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Being physically active minimizes the effects of leg muscle fatigue on obstacle negotiation in people with Parkinson's disease

Paulo Cezar Rocha dos Santos [a,*], Fabio Augusto Barbieri [b], Diego Orcioli-Silva [a], Victor Spiandor Beretta [a], Tibor Hortobágyi [c,d,e], Lilian Teresa Bucken Gobbi [a]

[a] São Paulo State University (UNESP), Graduate Program in Movement Sciences, Institute of Biosciences, Posture and Gait Studies Laboratory (LEPLO), Rio Claro, São Paulo, Brazil
[b] São Paulo State University (UNESP), Graduate Program in Movement Sciences, Department of Physical Education, Human Movement Research Laboratory (MOVI-LAB), Bauru, São Paulo, Brazil
[c] University of Groningen, University Medical Center Groningen, Center for Human Movement Sciences, Groningen, the Netherlands
[d] Institute of Sport Sciences and Physical Education, Faculty of Sciences, University of Pécs, Pécs, Hungary
[e] Somogy County Kaposi Mór Teaching Hospital, Kaposvár, Hungary

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ABSTRACT

It is challenging for people with Parkinson's disease (PwPD) to adjust their gait to perturbations, including fatigue. Obstacle negotiation increases the risk of tripping and falling in PD. Being physically active can improve gait control and the ability to negotiate obstacles while walking under fatigue state. We thus determined the effects of Parkinson's disease, fatigue, and level of physical activity on gait during the approach to and crossing an obstacle during gait. Forty participants were stratified to people with Parkinson's disease active and inactive, and control individuals active and inactive. Participants walked on an 8 m walkway and stepped over an obstacle placed at the middle (4 m). They performed three trials before and after repeated sit-to-stand (rSTS)-induced fatigue state. Maximum voluntary force was assessed before and after rSTS. We measured the length, width, duration, and velocity of the approach (stride before obstacle) and crossing (step over the obstacle) phases and the leading and trailing placements and clearance during crossing phase. Fatigue trait was determined by multidimensional fatigue inventory. Before rSTS, people with Parkinson's disease inactive vs. other subgroups approached the obstacle using 18–28% shorter, wider and slower steps and crossed the obstacle slower (all $p < 0.04$). After rSTS, people with Parkinson's disease inactive increased (23–34%) stride length and velocity and decreased (-21%) the step width ($p < 0.01$). People with Parkinson's disease approached the obstacle similarly to control individuals. Physical activity minimizes Parkinson's disease-typical gait impairments during obstacle negotiation and affords a protective effect against fatigue-effects on obstacle negotiation.

1. Introduction

People with Parkinson's disease (PwPD) have difficulty in adjusting their gait to changes in the environment, especially when an obstacle appears in the path of ambulation (Galna et al., 2009). During obstacle negotiation, trips represent high risks of falls in older adults (Kulkarni et al., 2021) and, in PwPD, cause ~30% of falls (Stolze et al., 2004). A decline in basal ganglia function affects the neural commands to muscle, resulting in reductions in walking and movement speed (bradykinesia) and movement amplitude (hypokinesia) (Mirelman et al., 2019). Specifically, PwPD vs. healthy individuals (control group, CG) approached and crossed the obstacle 10–25% slower and shorted steps and placements to the obstacle (Galna et al., 2010; Orcioli-Silva et al., 2018). To reduce fall risk posed by an obstacle while walking, it seems insightful to understand how Parkinson's disease (PD) affects the ability to adjust gait to perturbation. To this effect, previous studies have examined gait adaptability in PwPD to fatigue (Huang et al., 2017; Santos et al., 2016). In addition, regular practices of exercise might minimize PD typical signal on gait (Ni et al., 2018) and the fatigue impact on daily life (Bonavita, 2020).

Fatigue can be determined as a symptom (trait) or state (Enoka and Duchateau, 2016). A decline in the generate force capacity is a

* Corresponding author at: UNESP, Graduate Program in Movement Sciences, Institute of Biosciences Posture and Gait Studies Laboratory (LEPLO), Avenida 24-A, 1515. Bela Vista, Zip-Code:13506-900 Rio Claro, São Paulo, Brazil.
E-mail address: paulocezarr@hotmail.com (P.C.R. Santos).

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Table 1
Groups and Subgroups' characteristics, rSTS duration, and clinical parameters of the PwPD.

