (0.65)	**0.005** (0.27)	0.509
	AP median frequency (Hz)	0.69 ± 0.18	1.27 ± 0.62	0.96 ± 0.43	0.67 ± 0.25	1.02 ± 0.55	1.11 ± 0.54	0.490	**0.001** (0.36)	**0.038** (0.15)
	ML median frequency (Hz)	2.19 ± 0.92	2.14 ± 1.04	2.40 ± 0.84	1.53 ± 0.47	2.25 ± 1.59	2.44 ± 1.19	0.278	**0.042** (0.16)	**0.043** (0.14)

P-values refers to main effects of fatigue and condition and interaction effects between fatigue and condition. Significant effect sizes are given in parentheses. AP, anterior-posterior; ML, medial-lateral; RMS, root mean square.

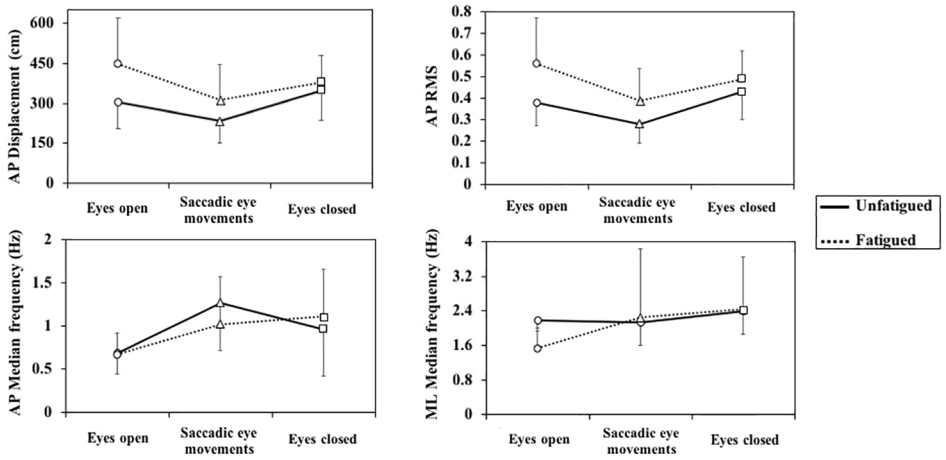

FIGURE 2 | Fatigue × vision interactions for center of pressure parameters. AP, anterior-posterior; ML, medial-lateral.

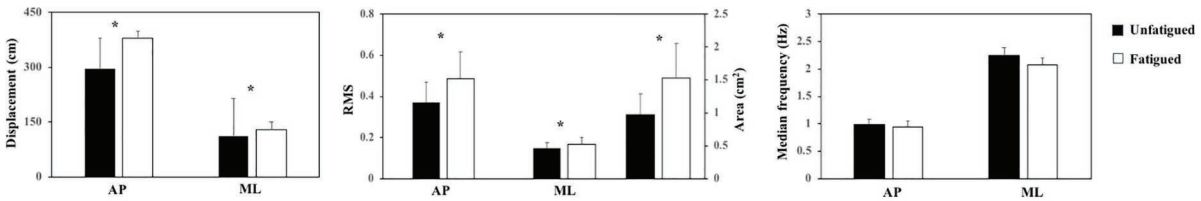

FIGURE 3 | Means and standard deviations (main effect of fatigue) of the center of pressure parameters before and after ankle muscle fatigue. AP, anterior-posterior; ML, medial-lateral. *Indicates a difference between before and after ankle muscle fatigue.

EO, while during muscle fatigue closing the eyes reduced AP displacement (p = 0.048) and had no significant effect on AP RMS (p = 0.096). Ankle muscle fatigue had no effects on AP displacement and RMS in the EC (p = 0.133 and p = 0.056, respectively), and it increased AP displacement and RMS with EO (p = 0.003 and p = 0.002, respectively) and with SE (p = 0.011 and p = 0.026, respectively). Overall, these results suggest less visual dependence in the fatigued state and higher sensitivity to fatigue with eyes open, in contrast to our hypothesis.

