Medicine & Science IN Sports & Exercise
The Official Journal of the American College of Sports Medicine
www.acsm-msse.org

. . . Published ahead of Print

Evidence That Neuromuscular Fatigue Is Not a Dogma in Patients with Parkinson's Disease

Camilla Martignon[1], Fabio Giuseppe Laginestra[1], Gaia Giuriato[1], Anna Pedrinolla[1], Chiara Barbi[1], Ilaria Antonella Di Vico[1], Michele Tinazzi[1], Federico Schena[1], and Massimo Venturelli[1,2]

[1]Department of Neurosciences, Biomedicine, and Movement, University of Verona, Italy
[2]Department of Internal Medicine, University of Utah, Salt Lake City, UT

Accepted for Publication: 31 August 2021

Medicine & Science in Sports & Exercise, Publish Ahead of Print
DOI: 10.1249/MSS.0000000000002791

Evidence That Neuromuscular Fatigue Is Not a Dogma in Patients with Parkinson's Disease

Camilla Martignon[1], Fabio Giuseppe Laginestra[1], Gaia Giuriato[1], Anna Pedrinolla[1], Chiara Barbi[1], Ilaria Antonella Di Vico[1], Michele Tinazzi[1], Federico Schena[1], and Massimo Venturelli[1,2]

[1]Department of Neurosciences, Biomedicine, and Movement, University of Verona, Italy

[2]Department of Internal Medicine, University of Utah, Salt Lake City, UT

Corresponding author:

Massimo Venturelli, Ph.D.

Associate Professor

Department of Neurosciences, Biomedicine and Movement Sciences. University of Verona

Via Felice Casorati 43

37131 Verona, Italy;

orcid.org/0000-0002-2469-8787

massimo.venturelli@univr.it

This work was partially supported by the Italian Ministry of Research and University (MIUR – Rome, Italy) 5-year special funding (https://www.miur.gov.it/dipartimenti-di-eccellenza). No conflicts of interest, financial or otherwise, are declared by the author(s). The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation, and do not constitute endorsement by ACSM.

ABSTRACT

Purpose: Given the increased level of fatigue frequently reported by patients with Parkinson's disease (PD), this study investigated the interaction between central and peripheral components of neuromuscular fatigue (NF) in this population, compared to healthy peers. **Methods:** Changes in maximal voluntary activation (ΔVA, central fatigue) and potentiated twitch force ($\Delta Q_{tw,pot}$, peripheral fatigue) pre-post exercise were determined via the interpolated twitch technique in 10 patients with PD and 10 healthy controls (CTRL) matched for age, sex and physical activity. Pulmonary gas exchange, femoral blood flow (FBF), and quadriceps electromyography (EMG) were measured during a fatiguing exercise (85% of peak power output (PPO)). For a specific comparison, on another day, CTRLs repeat the fatiguing test matching the time to failure (TTF) and PPO of PDs. **Results:** At 85% of PPO (PD=21±7W; CTRL=37±22W), both groups have similar TTF (~5.9 min), pulmonary gas exchange, FBF, and EMG. After this exercise, the maximal voluntary contraction force (MVC) and Q_{twpot} decreased equally in both groups (-16%, p=0.483; -43%, p=0.932), while VA decreased in PD compared to CTRL (-3.8% Vs -1.1%, p=0.040). At the same PPO and TTF of PDs (21W; 5.4min), CTRLs showed a constant drop in MVC, and Q_{twpot} (-14%, p=0.854; -39%, p=0.540), instead VA decreased more in PD than in CTRL (-3.8% Vs -0.7%, p=0.028). **Conclusion:** In PDs, central NF seems exacerbated by the fatiguing task which, however, does not alter peripheral fatigue. This, besides the TTF like CTRLs, suggests that physical activity may limit NF and counterbalance PD-induced degeneration through peripheral adaptations.

Key words: muscle dysfunction, neuromuscular fatigue, Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) is a neurological disease with an increasing prevalence, affecting 1% of people over 60 and 3% older than 80 years old worldwide (1). Motor symptoms, including bradykinesia, rigidity, resting tremor, and postural impairment are the cardinal features of PD (2). However, numerous non-motor symptoms have been increasingly recognized as part of the clinical spectrum of PD and often can dominate the clinical presentation (2) Specifically, fatigue, defined as a subjective feeling of exhaustion, weariness or increased sense of effort disproportioned to the actual performance, seems to be more pronounced in patients with PD, and affects indeed almost 50% of patients (3, 4). Arguably, neuromuscular fatigue (NF) is defined as the gradual reduction in the ability to exert muscle force or power during exercise and has central and peripheral components (5). Central fatigue describes the impairment of the neural drive to a muscle, while peripheral fatigue entails biochemical changes occurring at or distally to the neuromuscular junction (6). So far, the symptom of fatigue in PD has been evaluated through questionnaires or self-report (7) and only few studies have examined the neurophysiological components of NF with accurate methods in patients with PD (8) and, even less, the correlation between perceived fatigue and NF in neurodegeneration. It has been hypothesized that NF in PD is associated with the altered brain circuits affecting voluntary activation and, motor unit recruitment (9). However, the current literature offers little certainty and no studies have exploited a dynamic task to ascertain the role of central fatigue in PD at various time of exercise with respect to healthy controls.

Previous investigations have observed higher NF coupled with lower strength in PD (10). General deconditioning or muscle atrophy caused by disuse are potential sources for a decrement in motor tasks, as well as in daily activities (11, 12). Instead, physical activity benefits have been associated with better performance and decreased fatigue levels in the elderly (13). However, there is still limited knowledge of this phenomenon in patients with PD. The effect of physical activity may help improve fatigue and cardiovascular fitness in patients with chronic diseases (14, 15). Similarly, patients with PD perceiving more global fatigue show higher sedentary behaviours and lower physical function compared with patients without fatigue (16). Specific neuromuscular deficits of PD, such as reduction of motor unit recruitment, firing rate discharge, and maximal force expression, but also the whole clinical spectrum could be improved by physical activity (17). Nevertheless, the interpretation of the NF phenomenon in the PD scenario remains confounded by the reduced level of physical activity typical of this clinical population, and at the same time the contribution of PD to the central and peripheral components of NF is not clear. Moreover, the direct assessment of NF in patients with PD and healthy controls, matched for the level of physical activity, has not yet been investigated.

Therefore, this study included a homogeneous sample of patients with PD and healthy CTRL individuals, matched for sex, age, and energy expenditure profile, as an index of physical activity. Also, this investigation's novelty lies on the absolute and relative comparison of the fatiguing exercise task between PD and CTRLs. The latter group performed the exercise at the 85% of the peak power output (PPO) and on a different day matching the same PPO and time to failure (TTF) of PDs. This strategy allowed to highlight the contribution of the pathology, per sè, on NF, standardising other confounding factors. Accordingly, the present study aims to 1) verify

whether NF in the lower-limb muscles is higher in physically active patients with PD; 2) identify the contribution of central and peripheral components of NF consequent to a dynamic task to failure in PD population compared to CTRL. We hypothesized a marked reduction of the TTF coupled with a greater NF development highly related to central limitations in patients with PD.

MATERIALS AND METHODS

Subject characteristics

Based on previous research (18), for the present study we used the TTF as the main outcome. With an α level of 0.05 and a required power (1-β) of 0.80, the desired sample size, computed using statistical software (IBM SPSS Statistics Software) resulted in 8 participants per group. Accordingly, the total study sample was set to 16 participants. However, to compensate for the possible dropout the entire number of participants was 20.