	PwPD		CG	
	Inactive	Active	Inactive	Active
Height (m)	1.7 ± 0.6	1.7 ± 0.9	1.7 ± 0.7	1.7 ± 0.7
Body mass (kg)	73.1 ± 10.1	72.6 ± 7.6	78.7 ± 12.8	68.6 ± 9.4
Age (years)	71.7 ± 5.0	67.0 ± 5.2	71.4 ± 6.4	67.5 ± 6.5
PAL (Baecke score)	2.9 ± 1.3	7.9 ± 2.0§	1.3 ± 0.5	9.1 ± 2.0§
MFI (Score)	44.9 ± 10.8	56.0 ± 6.3§	34.3 ± 5.6+	38.8 ± 10.7§+
UPDRS III (score)	29.1 ± 6.7	31.8 ± 6.9	———	———
H&Y (score)	1.8 ± 0.2	2.0 ± 0.2	———	———
MMSE (score)	29.1 ± 1.5	28.7 ± 1.6		
rSTS duration (s)	80.8 ± 21.3	107.6 ± 39.5	122.3 ± 133.2	408.6 ± 234.5
Perceived Exertion (Borg)				
Before rSTS	7.7 ± 1.7	8.5 ± 1.8	7.4 ± 1.3	9.4 ± 2.2
After rSTS	17.3 ± 1.9	18.2 ± 2.0	19.2 ± 1.1	17.5 ± 2.0

Legend: PwPD: Parkinson's disease Group; CG: Control Group, PAL: Physical Activity Level; Multimodal Fatigue Inventory (MFI); H&Y: Hoehn e Yahr Scale, UPDRS III: Unified Parkinson's Disease Rating Scale motor section; MMSE: Mini-Mental State Examination. § different of Inactive; + different of PwPD.

characteristic of fatigue state as a result of muscle fatigability (Enoka and Duchateau, 2016). Muscle fatigability is a perturbation model that limits the availability of internal resources (Enoka and Duchateau, 2016). In PwPD, muscle fatigability and fatigue trait are ubiquitous during daily life (Friedman et al., 2007). Inducing muscle fatigability is an attractive perturbation model for examining gait adaptability in PwPD. Greater susceptibility to muscle fatigability in PwPD vs. CG is based on evidence showing muscle weakness and self-reported fatigue in PwPD (Cano-de-la-Cuerda et al., 2010; Huang et al., 2017; Stevens-Lapsley et al., 2012). A higher fatigue trait in PwPD is likely related to PD-typical dysfunctions in brain networks (e.g., dopaminergic pathways) (Lazcano-Ocampo et al., 2020), leading to gait control impairments (Rochester et al., 2006).

Repetitive sit-to-stand task (rSTS), a muscle fatigability model, is a highly demanding task that reduced knee extensor maximal voluntary isometric contraction (MVC) by 5–18% in CG and PwPD (Bryanton and Bilodeau, 2017; Santos et al., 2019, 2016). After rSTS, evidence suggested a compensatory increase in stride length and velocity and a decrease in duration in both PwPD and CG (Santos et al., 2019, 2016). However, rSTS did not affect step width and single support time in PwPD (Santos et al., 2016), suggesting a compromised ability to adapt to rSTS. Thus, rSTS effects combined with PD effects on gait (i.e., bradykinesia) may increase the risks for a loss of balance, tripping, and falling during challenging walking tasks. During obstructed gait in older adults, rSTS reduced heel clearance (Barbieri et al., 2014), increasing the tripping risk (Nagano et al., 2014). However, in PD, the fatigue-related obstacle negotiation adaptation remains unexplored.

Physical activity (PA) effectively reduces motor and cognitive symptoms in PwPD (Johansson et al., 2020; Mahalakshmi et al., 2020; Ni et al., 2018). Systematic PA can ameliorate motor dysfunctions (e.g., poor balance, slow gait, fatigue, and risks for falls), stimulate dopamine synthesis and release, and improve cortical-striatal plasticity (Bonavita, 2020; Johansson et al., 2020). Because PA can favorably affect exercise capacity, motivation, and fatigue (Bonavita, 2020; Johansson et al., 2020), it seems reasonable to expect improved resistance to fatigue state, hence a relatively maintained ability to negotiate obstacles during walking in a fatigued state. Therefore, we first determined the effects of PD, fatigue, and PA level on gait during the approach to and crossing an obstacle during gait. In view of previous evidence (Ghani et al., 2019; Huang et al., 2017; Santos et al., 2016), we hypothesized that fatigability would induce a reduction in foot clearance during crossing and