With respect to interaction effects between fatigue and vision condition on the sway frequency, *post hoc* tests indicated that SE coincided with increased frequency of AP sway in the unfatigued and in the fatigued conditions (p = 0.001 and p = 0.016) compared to the EO fixed gaze condition. Closing the eyes similarly increased AP sway frequency in the unfatigued and fatigued conditions (p = 0.018 and p = 0.002) compared to the EO. The frequency of ML sway increased during SE (p = 0.035) and closing the eyes (p < 0.001) relative to the EO fixed gaze condition in the fatigued condition only. A significant *post hoc* effect of fatigue on frequency content was found only for the ML direction in the EO, where fatigue coincided with increased frequency (p < 0.001).

The main effect of fatigue is presented in **Figure 3**. Ankle muscle fatigue increased AP and ML displacement ($F_{1,19}$ = 16.44 and $F_{1,19}$ = 12.99, respectively) and RMS of sway ($F_{1,19}$ = 17.99 and $F_{1,19}$ = 9.40, respectively), as well as sway area ($F_{1,19}$ = 36.59).

The main effect of vision conditions is presented in **Figure 4**. The vision conditions affected AP displacement ($F_{2,34}$ = 15.04) and RMS ($F_{2,34}$ = 15.73) of sway and area of sway ($F_{2,32}$ = 7.03). In line with our hypothesis, SE reduced AP displacement and RMS of sway and area of sway compared to EO (p < 0.001) and EC (p < 0.01). However, in contrast to our hypothesis, differences between EO and EC were not significant. Vision condition also affected AP ($F_{2,38}$ = 10.83) and ML sway frequency ($F_{2,33}$ = 3.67). Both saccadic eye movements and closing the eyes increased the frequency of AP sway compared to the EO (p < 0.001 and p < 0.005, respectively). ML sway frequency was higher with eyes closed than with eyes open (p = 0.006).

Effects of Muscle Fatigue on Gaze Behavior

In the fatigued EO condition, the number of fixations was higher (t_{19} = −2.32), and the mean duration of fixations was lower (t_{19} = 2.67) compared to the unfatigued EO condition (**Table 2**). In addition, the variability of the location of fixations was larger in the fatigued condition (t_{19} = −2.68). There were no effects of muscle fatigue on eye movement parameters in the SE (p > 0.05).

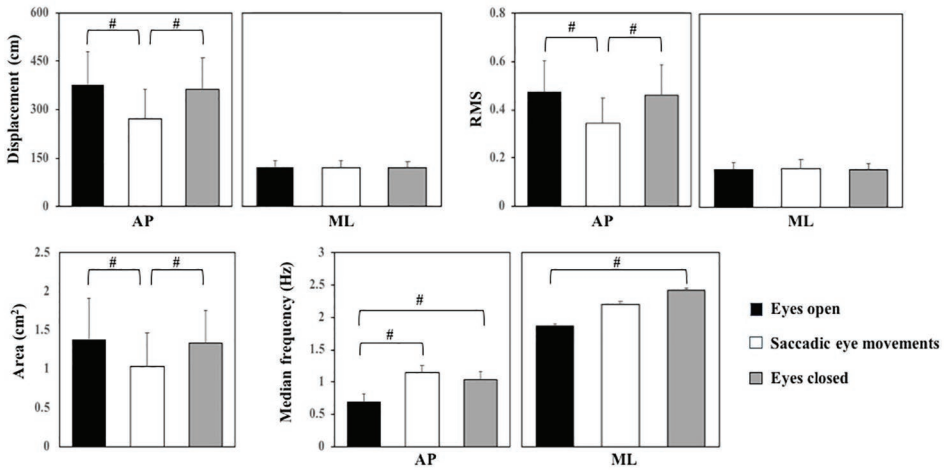

FIGURE 4 | Means and standard deviations (main effect of vision conditions) of the center of pressure parameters for eyes open, saccadic eye movements, and eyes closed condition. AP, anterior-posterior; ML, medial-lateral. #Indicates a significant *post hoc* difference between conditions.