Ten subjects with PD (5 males, 5 females; range 54–74 yrs), and ten healthy CTRLs (5 males, 5 females; range 57–75 yrs) volunteered and to participate in this study (Figure 1). The preliminary screening included a health history, a physical-clinical assessment, and a familiarization with the study exercise procedures. The local Ethics Committee approved the study (prot n 27111), and all experimental procedures were performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before the inclusion in the study. All participants were selected from groups that regularly perform a mixed aerobic and strength exercise training at the Department of Neuroscience, Biomedicine and Movement of the University of Verona. CTRL subjects were usually physically active with a training frequency between 2-3 times per week. Patients with PD were included observing the following eligibility

criteria: diagnosis of Idiopathic Parkinson's Disease, according to the Movement Disorders Society (MDS) clinical diagnostic criteria (2); age 40-80 years old; I-III stages of PD, according to the modified Hoehn & Yahr (H&Y) scale. Exclusion criteria were any type of dementia (DSM-V criteria); inability to walk unassisted. Demographical (age, sex) and clinical variables (disease duration, dominant phenotype, dopaminergic treatment) were collected. Patients were evaluated for the motor (III) scores of the Unified Parkinson Disease Rating Scale (UPDRS), and screened for independence in activities of daily living with the Activities of Daily Living (ADL), Instrumental Activities Daily Living (IADL) scales, and the Fatigue Severity Scale (FSS) (19). Furthermore, patients were tested only during the medication 'on' condition of the dopaminergic treatment.

Study Design

The study included 4 phases of examination (Figure 1). On Phase 1, participants underwent clinical and physical screening through rating scales and questionnaires; they were familiarized with the experimental procedures in the laboratory. Finally, they were given a wristwatch (Polar Vantage V) for daily energy expenditure (DEE) assessment. On Phase 2, after a preliminary warm-up, participants performed an incremental test (+5W/min) with active extension, from 90° to 170°, and passive return of the lower dominant leg on a single-leg-knee extensor ergometer (SLKE), until the subject was no longer able to continue. The PPO of the ergometer was recorded.

On Phase 3, the neuromuscular assessment of the dominant lower limb was performed by means of Interpolated Twitch Technique (ITT) in both PDs and CTRLs. The subject was asked to perform 6 maximal voluntary contractions, during which the muscle of the dominant limb was electrically stimulated during and after the contraction. Following the neuromuscular assessment, the subject performed constant load exercise until exhaustion on the SLKE ergometer (60 RPM at 85% PPO). Task failure was defined as a drop in cadence below 50 RPM for 10 seconds, setting the TTF. The neuromuscular assessment, performed immediately after the fatiguing exercise task (by 30 s), was repeated with ITT.

On Phase 4, only the CTRLs were involved. Each CTRL participant repeated the protocol of phase 4 matching both PPO and TTF obtained, during Phase 3, from the counterpart subjects with PD.

Daily energy expenditure assessment

DEE profile was assessed before the experimental procedure. For this purpose, each participant was instrumented with a Polar Vantage V wristwatch for six consecutive days, nights, and weekend included (20). The average step count, daily calories, hours of activity and inactivity were evaluated for each subject to estimate the average daily metabolic equivalent tasks (METs) for each group. Based on METs (21), the intensity of physical activity was verified in order to match participants.

Surface electromyography

Vastus lateralis (VL) electromyography (EMG) was recorded through a wireless system (Wave wireless EMG, Cometa, Milan, Italy) with two full-surface solid adhesive hydrogel electrodes (H59P, Tyco Healthcare Group, Mansfield, MA, USA) positioned lengthwise over the muscle belly, in line with the underlying muscle fibres arrangement and with a 20 mm inter-electrode distance (centre-to-centre). Before the electrode's application, the skin was shaved and cleaned with an alcohol swab in order to minimize electrical impedance. During femoral nerve stimulation and during the dynamic exercise, the M-waves and EMG bursts were continuously recorded in the VL muscle. The raw EMG signal, digitized online at a 1 kHz sampling frequency, was amplified and filtered with a band-pass filter (low-pass cut-off frequency 5 Hz, high-pass cut-off frequency 450 Hz), rectified and the analysis of the root mean square (RMS) was calculated by the software. Accurate identification of EMG activity was verified by visual inspection. The EMG data were acquired using a computer-based data acquisition and analysis system (PowerLab 16SP hardware and LabChart 6, software, ADInstruments, Bella Vista, New South Wales, Australia). EMG for each contraction throughout the protocol was calculated using the aforementioned software and averaged over the last 30s of each minute.

Neuromuscular assessment and nerve stimulation

Maximal voluntary and electrically evoked muscle contractions of the quadriceps muscle were measured utilizing a custom-made setup. Subjects were seated in an upright position with back support. Seat belts were applied to the pelvis and torso to secure the subject to the chair and prevent movement of other parts of the body. The knee was flexed at 90°, and the ankle of the dominant limb was attached, via a strap and a rigid steel bar, to the force transducer (DBBSE-

100kg, A2829. Applied Measurements Limited, Aldermaston Berkshire, UK). The output from the force transducer was amplified (INT2-L, London Electronics Limited, Sandy Bedfordshire, United Kingdom) and recorded with a PowerLab-16/35 data acquisition system (ADI Instruments, Bella Vista NSW, Australia).

Each test procedure began with the determination of the maximal M-wave and resting twitch ($Q_{tw,pot}$) responses in the resting quadriceps muscle. Briefly, the current intensity was progressively increased by 25 mA (+25 mA each step) to the value beyond which there was no further increase in M-wave peak-to-peak amplitude and $Q_{tw,pot}$. The 125% of the intensity evoking the individual maximal M-wave response. Electrical stimuli were delivered after positioning self-adhesive electrodes (50 x 90mm, MyoTrode PLUS, Globus corporation, Fallbrock, CA, USA) with the cathode positioned over the femoral triangle, 3–5 cm below the inguinal ligament, and the anode placed over the posterior iliac crest. The $Q_{tw,pot}$ was evoked in the resting muscle using electrical stimulation consisting of single square-wave pulses of 1-ms duration at 350V, delivered by a constant-current stimulator (Digitimer DS7h, Welwyn Garden City, UK). Before starting the trial, each subject was instructed on how to perform the trial correctly. The $Q_{tw,pot}$ was evoked 2 seconds after a 5-second MVC of the quadriceps and this procedure was repeated six times. Hence, it should be noted that $Q_{tw,pot}$ was assessed in the potentiated state. The interval between the MVCs was 1 minute. Peak force was evaluated for each $Q_{tw,pot}$ (22). Muscle voluntary activation (VA) of the quadriceps muscle during the MVCs was assessed using the ITT and the following formula:

$VA = 100(T_{interpolated}/T_{control})$

where $T_{interpolated}$ is the size of the interpolated twitch and $T_{control}$ is the size of a control twitch produced by identical nerve stimulation in a relaxed potentiated muscle (6). The force produced during a single twitch superimposed on the MVC was compared with the force produced by the electrically evoked $Q_{tw,pot}$ produced, at rest, 2 seconds after the MVC.

Exercise responses

Pulmonary gas exchange (VO_2 and VCO_2,) and ventilatory (VE) responses were measured breath-by-breath with a metabolic cart (Quark CPET, Cosmed, Italy). Before each session and after calibration of the gas analyser and the turbine flowmeter, an appropriate warm-up was performed. Heart rate (HR) was constantly determined through a wearable heart rate monitor during the test. The data were averaged over the last 30s of each minute. Systolic and diastolic blood pressures were measured manually, through a sphygmomanometer and an adult size cuff at each minute of exercise. Mean arterial pressure (MAP) was calculated as follows: diastolic blood pressure + [1/3 × (systolic blood pressure – diastolic blood pressure)].