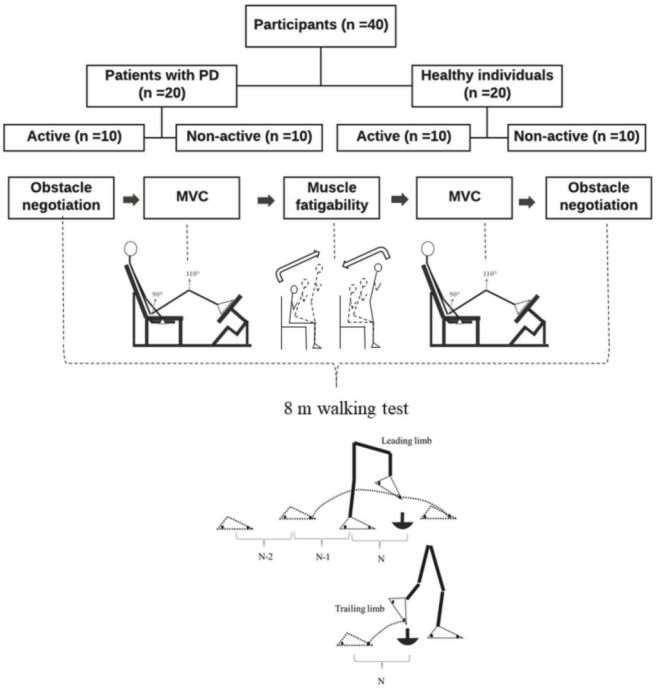

Fig. 1. Experimental design of the procedures developed on the second day. MVC: maximum isometric voluntary contraction.

increase in length and velocity in both phases and groups, but less so in PwPD. Considering positive PA effects on mobility, we expected a hierarchical response pattern to fatigue along the continuum from inactive PwPD, active PwPD, inactive CG, and active CG. Additionally, we determined the relationship between fatigue trait, PA and MVC with obstacle negotiation before and after rSTS. In view of extant evidence (Pechstein et al., 2020; Rochester et al., 2006), we expected a relationship between fatigue trait with a reduction in gait performance (e.g., reduced stride length and speed). Because fatigue trait and PA are independent of fatigue state (Lazcano-Ocampo et al., 2020; Pechstein et al., 2020), we expected no relationship between fatigue trait and PA with gait changes induced by muscle fatigability.

2. Methods

2.1. Participants

A sample size (G*Power software) of at least 32 individuals (8 in each sub-group) was needed for an 80% probability of detecting a difference between two groups in step velocity (type I error = 0.05). We included 20 PwPD without freezing of gait (diagnosed based on internationally accepted criteria (Hughes et al., 1992)) and 20 neurologically healthy individuals (CG), stratified into subgroups by PA levels (Table 1). Exclusion criteria were: diagnosis of additional neurological disorders, inability to walk safely and independently, uncontrolled diabetes, hypertension, and cardio-respiratory diseases, PD Stage > 3 on Hoehn & Yahr Scale (H&Y) (Schenkman et al., 2001). All participants signed an informed consent document approved by the local ethics committee – UNESP (#3083/2011). Participants were enrolled in a previous study (Santos et al., 2016).

2.2. Experimental design

Participants completed the experiments over 2 days: 1) filled out a medical history, PA questionnaires, Multidimensional Fatigue Inventory (MFI), and clinical exams; 2) performed the obstacle negotiation task, MVC, and rSTS (Fig. 1).

Table 2
ANOVA outcomes for main effects and interaction among factors.

ANOVA outcomes					
Outcomes		Effect	$F_{1,36}$	p	η_p^2
LAP		Subgroup	147.78	<0.01	0.80
rSTS duration		Groups*Subgroups	15.96	<0.01	0.31
MFI		Groups	23.08	<0.01	0.40
		Subgroups	6.65	0.01	0.16
MVC		Groups	12.10	<0.01	0.25
		Fatigue state	10.14	<0.01	0.22
Approach (Stride)					
	Length	Groups	4.63	0.04	0.12
	Length	Subgroups*Fatigue state	8.06	<0.01	0.19
	Width	Subgroups*Fatigue state	8.77	<0.01	0.20
	Velocity	Subgroups*Fatigue state	10.31	<0.01	0.23
	Length	Groups*Subgroups*Fatigue state	5.99	0.02	0.15
	Width	Groups*Subgroups*Fatigue state	18.30	<0.01	0.43
	Duration	Groups*Subgroups*Fatigue state	6.54	0.02	0.16
	Velocity	Groups*Subgroups*Fatigue state	10.94	<0.01	0.24
Crossing					
	Length	Groups	6.10	0.02	0.15
	Velocity	Groups	4.65	0.04	0.12
	Leading placement	Groups	20.17	<0.01	0.37
	Trailing placement	Groups	41.05	<0.01	0.54
	Leading clearance	Groups	114.17	<0.01	0.77
	Trailing clearance	Groups	11.66	<0.01	0.25
	Trailing clearance	Fatigue state	5.80	0.02	0.14
	Leading placement	Groups*Subgroups	4.54	0.04	0.12
	Trailing placement	Groups*Fatigue state	4.52	0.04	0.11
	Trailing clearance	Groups*Fatigue state	9.93	0.03	0.22
	Length	Subgroups*Fatigue state	5.77	0.02	0.14
	Velocity	Subgroups*Fatigue state	9.33	<0.01	0.21
	Trailing placement	Subgroups*Fatigue state	4.87	0.03	0.12
	Velocity	Groups*Subgroups*Fatigue state	7.09	0.02	0.17