TABLE 2 | Means and standard deviations of gaze parameters for eyes open and saccadic eye movements before and after ankle muscle fatigue.

		Unfatigued condition			Fatigued condition		
		Eyes open	**Saccadic eye movements**	**Eyes closed**	**Eyes open**	**Saccadic eye movements**	**Eyes closed**
Gaze parameters	Number of fixation (*n*)	29.91 ± 19.14 (***p* < 0.03, 0.15**)	111.57 ± 24.40 (*p* = 0.64)	–	35.78 ± 16.84	113.02 ± 16.49	–
	Mean duration of the fixations (s)	3.12 ± 1.89 (***p* < 0.01, 0.24**)	0.47 ± 0.10 (*p* = 0.74)	–	2.12 ± 1.35	0.47 ± 0.07	–
	Normalized total duration of fixations (%)	95.68 ± 4.14 (*p* = 0.21)	84.94 ± 10.33 (*p* = 0.31)	–	93.36 ± 7.41	87.26 ± 6.09	–
	Area of fixation displacement (pixels)	579.08 ± 350.30 (***p* = 0.015, 0.27**)	RS: 1238.01 ± 674.86 (*p* = 0.88) LS: 1199.74 ± 546.47 (*p* = 0.49)	–	934.08 ± 697.92	RS: 1220.96 ± 688.64 LS: 1302.17 ± 773.36	–

RS, right side; LS, left side. The P-values and significant effect sizes are given in parentheses.

DISCUSSION

We investigated the effects of visual information manipulations and ankle muscle fatigue on postural sway in young adults. The calf muscles are considered to play a major role in postural control (Panzer et al., 1995), and in line with this hypothesis, ankle muscle fatigue increased postural sway, in agreement with previous studies (Vuillerme et al., 2001, 2006; Boyas et al., 2011, 2013). We showed reduced ankle muscle strength after the fatigue protocol, which may have impaired neuromuscular control of upright posture (Gribble and Hertel, 2004a), as it may have limited the ability to produce or sustain the required force output of the ankle muscles for stabilization of the upright posture (Ledin et al., 2004; Vuillerme et al., 2006). In addition to impairments in muscle contractile efficiency, decreased proprioceptive acuity may have contributed to impaired control (Gribble and Hertel, 2004a; Boyas et al., 2011). Ankle muscle fatigue affected the gaze behavior in the EO condition. A higher number of fixations, reduced mean duration of fixations, and more variability in location of the fixations may suggest reduced attention to the visual task in the fatigued condition (Stoffregen et al., 2006; Bonnet and Baudry, 2016b) but may also reflect that increased sway interferes with gaze fixation on a stationary target. These effects of muscle fatigue on postural and gaze behavior can be explained by physiological mechanisms, which are characterized by peripheral disturbances at the level of the active muscles, and the central nervous system fails to drive the motoneurons adequately (Gandevia, 2001).

The novelty of this study was that the interaction effects of vision and fatigue were not consistent with our hypothesis. Saccadic eye movements did reduce sway similarly in the fatigued and unfatigued conditions, and closing the eyes only affected sway in the unfatigued condition. So, in contrast to our hypothesis, these results indicate overall reduced rather