During the SLKE exercise, a Doppler ultrasound (Logic 7 Doppler system; General Electric Medical Systems, Milwaukee, USA) equipped with a 12-14 MHz linear array transducer, was utilized to assess femoral blood flow (FBF) and to calculate leg vascular conductance (LVC) as $FBF \cdot MAP^{-1}$. Femoral artery blood velocity (V_{mean}) and arterial diameter were measured distally from the inguinal ligament and proximal to the bifurcation of the superficial and deep femoral artery. V_{mean} was measured using the probe positioned at an insonation angle of 60° or less, with

a frequency of 5 MHz, and the sample volume regulated according to vessel size. Then, FBF was calculated as the following formula: $V_{mean}\pi\cdot(\text{arterial diameter}/2)^2\times 60$

The rate of perceived exertion (RPE 0-10) was obtained after every minute of exercise using the Borg's modified CR10 scale (23).

Statistical analysis

IBM SPSS Statistics Software (Chicago, IL, USA) was used to perform all the statistical analyses. The results concerning demographic, age, sex data, and the differences in time to exhaustion between groups compared using the parametric Student t-test for independent groups. In consideration of fatigue data, normality was assessed by Shapiro–Wilk test, and sphericity was verified by Mauchly's test. Subsequently, two-way analysis of variance (ANOVA) for repeated measures was performed to assess time, group, and time x group interaction, followed by the Bonferroni test as post hoc analysis. Pearson correlation analysis was performed using together the data of the 2 groups with the 95% CI bands and post hoc Bonferroni correction test. Correlations within each group were applied but marginally considered due to the limited sample size. If not differently stated, data are presented as mean ± standard deviation (SD). The threshold for statistical significance was set a priori at $\alpha < 0.05$. Graphs and figures were made with SigmaPlot 12.5 version (Systat Software, Inc., 2011).

RESULTS

Participants' characteristics

Demographical, and physical characteristics of the PD, and CTRL are reported in Table 1. No significant difference regarding age, BMI, body weight, and stature of the participants was found. The PD and CTRL, based on mean daily METs calculation, were active individuals with regular training frequency (2-3 per week), and similar DEE profile. The main clinical characteristics, including dopaminergic equivalent dose, of PD patients are shown in Table 1. In the CTRL group, 8 out of 10 participants were right-dominant. In the PD group, all patients were right-dominant, although the side of appearance of the first motor symptom was the left limb in 5 out of 10 cases.

Neuromuscular fatigue-related indices during 85% of exercise PPO

The intensity of exercise during the SLKE task executed at the 85% of the PPO was lower for PD subjects, compared to CTRL group (21±7 Vs 37±22 W, p = 0.043, t = -2.183, CI = -32, -0.61). However, TTF at 85% of the PPO was not significantly different between PD and CTRL (5.4±3.9 Vs 6.6 ± 3.1 min, $p > 0.05$, t = -0.639, CI = -4.2, 2.2), as well as the mean RPE (6.2±1.5 Vs 6.7±1.5, p = 0.461, t = -0.753, CI = -1.9, 0.9) (Figure 2, Panel H).

The MVC was significantly reduced after the fatiguing test in the patients with PD (423±233 Vs 350 ± 173 N, p = 0.031, F = 6.527, CI = 8.3, 136). The same trend in MVC drop was displayed in the CTRLs (366±113 Vs 299±90 N, $p < 0.001$, F = 41, CI = 44, 91) (Figure 3). The pre-post exercise reduction in the $Q_{tw,pot}$ decreased in PD group (170±53 Vs 96 ± 46 N, F = 22, p = 0.001, CI = 38, 110) and in the CTRL group (190±53 N; 103±48 N, F = 25, $p < 0.001$, CI = 48, 127).

Similarly, the same decrement was observed in the MRFD of PDs (4593±1850 Vs 2014 ± 873 Ns^{-1}, F = 27, $p < 0.001$, CI = 1457, 3702), but not in CTRLs (10822±15837 Vs 2528±1334 Ns^{-1}, F = 2.795, $p = 0.129$, CI = -2928, 19516). Also, MRR was markedly reduced after the fatiguing task for both PDs (1730±1856 Vs 511±450 Ns^{-1}, F = 7.2, $p = 0.025$, CI = 194, 2244) and in CTRLs (3234±2913 Vs 1010±786 Ns^{-1}, F = 8.36, $p = 0.018$, CI = 484, 3965). Interestingly, pre-post change in VA appeared in PD (88±7 Vs 84±7 %, F = 16, $p = 0.003$, CI = 1.8, 5.5). While at contrary, no change was observed in CTRLs (90±6; 89±6 %, F = 0.821, $p = 0.388$, CI = -1.4, 3.2) that does not differ significantly from the pre-post change in PDs (-1.1% Vs -3.8%, $p = 0.081$). No effect of group between PD and CTRL resulted significant for MVC ($p = 0.455$), $Q_{tw,pot}$ ($p = 0.464$), MRFD ($p = 0.207$), MRR ($p = 0.148$), and VA ($p = 0.244$), nor interactions between time and group were found significant for MVC ($p = 0.870$), $Q_{tw,pot}$ ($p = 0.573$), MRFD ($p = 0.267$), MRR ($p = 0.275$), and for VA ($p = 0.090$).

From pre-post change in EMG was not significant in terms of M-wave amplitude for effect of time between the groups ($p = 0.251$). The rise in the EMG signal was significant from the first minute of exercise to task failure within each group for effect of time (F = 4.106, $p = 0.024$, CI = 1.1, 1.4). However, PDs and CTRLs showed a similar rate of rise ($p = 0.794$), and no significance was observed for effect of group (Figure 4).

Neuromuscular fatigue-related indices at the same exercise time and PPO

On Phase 4, each CTRL participant performed the fatiguing test matching the TTF and workload of the patient with PD. Not surprisingly, the mean RPE of CTRLs during the dynamic task was significantly lower, compared to PD (4.1±0.3 Vs 5.8±0.5, $p = 0.006$, t = 3.157, CI = 0.57, 2.8).

MVC in CTRL decreased significantly after this exercise task (379±111 Vs 329±121 N, F = 8.725, p = 0.016, CI = -12, -89). Detectable differences were found within CTRL in $Q_{tw,pot}$ (188±53 Vs 123±55, F = 42, p < 0.001, CI = 43, 89), MRFD (4959±1277 Vs 3000±1522 Ns^{-1}, F = 24, p < 0.001, CI = 4045, 5873) and MRR (3807±3356 Vs 1327±927 Ns^{-1}, F = 5.839, p = 0.039, CI = 4803, 158). CTRLs exhibited no pre-post change in VA (91±4 Vs 90±3 %, F = 0.800, p = 0.395, CI = -1.1, 2.4) that differs significantly from the pre-post change in PDs (0.7% Vs -3.8%, p = 0.028). No effect of group between PD and CTRL resulted significant for MVC (p = 0.663), $Q_{tw,pot}$ (p = 0.294), MRFD (p = 0.236), and VA (p = 0.089). Only effect of group for MRR (p = 0.050) appeared. No interactions between time and group were found significant for MVC (p = 0.510), $Q_{tw,pot}$ (p = 0.669), MRFD (p = 0.345), and MRR (p = 0.276). Only interaction between time and group for VA (p = 0.034) emerged.

From pre-post change in EMG was not significant in terms of M-wave amplitude for effect of time between the groups (p = 0.362). The EMG signal was significantly increased from the first minute of exercise to task failure within PDs and CTRLs in this condition for effect of time (F = 3.471, p = 0.041, CI = 1.1, 1.3). Also, significance for group effect did not appear (p = 0.309) (Figure 4).