2.3. Day 1

Within the PwPD and CG, two subgroups (n = 10) were formed according to the PA levels quantified by the Modified Baecke Questionnaire for Older Adults (Voorrips et al., 1991) (active ≥ 5 and inactive ≤ 4 (Santos et al., 2016)). In complement, we considered active only participants enrolled in PA at least three months before the experiment, indicated at the 'sports' section of the questionnaire (Voorrips et al., 1991). Fatigue trait was assessed by MFI (Smets et al., 1995). A trained evaluator determined PD motor severity (Unified Parkinson's Disease Rating Scale – motor section (UPDRS-III) (Fahn S, Elton R, 1987), PD stage (H&Y (Schenkman et al., 2001)), and global cognition (Mini-Mental State Examination) (Brucki et al., 2003)).

2.4. Day 2

2.4.1. Obstacle negotiation task

At a self-selected speed, participants walked over an 8 m-long wooden walkway and stepped over an obstacle (H = 15 cm; W = 80 cm; Thickness = 2 cm) placed in the middle of the walkway. Participants performed three trials before and after rSTS. The starting point was adjusted so that the right leg was the leading during obstacle negotiation. We assessed the stride before and the step over the obstacle as the approach and crossing phases, respectively (Fig. 1).

2.4.2. Maximum voluntary contraction protocol

Seated on a customized leg press device equipped with a force transducer (EMG system TM, SP, Brazil, sampling = 2 kHz, precision = 0.98 N), participants performed a bilateral leg press MVC (Fig. 1) (9,29). Participants were instructed to push with both legs as forcefully and rapidly as possible and hold for 5 s. Two trials, separated by 2 min of rest, were performed before and after the rSTS and the average computed.

2.5. Muscle fatigue protocol

Participants performed the rSTS at 0.5 Hz with the arms folded at the chest and knees and hips fully extended when standing up (chair height = 43; width = 41; depth = 42 cm) (Barbieri et al., 2016; Santos et al., 2016). Participants stopped when they were unable to keep the pace or continue the task. Duration of rSTS and rate of perceived exertion (6–20 Borg Scale (Borg, 1982)) before and after rSTS were recorded.

2.6. Data analysis

On the right plane, a 3D optoelectronic system (OPTOTRAK Certus – 3D - NDI, Waterloo, Ontario, Canada) recorded the markers' movements (100 Hz). Infrared emitters were placed over the lateral aspect of the calcaneus and the head of the fifth metatarsus of the right limb, medial aspect of the calcaneus, and the head of the first metatarsus of the left limb, and on the top edge and base of the obstacle.

Using custom-made Matlab codes (MathWorks, USA), the gait data were 6 Hz (cutoff frequency) 5th order low-pass Butterworth filtered. We calculated stride and step length, width, duration, and velocity on approach and crossing phases and leading and trailing foot placements before the obstacle (horizontal distance from the metatarsal marker to the marker at the base of the obstacle), leading and trailing foot clearance (vertical distance from the metatarsal to top edge marker).

2.7. Statistical analysis

In SPSS software (IBM Corp, NY), the data were homogeneously and normally distributed (Levene's and Shapiro-Wilk tests). A *t*-test was used to compare height, body mass, and age between-Subgroups (active*-inactive PwPD and CG). Baecke Questionnaire score, MFI, and duration of rSTS were compared by two-way ANOVA as between-Group (PwPD*CG) and Subgroups (active*inactive) factors. We conducted ANCOVAs, as between-Group and Subgroups, and within-Fatigue state

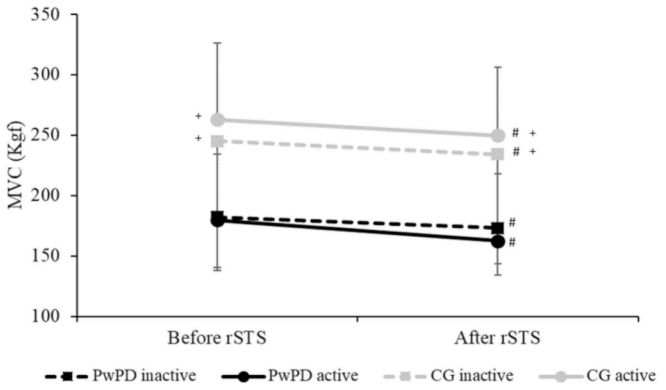

Fig. 2. Means and standard deviations of the muscular voluntary contraction (MVC) of the inactive and active Parkinson's Disease Group (PwPD) and Control Group (CG) before and after rSTS. + Group main effect: GC (active and inactive) ≠ PwPD (active and inactive); # Fatigue state main effect: Before ≠ After rSTS.