than increased effects of visual information with fatigue. The attenuation of postural sway during SE in ankle muscle fatigue suggests that fatigue did not reduce the benefit of an increased retinal flow caused by saccades for postural control (Rodrigues et al., 2015). Although we did not measure any physiological parameter, the literature is consistent to indicate that muscle fatigue causes central and peripheral disturbances, such as decreased somatosensory input (Gribble and Hertel, 2004b) and reduced neural transmission (Qu et al., 2009). However, our results suggest that physiological disturbances may not enough to impair the functional integration between posture and gaze control, which partially compensate the effects of ankle muscle fatigue on body sway. Therefore, using eye saccadic movement may serve as a strategy for increasing postural stability under ankle muscle fatigue. In addition, SE coincided with reduced postural sway in comparison to the EO and EC conditions. Similarly, previous studies indicated that although saccades briefly suppress visual perception, they coincide with improved postural control (Stoffregen et al., 2006; Rodrigues et al., 2013, 2015). Possibly, SE requires greater postural stability to allow more accurate gaze shifts (Stoffregen et al., 2006). Alternatively, postural control during saccadic eye movements may improve, as it becomes more automatic and regulated by lower-level structures, such as the cerebellum or basal ganglia (Bonnet and Baudry, 2016a). We observed an increase in the frequency of AP sway when performing saccadic eye movements, which may reflect a compensatory strategy to deal with the reduced sensory input during the saccades, as discussed above. In addition, the saccadic movement reduced visual information, which can lead to stiffening of the ankle joints through cocontraction, causing reduced and higher frequency of sway.

Surprisingly and in contrast to our hypothesis, closing the eyes increased body sway relative to the eyes open with fixed gaze direction condition only in the unfatigued condition. The absence of this effect in the fatigued condition contrasts with quite consistent effects of closing the eyes on postural sway reported in the literature (Winter, 1995; Agostini et al., 2016). However, vision has been estimated to account only for 10% of the sensory input used for balance control when standing (Peterka, 2002). Fatigue is thought to affect sensory information mainly through a change in muscle spindle thresholds (Corbeil et al., 2003). This may suggest that information from other modalities (e.g., foot sole pressure and vestibular information) could compensate for these effects, without increasing visual dependence. In turn, this would suggest that ankle muscle fatigue affects balance more through its effects on motor output of the postural control system than through its effects on the sensory estimates of body orientation. In the present experiment, subjects were found to increase the frequency of postural sway when closing their eyes, which may reflect lower thresholds of postural responses in intermittent feedback control (Tanabe et al., 2016), increased gains in continuous feedback control (Maurer and Peterka, 2005; Pruszynski and Scott, 2012), or increased stiffness through increased tonic ankle muscle contraction (Ledin et al., 2004; Bonnet, 2016). The latter could be a compensatory strategy to deal with the reduced sensory input when closing the eyes, especially in the presence of fatigue. In this context, it is important to note that sway is not minimized in a normal upright stance and be reduced at the cost of somewhat increased muscle activity (Houdijk et al., 2015). Since tonic muscle activity in bipedal stance is low, this strategy might still be feasible in the fatigued condition. However, we did not observe a consistent increase in sway frequency with fatigue.

The muscle fatigue protocol used in the present study allowed for variability in exertion, and endurance was quite variable between participants. However, all participants reported a hard to extremely hard level of exertion during the fatigue protocol, and MVIC was reduced after the fatigue protocol in all of them. This would suggest that levels of fatigue were comparable. The findings cannot be generalized to different fatigue levels or to fatigue in other muscle groups involved in postural control.

In conclusion, postural sway increased after induction of ankle muscle fatigue. Saccadic eye movements consistently reduced postural sway in fatigued and unfatigued conditions. Surprisingly, closing the eyes increased sway in the unfatigued condition but reduced sway in the fatigued condition. The implication of these findings that individuals can adjust sensory weights to improve postural control after ankle muscle fatigue, but these adjustments are dependent upon vision conditions. This suggests that when tasks, which require stability and accuracy, are performed under muscle fatigue, the quality of visual information can positively influence postural control and, consequently, task performance. Eye movement or vision manipulations may serve as a strategy for increasing postural stability under ankle muscle fatigue.

ETHICS STATEMENT

The protocol applied in this study was approved by the local Research Ethics Committee (#48439015.0.0000.5398).

AUTHOR CONTRIBUTIONS

FB, TP, and LS designed the study. All authors edited the manuscript. TP, LS, and RB did the experiment and analyzed the data. AZ, SR, PP, JD, FB, and MP contributed to the interpretation of the results and drafted the manuscript. FB, TP, and JD performed the statistical analysis. FB, SR, and PP administrated this project.

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