Ventilatory and hemodynamic variables during SLKE exercise

The ventilatory and hemodynamic responses collected during the performance trials are reported in Figure 2. Within PDs and CTRLs significance only for time effect was found for HR, MAP, VO_2, VCO_2, VE, LVC, and FBF (p < 0.001). Moreover, a time x group interaction appeared

significant for MAP (p = 0.024), but the other variables were similar between PDs and CTRLs in both conditions. No group effect emerged.

DISCUSSION

With an integrative physiological approach, this study has investigated central and peripheral components of NF in PD patients compared to healthy volunteers. Specifically, in patients with PD and healthy volunteers, exercise-induced changes in VA (central component of NF) and $Q_{tw,pot}$ (peripheral component of NF) were assessed with the ITT. Between-groups differences were determined at 85% of the PPO (relative exercise intensity) and matching the PPO and the TTF (absolute exercise intensity), respectively. Contrary to our first hypothesis, similar level of NF between the two groups were observed by the equal changes in MVC, after the exercise executed at both relative and absolute intensity. Interestingly, and in accordance with our second hypothesis, the drop in the VA following the exercise, executed at both relative and absolute intensities, was significant in patients with PD in comparison to the controls. This result suggests a central limitation associated with this phenomenon, that was counterbalanced by a limited peripheral NF (i.e., equal drop in $Q_{tw,pot}$) in the group of patients with PD. These results indicate that the exacerbation of NF in patients with PD is not a dogma. The negligible level of NF is likely due to the active lifestyle exhibited by the patients with PD, which may have compensated the PD-induced central limitation with peripheral positive adaptations.

Is NF exacerbated in patients with PD?

Previous studies investigating fatigue in patients with PD have reported heterogeneous results. For instance, Kluger et al. reviewed the literature and showed that fatigue is one of the most disabling symptoms in PD, although often assessed through clinical subjective scales and confused with other signs of comorbidity (3). In another study, Lou and colleagues revealed that patients with mild to moderate PD, rated through questionnaires, have increased fatigue compared to healthy individuals (24). To the best of our knowledge, there are very few investigations in which NF have been investigated in patients with PD through a neurophysiological approach. For instance, Huang et al. (12) reported more exercise-induced fatigue in PDs than in the healthy controls after a protocol of isometric knee extension. Instead, in a recent investigation Pereira et al. (25) revealed similar values of force isometric voluntary contractions, after a repeated sit-to-stand task to induce fatigue, in patients with mild to moderate PD and healthy controls. The results of our study, differently from the initial hypothesis, agree with this interesting finding of Pereira et al. and reinforce the idea that NF may be independent of PD symptoms.

It is important to mention that several factors influence the physiological phenomenon of M NF in patients with PD, but the most relevant to report in this scenario are the severity of the PD symptoms and the level of physical activity of the participants. Specifically, most of the studies, like the present investigation, have included patients with PD at an initial stage of the disease (stages I–III of the H&Y scale). Therefore, we cannot exclude an exacerbation of NF in the more severe phases of the pathology, but further investigations are necessary to determine this physiological manifestation in severe PD. It has to be mentioned that the participants with PD

selected in the current study, besides an early stage, were physically active with a DEE profile similar to the CTRLs, suggesting that PD, at this stage, in addition to a dynamic lifestyle, may not worsen the phenomenon of NF which, instead, follows the physiological pattern of aging, as it happens for the maximal force expression in PD (20).

Another point to consider in this scenario is the exercise task selected for the current investigation. Precisely, we have chosen the SLKE exercise task in order to isolate the phenomenon of NF to the exercising muscles (knee extension muscle) and minimize potentially confounding effects from other body districts. As reported by the study of Rossman et al., when the exercise is confined to a small muscle mass the development of fatigue may be greater in comparison to whole-body exercise (26). With this simple exercise approach, potential PD-induced alterations of motor control during complex multi-joints movements such as walking or sit-to-stand tasks were lessened. Consequently, the comparison between patients with PD and the CTRLs was not biased by the reduced coordination associated with the PD-induced motor symptoms.

During the fatiguing task, this study also monitored pulmonary gas exchange and hemodynamic factors as crucial for the development of NF (27). These data are in line with the results on NF, confirming no differences between the groups. Previous reports found that autonomic changes in the cardiovascular and hemodynamic systems occur in PDs, leading to an altered tissue blood flow distribution and an excess of NF that can be the cause of a sedentary lifestyle (28). Our results, instead, suggest that an active lifestyle and regular physical activity can counterbalance

the detrimental effects of PD on the cardiovascular system and there is no evidence of reduced blood flow to the exercising muscle in patients with PD.

Is central component of NF impacted by PD?

Central components of NF develop during a prolonged exercise until the central nervous system fails to adequately activate the exercising muscle and task failure occurs (6). Although the literature indicates the contribution of numerous factors in the development of central components of NF in young healthy subjects, this argument is still controversial in patients with PD (29). In line with a recent investigation that assessed voluntary activation level and twitch forces in patients with PD (12), our study found a significant reduction in VA of PD group, after the fatiguing task to failure at 85% of the PPO. On the contrary, during the sessions at relative and matched intensity, the CTRL group showed no changes of VA. Moreover, the difference between the groups becomes even more significant if values of VA (i.e., central components of NF) were compared at the same workload. Therefore, our data suggest that PD, per sé, accelerates the development of the central components of NF.

From a neurophysiological point of view, it appears that this phenomenon could be due to altered biochemical mechanisms that originate in basal ganglia, spread toward the cortex, and descend to the periphery, justifying not only motor signs of PD but also non-motor symptoms (9). Indeed, individuals with PD present dopamine alterations and dysfunctions in serotonin and acetylcholine pathways contributing to modifying corticospinal impulses from brain to muscles (30). Interestingly, and in line with these results, a recent monkey study succeeded in re-

establishing dopamine concentrations and improved all PD signs by implanting dopaminergic neuronal grafts, supporting the evidence of the key role of the central motor drive (31).

Differently to various approaches, the use of the ITT is considered one of the most sensitive methods to evaluate VA without interference from peripheral muscle factors (32). Despite this, few groups have exploited this technique among patients with PD to study the central and peripheral components of NF. For instance, Catalá and colleagues used this strategy in PD scenario to split strength impairments arising in the central nervous system from the muscle contractile capacity (32). Instead, Decorte et al. found significant reductions in VA of healthy men during intense cycling and until exhaustion, suggesting that central components of NF may be a critical factor responsible for task failure (33). It was supposed that the decrease in central motor drive acts to protect several organs from further stress, by limiting peripheral activation and disfavouring maximal task output (6). Central alterations are certified by a decline in VA also in our patients with PD. Surprisingly, our data revealed that the TTF does not change between the two groups when compared at relative workload. Hence, it is plausible that, in PDs, other mechanisms counterbalance the central deficit which, instead, cannot be reversed (20, 34).

Can central fatigue affect the perception of effort?

A relevant factor in supporting the greater involvement of central component of NF is the RPE. It is important to note that perceived effort and NF are not necessarily related (35). Interestingly, previous investigations reported a significant correlation between the perceived effort and the inability to sustain the desired exercise performance more in Huntington disease and multiple sclerosis than in healthy (36). In addition, the study of Solomon & Robin agrees on the fact that

effort perception is aberrant in patients with PD that used self-ratings scales and handgrip exercise at various pressure levels reporting higher RPE levels than control subjects (37). Our study is in line with those findings and shows that the RPE of PDs was higher when CTRLs were compared at absolute exercise workload (Figure 2; Panel G). Specifically, we found a negative correlation between VA and RPE (Figure 5; Panels C-D). Interestingly, this significant correlation does not occur between peripheral factor ($Q_{tw,pot}$) and RPE (Figure 5; Panels A-B), and limit the involvement of the peripheral fatigue component. In PDs, the origin of the altered RPE seems to be located in the basal ganglia, already responsible for modifying cortical activation of motor and non-motor areas (38). This model is also consistent with other neurological disorders in which subjective perceptions seem to be the consequence of an exaggerated mental effort needed to carry out movements (39, 40). Thus, our study supports the hypothesis that NF in patients with PD is predominantly a central phenomenon associated with an altered subjective effort perception.