(before*after rSTS) factors, with MFI as a covariate, to compare MVC, perceived exertion, and gait outcomes. We set post hoc with the significance level ($p < 0.05$) corrected by Bonferroni. For post hoc comparisons, Cohen's d (d) effect sizes were calculated (small = 0.21–0.50, medium = 0.51–0.79, and large > 0.79) (Cohen, 1988). We computed Pearson's correlations (r, high = 0.5–1, moderate = 0.3–0.49, and low > 0.29) between MFI score, MVC, and PA level with gait outcomes before rSTS and with changes (Delta, after-before rSTS) of gait outcomes that revealed a significant main effect or interaction involving fatigue state.

3. Results

Table 2 summarizes the ANOVA and ANCOVA results.

3.1. Group characteristics, fatigue, and MVC data

Table 1 shows the participants' characteristics. Baecke Questionnaire scores were 75% higher in active vs. inactive ($d = 3.93$, $p < 0.001$). According to MFI, PwPD vs. CG had ~ 38% higher fatigue trait ($d = 1.46$, $p > 0.001$), and Active vs. inactive reported ~ 17% higher fatigue trait ($d = 0.7$, $p = 0.007$). CG active performed rSTS 70–80% longer than PwDG active and inactive, and CG inactive ($d = 1.50$–1.97, $p < 0.001$, Groups*Subgroups interaction).

MVC was 30% lower in PwPD than CG ($d = 1.12$, $p < 0.001$, Fig. 2). MVC decreased by 7% after rSTS in all groups ($d = 0.20$, $p = 0.003$). Perceived exertion increased from ~ 8.0 ± 2.0 to ~ 18.0 ± 2.0 ($d = 5.0$, $p < 0.001$).

3.2. Obstacle analysis: Approach phase

Fig. 3a-d show Groups*Subgroups*fatigue interaction. Before rSTS, PwPD inactive vs. PwPD active, CG inactive and CG active approached the obstacle with 16–27% slower (d range = 0.87–1.78, all $p < 0.04$), 13–23% shorter stride (d range = 0.99–1.71, all $p < 0.02$). PwPD inactive vs. PwPD and CG actives approached the obstacle with 26% and 27% wider stride ($d = 1.26$ and 1.28, all $p < 0.01$). After rSTS vs. before rSTS, while PwPD inactive approached the obstacle with 34% faster, 23% greater and 21% narrower stride ($d = 1.25$ and 1.75, all $p < 0.01$, Fig. 3d, a, and b), PwPD active and CGs increased the width (25% and 23%, Fig. 3b) to approach the obstacle ($d = 1.25$ and 1.07, all $p < 0.01$). After rSTS, PwPD inactive vs. other subgroups approached the obstacle with similar velocity and length ($p > 0.05$, Fig. 3d and a), but with ~ 21% and 23% narrower stride vs. PwPD active and CG inactive, respectively (d range = 1.53–1.62, all $p < 0.01$, Fig. 3b). Supplementary Table 1 details the main effects.