Are EMG and central components of NF associated in PD?

Growing evidence suggests that patients with PD demonstrate deficits in muscle activation such as decreased amplitude and inappropriate bursting in the EMG signal (41). However, the literature provides very little information based on EMG analysis and NF in this population. For instance, Antonen et al. concluded that the anti-parkinsonian treatment affects the response of the EMG parameters to exercise. Indeed, after a fatiguing task based on MVCs, the authors observed similar fatigue levels between the PD patients on medication and the healthy subjects (42).

Our EMG results recorded during the exercise fatiguing task do not show significant differences between groups (Figure 4). Indeed, our participants with PD were assessed in the on-medication status. However, patients with PD are known to have an an altered neural drive to the muscle, compared to CTRLs.

In agreement with previous investigations, the blunted EMG difference could be due to the qualitative and quantitative recovery of dopaminergic drive after levodopa intake. Also Cioni et al. observed that, when levodopa ends its effect, kinematic and spatio-temporal parameters of EMG are profoundly affected (43). This corresponds to the time when the alterations in the central motor drive and motor unit recruitment in PD begin to manifest again, inevitably bringing out the cardinal motor signs of the disease at the peripheral level.

Is peripheral component of NF influenced by PD?

Peripheral components of NF are generally affected by perturbations in neuromuscular transmission, incorrect propagation of the signal to the skeletal muscle and inefficient contractile mechanisms of the fibres (44). In this regard, several studies have been conducted in order to clarify the inhibitory effect of peripheral components of NF during exercise in healthy populations (45). On the contrary, potential alterations of this important aspect of NF are rarely investigated in patients with PD, instead preferring general fatigue indices that are easier to assess. One of the few studies in the literature to differentiate the components of NF is that of Huang et al. Indeed, the authors observed a lack of a significant difference in $Q_{tw,pot}$ (i.e., peripheral component of NF) quantified after a MVC protocol, and twitch force delivery between PD and CTRL (12). In line with this, Kostic et al. presented a review focused on the central role

of cortical abnormalities in PD, while excluding the involvement of peripheral phenomena in the development of fatigue (11). In agreement with these data, the current study revealed that the exercise-induced drop in $Q_{tw,pot}$ was similar between the two groups. Interestingly, these data appear to be the expected consequence of the fatiguing task, implicating that peripheral components of NF are equally impacted in our sample of healthy and pathological individuals.

Clinical considerations and conclusions

The assessment of NF gives rise to several clinical implications. First, when coupled with validated functional tests, fatigability evaluation can act as an early prognostic index in detecting the onset or progression of physical and cognitive deficits. Indeed, fatigue seems to precede the development of more severe symptoms before diagnosis or early in the disease (2). In practical terms, more cases of early fatigue detection mean prompt intervention and slowed onset of the pathology.

Second, the benefits of an immediate treatment that combines exercise training and drug therapy are of great importance due to their positive impact on motor symptoms, cognition, and general health (17). The literature provides contrasting results in terms of frequency, intensity of training and duration of the program, as the severity of the disease makes the planning difficult. However, as noted by our and several studies, physical activity and a dynamic lifestyle should always be recommended as a valid strategy for improving NF, strength, perceived effort, cardiorespiratory fitness, and reducing daily activity limitations in PD and frail populations (12, 17, 46, 47).

The present study revealed no detectable differences between PDs and CTRLs in terms of NF. At first, we hypothesized that PD might hinder voluntary activation and motor unit recruitment, leading to exacerbated NF. This study confirms the presence of higher alterations in central components of NF in physically active patients with PD. Instead, these patients showed similar levels of peripheral component of NF, compared to their healthy counterparts. These findings suggest that physical activity can counteract the PD-induced changes in central components of NF via peripheral adaptations within the skeletal muscle. In conclusion, knowing the processes involved in NF attenuation in patients with PD may help improving standard and conventional approaches and manage the symptoms.

Acknowledgements

The authors thank all participants of the study for their time and effort. No conflicts of interest, financial or otherwise, are declared by the author(s). The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation, and do not constitute endorsement by ACSM.

Author contributions

CM, GG, FGL, and IADV collected the data; CM analysed the data and drafted the manuscript; MV, AP, GG, CB, and FGL revised and edited it critically; MV, FS, and MT supervised the manuscript. All authors approved the final version and agreed on all aspects of the work. All persons who qualify for authorship are listed.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

Funding

This work was partially supported by the Italian Ministry of Research and University (MIUR – Rome, Italy) 5-year special funding (https://www.miur.gov.it/dipartimenti-di-eccellenza).

REFERENCES

1. Lee A, Gilbert RM. Epidemiology of Parkinson Disease. *Neurol Clin*. 2016;34(4):955–65.
2. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*. 2015;30(12):1591–601.
3. Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic inllnesses. *Neurology*. 2013;80:409–16.
4. Kluger BM, Herlofson K, Chou KL, et al. Parkinson's Disease-related Fatigue: A Case Definition and Recommendations for Clinical Research. *Mov Disord*. 2016;31(5):625–31.
5. Bigland-Ritchie B, Woods J. Changes in muscle contractile properties and neural control during human muscular fatigue. *Muscle Nerve*. 1984;7(9):691–9.
6. S. C. Gandevia. Spinal and Supraspinal Factors in Human Muscle Fatigue. *Physiol Rev*. 2001;81(4):1725–89.
7. Friedman JH, Alves G, Hagell P, et al. Fatigue rating scales critique and recommendations by the Movement Disorders Society Task Force on rating scales for Parkinson's disease. *Mov Disord*. 2010;25(7):805–22.
8. Fundaró C, Gazzoni M, Pinna GD, Dallocchio C, Rainoldi A, Casale R. Is fatigue a muscular phenomenon in Parkinson's disease? Implications for rehabilitation. *Eur J Phys Rehabil Med* [Internet]. 2021; doi:10.23736/S1973-9087.21.06621-1.
9. Stevens-Lapsley J, Kluger BM, Schenkman M. Quadriceps muscle weakness, activation deficits, and fatigue with parkinson Disease. *Neurorehabil Neural Repair*. 2012;26(5):533–41.
10. Kelly NA, Ford MP, Standaert DG, et al. Novel, high-intensity exercise prescription improves muscle mass, mitochondrial function, and physical capacity in individuals with

Parkinson's disease. *J Appl Physiol*. 2014;116(5):582–92.

11. Kostić VS, Tomić A, Ječmenica-Lukić M. The Pathophysiology of Fatigue in Parkinson's Disease and its Pragmatic Management. *Mov Disord Clin Pract*. 2016;3(4):323–30.
12. Huang YZ, Chang FY, Liu WC, Chuang YF, Chuang LL, Chang YJ. Fatigue and Muscle Strength Involving Walking Speed in Parkinson's Disease: Insights for Developing Rehabilitation Strategy for PD. *Neural Plast* [Internet]. 2017;2017 doi:10.1155/2017/1941980.
13. Soyuer F, Şenol V. Fatigue and physical activity levels of 65 and over older people living in rest home. *Int J Gerontol*. 2011;5(1):13–6.
14. Witlox L, Hiensch AE, Velthuis MJ, et al. Four-year effects of exercise on fatigue and physical activity in patients with cancer. *BMC Med*. 2018;16(1):1–9.
15. Razazian N, Kazeminia M, Moayedi H, et al. The impact of physical exercise on the fatigue symptoms in patients with multiple sclerosis: a systematic review and meta-analysis. *BMC Neurol*. 2020;20(93):1–11.
16. Garber CE, Friedman JH. Effects of fatigue on physical activity and function in patients with Parkinson's disease. *Neurology*. 2003;60(7):1119–24.
17. Helgerud J, Thomsen SN, Hoff J, et al. Maximal strength training in patients with Parkinson's disease: Impact on efferent neural drive, force-generating capacity, and functional performance. *J Appl Physiol*. 2020;129(4):683–90.
18. Rannou F, Nybo L, Andersen JE, Nordsborg NB. Monitoring Muscle Fatigue Progression during Dynamic Exercise. *Med Sci Sports Exerc*. 2019;51(7):1498–505.
19. Lawton M, Brody E. Assessment of older people: selfmaintaining and instrumental activities of daily living. Gerontologist. 1969;9:179–86. *Gerontologist*. 1969;9:1979–86.

20. Martignon C, Ruzzante F, Giuriato G, et al. The key role of physical activity against the neuromuscular deterioration in patients with Parkinson's disease. *Acta Physiol*. 2021;(January):1–14.

21. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: Updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007;116(9):1081–93.

22. Sandiford SD, Green HJ, Duhamel TA, Schertzer JD, Perco JD, Ouyang J. Muscle Na-K-pump and fatigue responses to progressive exercise in normoxia and hypoxia. *Am J Physiol - Regul Integr Comp Physiol*. 2005;289(2 58-2):441–9.

23. Borg G. Borg´s perceived exertion and pain scales. *Hum Kinet*. 1998;(July 1998):111.

24. Lou JS, Kearns G, Oken B, Sexton G, Nutt J. Exacerbated physical fatigue and mental fatigue in Parkinson's disease. *Mov Disord*. 2001;16(2):190–6.

25. Pereira VAI, Barbieri FA, Zagatto AM, et al. Muscle fatigue does not change the effects on lower limbs strength caused by aging and Parkinson's disease. *Aging Dis*. 2018;9(6):988–98.

26. Rossman MJ, Venturelli M, McDaniel J, Amann M, Richardson RS. Muscle mass and peripheral fatigue: A potential role for afferent feedback? *Acta Physiol*. 2012;206(4):242–50.

27. Amann M, Venturelli M, Ives SJ, et al. Group III/IV muscle afferents impair limb blood in patients with chronic heart failure. *Int J Cardiol*. 2014;174(2):368–75.

28. Pechstein AE, Gollie JM, Guccione AA. Fatigability and Cardiorespiratory Impairments in Parkinson's Disease: Potential Non-Motor Barriers to Activity Performance. *J Funct Morphol Kinesiol*. 2020;5(4):78.

29. Yoshii F, Takahashi H, Kumazawa R, Kobori S. Parkinson's disease and fatigue. *J Neurol*. 2006;253(SUPPL. 7):48–53.

30. Magrinelli F, Picelli A, Tocco P, et al. Pathophysiology of Motor Dysfunction in Parkinson's Disease as the Rationale for Drug Treatment and Rehabilitation. *Parkinsons Dis* [Internet]. 2016;2016 doi:10.1155/2016/9832839.

31. Kikuchi T, Morizane A, Doi D, et al. Human iPS cell-derived dopaminergic neurons function in a primate Parkinson's disease model. *Nature*. 2017;548(7669):592–6.

32. Moreno Catalá M, Woitalla D, Arampatzis A. Central factors explain muscle weakness in young fallers with Parkinson's disease. *Neurorehabil Neural Repair*. 2013;27(8):753–9.

33. Decorte N, Lafaix PA, Millet GY, Wuyam B, Verges S. Central and peripheral fatigue kinetics during exhaustive constant-load cycling. *Scand J Med Sci Sport*. 2012;22(3):381–91.

34. Lavin KM, Ge Y, Sealfon SC, et al. Rehabilitative Impact of Exercise Training on Human Skeletal Muscle Transcriptional Programs in Parkinson's Disease. *Front Physiol*. 2020;11(June):1–14.

35. Marcora S. Perception of effort during exercise is independent of afferent feedback from skeletal muscles , heart , and lungs. *J Appl Physiol*. 2009;106:2060–2.

36. Loy BD, Taylor RL, Fling BW, Horak FB. Relationship between perceived fatigue and performance fatigability in people with multiple sclerosis: A systematic review and meta-analysis. *J Psychosom Res*. 2017;100(June):1–7.

37. Solomon NP, Robin DA. Perceptions of effort during handgrip and tongue elevation in Parkinson's disease. *Park Relat Disord*. 2005;11(6):353–61.

38. LeWitt P, Bharucha A, Chitrit I, et al. Perceived Exertion and Muscle Efficiency in

Parkinson's Disease: L-Dopa effects. 1994;454–9.

39. Lafargue G, Sirigu A. Sensation of effort is altered in Huntington's disease. *Neuropsychologia*. 2002;40(10):1654–61.

40. Okada T, Tanaka M, Kuratsune H, Watanabe Y, Sadato N. Mechanisms underlying fatigue: A voxel-based morphometric study of chronic fatigue syndrome. *BMC Neurol*. 2004;4:1–6.

41. Glendinning DS, Enoka RM. Motor unit behavior in Parkinson's disease. *Phys Ther*. 1994;74(1):61–70.

42. Antonen EG, Meigal AI, Lupandin I V. Electromyography parameters of muscular fatigue and recovery in patients with Parkinson's disease before and on medication. *Fiziol Cheloveka*. 2005;31(4):81–7.

43. Cioni M, Richards CL, Malouin F, Bedard PJ, Lemieux R. Characteristics of the electromyographic patterns of lower limb muscles during gait in patients with Parkinson's disease when OFF and ON L-Dopa treatment. *Ital J Neurol Sci*. 1997;18(4):195–208.

44. Taylor JL, Amann M, Duchateau J, Meeusen R, Rice CL. Neural Contributions to Muscle Fatigue: From the Brain to the Muscle and Back Again. *Med Sci Sport Exerc*. 2016;48(11):2294–306.

45. Kirkendall DT. Mechanisms of peripheral fatigue. *Med Sci Sports Exerc* [Internet]. 1990;22(4).

46. Abrantes AM, Friedman JH, Brown RA, et al. Physical activity and neuropsychiatric symptoms of Parkinson disease. *J Geriatr Psychiatry Neurol*. 2012;25(3):138–45.

47. Martignon C, Pedrinolla A, Ruzzante F, et al. Guidelines on exercise testing and prescription for patients at different stages of Parkinson's disease. *Aging Clin Exp Res*. 2021;33(2):221–46.

Figure Captions

Figure 1. Timeline of the protocol design for Parkinson's disease (PD) and control (CTRL) subjects. PPO, peak power output; TTF, time to failure.

Figure 2. Group mean data (n = 20) ± SEM illustrating pulmonary and hemodynamic responses to constant-load single leg knee-extensor exercise at 85% of the individual peak power output of patients with Parkinson's disease (PD) and controls (CTRL) in both conditions. HR, heart rate; MAP, mean arterial pressure; VE, minute ventilation; VO2, oxygen consumption; VCO2, carbon dioxide production; FBF, femoral blood flow; RPE, rate of perceived exertion; LVC, leg vascular conductance. * Significance for time effect with $p < 0.001$; § Significance between $PD_{85\%}$ and $CTRL_{ISO}$; # Significance between $CTRL_{85\%}$ and $CTRL_{ISO}$; + Significance between all groups.