3.3. Obstacle analysis: Crossing phase

Before rSTS, PwPD inactive vs. PwPD active, CG inactive and CG

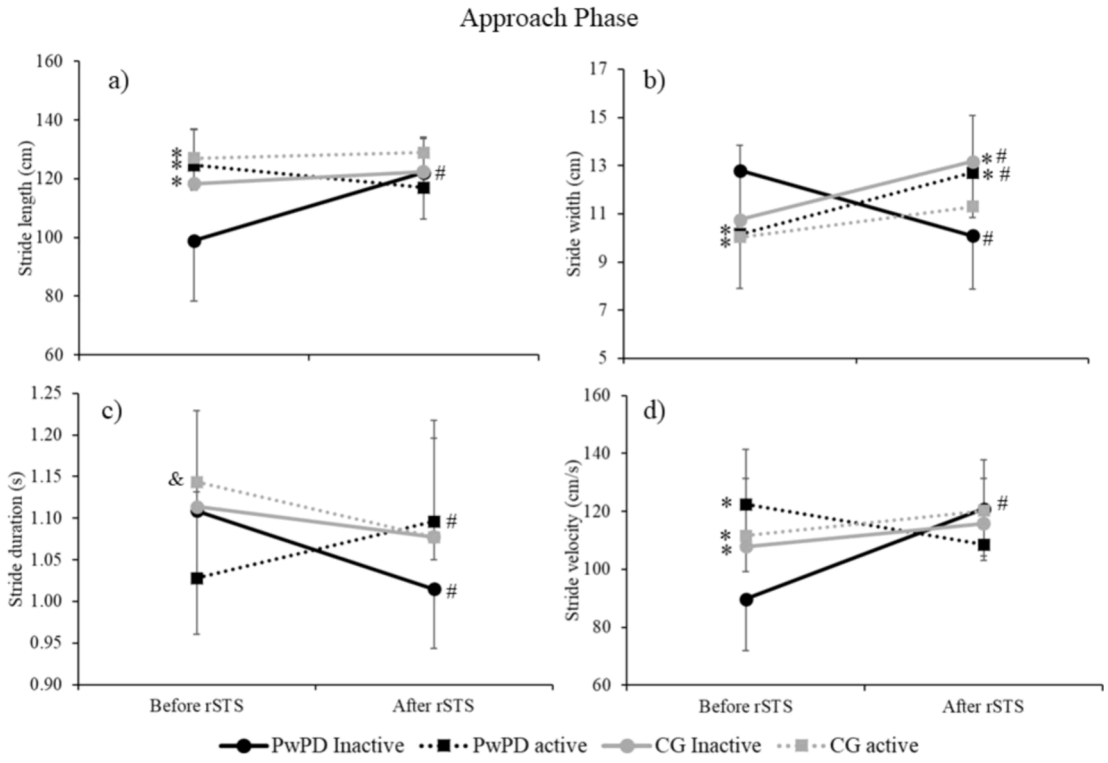

Fig. 3. Interaction for approach phase involving Groups*Subgroups*Fatigue state for a) stride length, b) width, c) duration, and d) velocity. * Different of PwPD inactive; & Different of PwPD active; # After rSTS ≠ Before rSTS.