Figure 3. Individual and group mean data (n = 20) illustrating the effect of the fatiguing test on muscle fatigue-related parameters. Both pre and post exercise values are showed in patients with Parkinson's disease at the 85% of their peak power output (PPO) ($PD_{85\%}$), control subjects at both the 85% of their PPO ($CTRL_{85\%}$) and at the same time and PPO of PD ($CTRL_{ISO}$). *Significance for time effect with $p < 0.05$; §Significance for time-group interaction with $p < 0.05$; No significance for group effect was found; MVC, maximal voluntary contraction; $Q_{tw,pot}$, potentiated single twitch; VA, maximal voluntary activation.

Figure 4. Electromyography (EMG) tracings of patients with Parkinson's disease at the 85% of their peak power output (PPO) ($PD_{85\%}$), control subjects at both the 85% of their PPO ($CTRL_{85\%}$) and at the same time and PPO of PD ($CTRL_{ISO}$) during the dynamic exercise. * Significance for time effect with $p < 0.05$.

Figure 5. Panels A-D show correlations in potentiated twitch force ($Q_{tw,pot}$), maximal voluntary activation (VA), and rate of perceived exertion (RPE) between patients with Parkinson's disease at the 85% of their peak power output ($PD_{85\%}$), control subjects at relative ($CTRL_{85\%}$) and absolute ($CTRL_{ISO}$) peak power output, respectively. * Significance with $p < 0.05$.

Figure 1

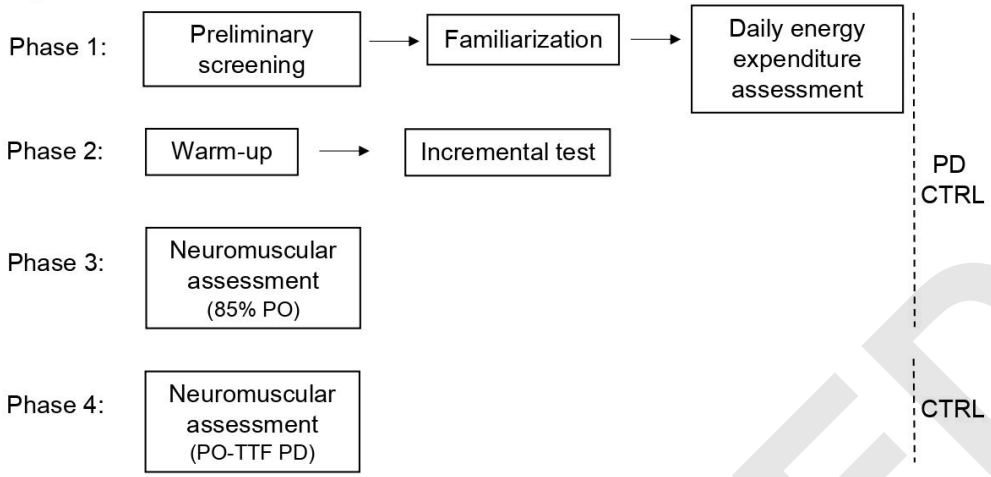


Figure 2

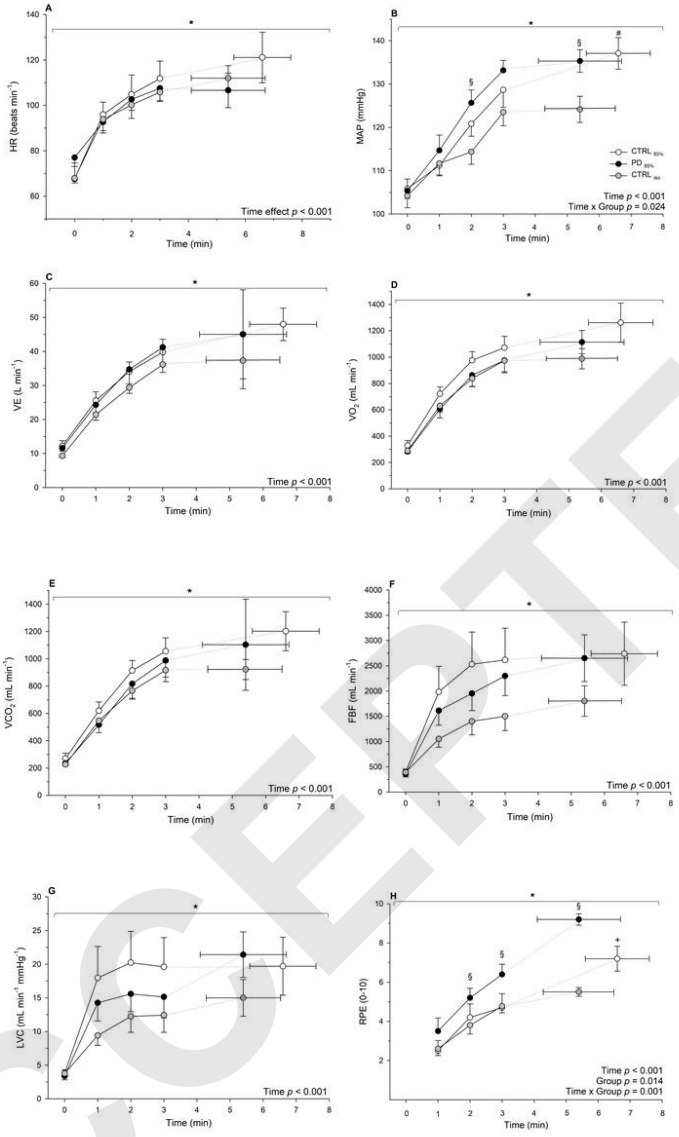


Figure 3

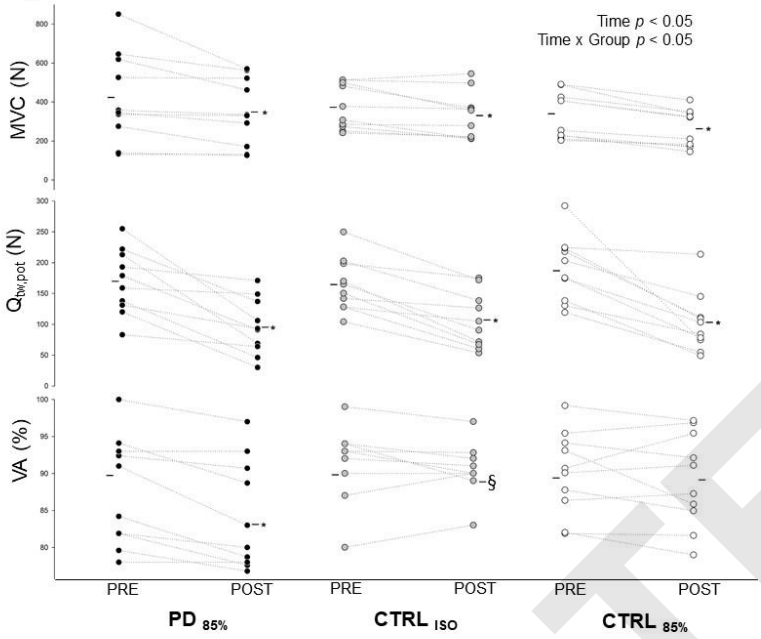


Figure 4

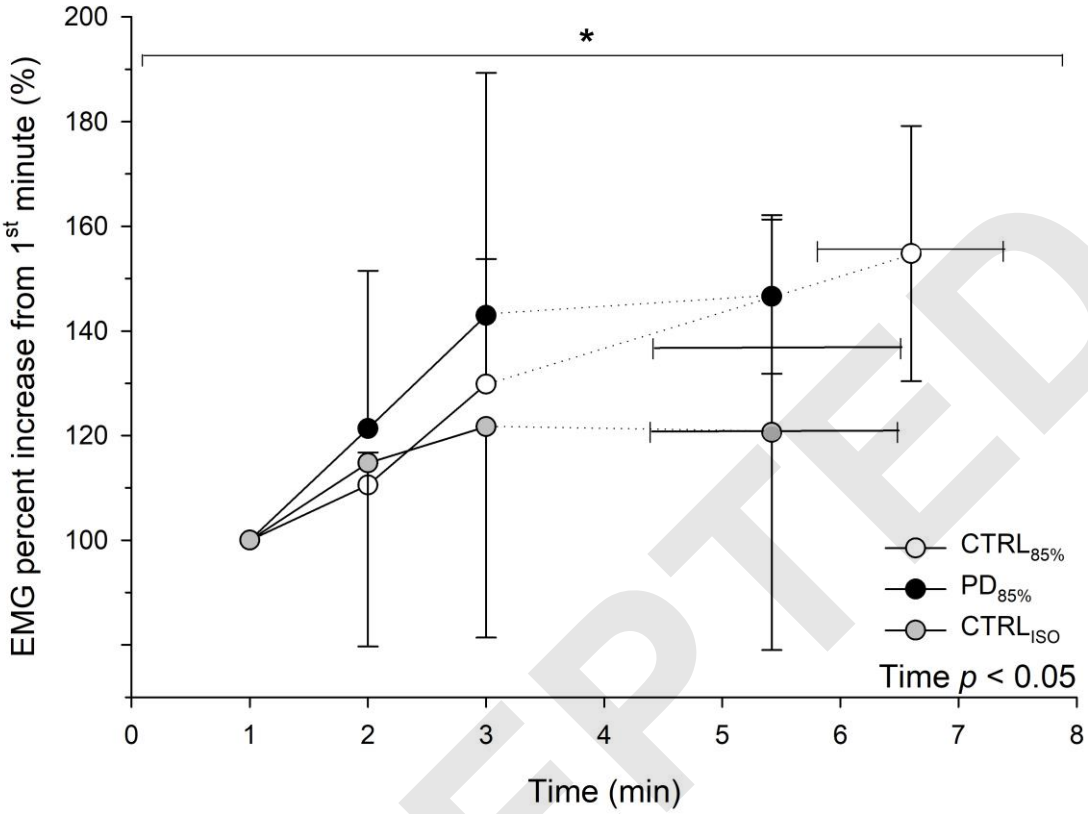
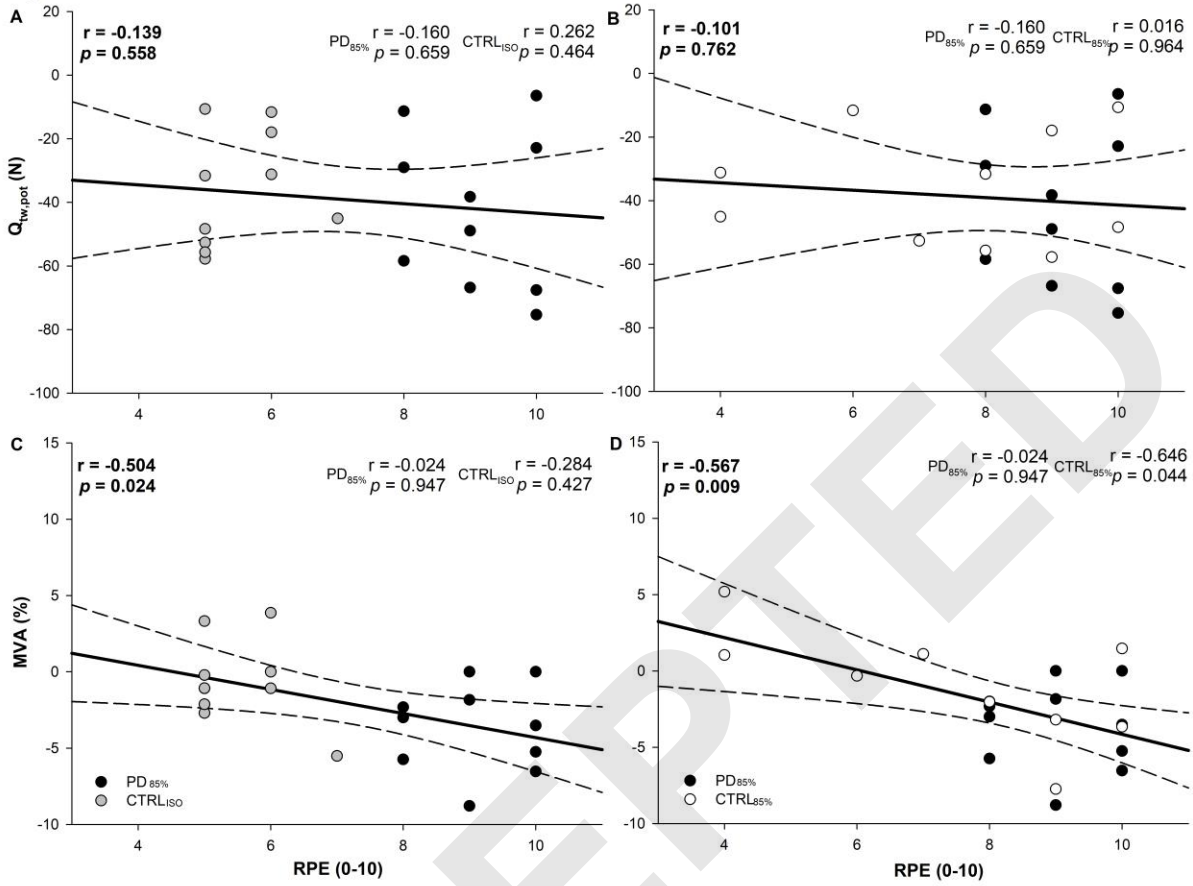


Figure 5



	PD			CTRL			t	*p*	d
Age (yrs)	66	±	7	70	±	6	-1.414	0.174	-0.316
BMI (Kg m^{-2})	27	±	4	26	±	4	0.769	0.452	0.171
Body weight (Kg)	73	±	15	72	±	12	0.095	0.925	0.021
Stature (cm)	163	±	8	166	±	9	-0.815	0.426	-0.182
Active time (hrs day^{-1})	8.6	±	2.4	7.5	±	1.5	1.173	0.256	0.269
Steps (steps day^{-1})	11234	±	6207	10066	±	1676	0.574	0.573	0.148
DEE (kcal day^{-1})	2590	±	403	2492	±	474	0.496	0.626	0.111
Inactivity time (hrs day^{-1})	0.25	±	0.30	0.67	±	0.10	1.750	0.097	0.429
METs (kcal Kg^{-1} hrs^{-1})	1.5	±	0.4	1.4	±	0.46	0.320	0.760	0.070
Disease duration (yrs)	6.2	±	4.2	-			-	-	-
UPDRS III	28	±	4	-			-	-	-
H&Y	2.1	±	0.3	-			-	-	-
ADL	5.44	±	0.73	-			-	-	-
IADL	7.11	±	1.83	-			-	-	-
LEDD	490	±	253	-			-	-	-
FSS	1.97	±	1.38	-			-	-	-
Dominant phenotype (n)	Bradykinetic/Rigid (3) Tremor-dominant (3) Tremor + Bradykinetic/Rigid (4)			-			-	-	-

Table 1. Participants' characteristics are presented as means ± SD (n = 20). * Significantly different from CTRL subjects ($p < 0.05$); BMI, body mass index; DEE, daily energy expenditure; METs, metabolic equivalent of task; H&Y, Hoehn & Yahr; ADL, activities of daily living scale; IADL, instrumental activities daily living scale; LEDD, Levodopa daily dose equivalent; FSS, Fatigue severity scale.