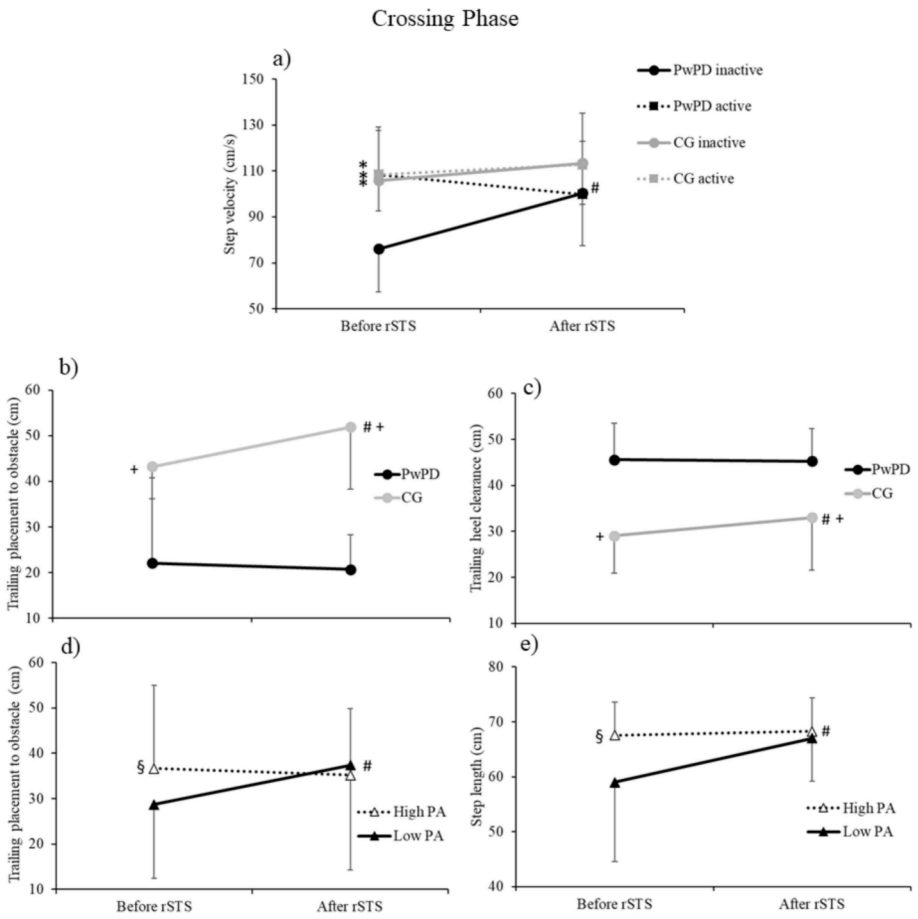

Fig. 4. Interactions for crossing phase involving: a) Groups*Subgroups*Fatigue state for step velocity; b) and c) Groups*Fatigue state for trailing placement to the obstacle and trailing foot clearance, respectively; d) and e) Subgroups*Fatigue state interaction for trailing placement to the obstacle and step length. * Different of PwPD inactive; + Different of PwPD; § different of inactive; # After rSTS ≠ Before rSTS.

active crossed the obstacle ~ 30% slower (d range = 1.59–1.88, all $p < 0.01$, Fig. 4a). PwPD vs. CG placed the trailing feet ~ 95% closer to the obstacle ($d = 1.50$, $p < 0.01$, Fig. 4b) and crossed with ~ 36% higher clearance ($d = 2.05$; $p = 0.01$, Fig. 4c). Inactive vs. active (both groups pooled) placed the trailing feet ~ 21% closer to ($d = 0.46$, $p = 0.04$, Fig. 4d), and crossed the obstacle with ~ 12% shorter step ($d = 0.77$, $p = 0.01$, Fig. 4e).

After rSTS vs. before rSTS, while the other subgroups did not change ($p > 0.05$), PwPD inactive increased ~ 31% the velocity ($d = 1.46$, $p > 0.01$, Fig. 4a). While CG increased ~ 20% and 13% the trailing placement ($d = 0.80$, $p < 0.02$) and clearance ($d = 0.40$, $p = 0.01$, Fig. 4b), respectively, the PwPD did not significantly change these outcomes after rSTS ($p > 0.05$, Fig. 4c). Inactive vs. active increased ~ 23% and 12% the placement distance of the trailing feet ($d = 0.44$, $p = 0.03$, Fig. 4d) and crossing step length after rSTS ($d = 0.69$, $p < 0.01$, Fig. 4e). Supplementary Table 2 details Group main effect.

3.4. Correlation analysis

Before rSTS, an increased fatigue trait correlated with shorter stride duration during approach, leading and trailing placement, and with higher leading and trailing clearance (Table 3). The maximum force correlates with step length and speed of crossing phase and trailing placement, and leading and trailing clearance (Table 3).

No correlations were observed regarding PA, MFI, and delta in MVC with changes in obstacle negotiation outcomes (Table 3).

4. Discussion

We determined the effects of PD, fatigue, and PA on gait during the approach to and crossing of the obstacle and the relationship between fatigue trait, PA and MVC with obstacle negotiation before and after rSTS. According to the hypothesis, the main observations were that PA improved obstacle negotiation performance in PwPD (data before rSTS) and afforded some protection against fatigability in the approach phase of the obstacle negotiation (only inactive PwPD was affected by muscle fatigability). We also observed associations between shorter foot placement and clearance to the obstacle with a higher fatigue trait (indicated by MFI) and lower MVC before rSTS. However, no associations were found regarding the absolute changes in gait with MVC changes induced by rSTS and fatigue trait. Our study extends the knowledge of the effects of PA and fatigability on gait, indicating that PA minimizes PD-typical gait impairments during obstacle negotiation and affords a protective effect against fatigue-effects on obstacle negotiation.

4.1. PA effects on gait

PA and disease state interacted. Before rSTS, inactive PwPD compared with active PwPD and the two CGs approached and crossed the obstacle using ~ 22–49% wider and shorter steps and slower velocity (Fig. 3a-d and 4a). This gait pattern resembles PD gait, which is associated with a decline in gait performance, slowness of movement, and falls in PwPD (Creaby and Cole, 2018). Physical inactivity thus potentiates PD symptoms, resulting in substantially slowed obstacle crossing. Such adaptations in inactive PwPD might be needed to step

Table 3
Correlation between fatigue trait (MFI), physical activity level (PAL) and maximum voluntary contraction (MVC) with absolute values gait outcomes before rSTS and with absolute changes Delta (after minus before rSTS) of gait outcomes induced by muscle fatigability.

Correlation before rSTS					
		MFI (score)	PAL (Baecke)	MVC (Kgf)	
Approach	Length (cm)	r = 0.04; p = 0.79	r = 0.3; p = 0.06	r = 0.28; p = 0.08	
	Width (cm)	r = 0.05; p = 0.74	r = -0.31; p = 0.06	r = 0.07; p = 0.67	
	Duration (s)	**r = -0.35; p = 0.03**	r = 0.06; p = 0.71	r = -0.03; p = 0.88	
	Speed (cm/s)	r = 0.18; p = 0.27	r = 0.26; p = 0.10	r = 0.25; p = 0.13	
Crossing	Length (cm)	r = -0.01; p = 0.96	r = 0.21; p = 0.19	**r = 0.43; p = 0.01**	
	Width (cm)	r = 0.14; p = 0.4	r = -0.12; p = 0.45	r = -0.02; p = 0.9	
	Duration (s)	r = -0.17; p = 0.28	r = -0.06; p = 0.73	r = 0.02; p = 0.91	
	Speed (cm/s)	r = 0.02; p = 0.93	r = 0.21; p = 0.19	**r = 0.32; p = 0.04**	
	Lead. placement (cm)	**r = -0.31; p = 0.05**	r = -0.03; p = 0.85	r = 0.21; p = 0.2	
	Trail. placement (cm)	**r = -0.42; p = 0.01**	r = 0.04; p = 0.81	**r = 0.39; p = 0.01**	
	Lead. clearance (cm)	**r = 0.54; p < 0.01**	r = 0.02; p = 0.92	**r = -0.41; p = 0.01**	
	Trail. clearance (cm)	**r = 0.50; p < 0.01**	r = 0.04; p = 0.79	**r = -0.36; p = 0.02**	
Correlation absolute changes (Delta: after minus before rSTS)					
		MFI (score)	PAL (Baecke)	MVC (delta, Kgf)	rSTS (s)
Approach	Length (delta, cm)	r = 0.01; p = 0.99	r = 0.23; p = 0.15	r = -0.3; p = 0.06	r = 0.24; p = 0.14
	Width (delta, cm)	r = 0.08; p = 0.63	r = -0.17; p = 0.29	r = 0.18; p = 0.26	r = -0.30; p = 0.06
	Duration (delta, s)	r = -0.29; p = 0.08	r = -0.01; p = 0.98	r = -0.16; p = 0.33	r = 0.03; p = 0.87
	Speed (delta, cm/s)	r = 0.08; p = 0.62	r = 0.2; p = 0.22	r = -0.16; p = 0.34	r = 0.13; p = 0.42
Crossing	Length (delta, cm)	r = 0.13; p = 0.44	r = -0.16; p = 0.34	r = 0.18; p = 0.27	r = -0.25; p = 0.12
	Speed (delta, cm/s)	r = -0.1; p = 0.52	r = -0.3; p = 0.06	r = 0.14; p = 0.39	r = -0.13; p = 0.43
	Trail. placement (delta, cm)	r = -0.26; p = 0.11	r = -0.24; p = 0.14	r = 0.22; p = 0.17	r = 0.24; p = 0.13
	Trail. clearance (cm)	r = 0.08; p = 0.63	r = 0.14; p = 0.39	r = -0.02; p = 0.89	r = 0.26; p = 0.11

over an object in daily life and avoid stumbling. A lack of apparent difference in the approach phase between active PwPD and both CGs supports the idea that PA can benefit PD gait (Mak et al., 2017; Ni et al., 2018). PA's beneficial effects on gait might be related to PA-induced neuroplasticity in the basal ganglia and dopaminergic pathways (Johansson et al., 2020; Mahalakshmi et al., 2020; Petzinger et al., 2013), reducing the unfavorable effects of PD on gait control (Mirelman et al., 2019).

Additionally, inactive PwPD adapted their gait to their clinical physical condition and reduced fitness by slowing the approach to and the obstacle crossing before rSTS as an attempt to perform the task cautiously. Indeed, slowed velocity might reflect in reduced extrapolated center of mass, indicating a conservative strategy during obstacle crossing (Hak et al., 2019), an interpretation confirmed by a lack of tripping in all the groups. This idea is also supported by the correlation results indicating that, before rSTS, higher trait (perception) of fatigue represented cautiousness during obstacle crossing (lower foot placement to obstacle and higher foot clearance).

Benefits of being physically active also extended to CG during obstacle crossing, as revealed by between-subgroup differences in the kinematics of this phase (Fig. 4d and e). Such an effect may be due to PA-induced improvements in neuromuscular control of gait, helping both healthy adults and PwPD to negotiate with an obstacle during ambulation (Ni et al., 2018). Although PA's potential benefits extended to both groups during obstacle crossing, this benefit is limited to stride length and trailing limb placement relative to the obstacle (Fig. 4d and e). Other outcomes (such as width, duration and speed, and limb placements) related to obstacle crossing maintained relatively similar between groups and subgroups. Thus, the PA-effects were evident mainly during the approach phase, suggesting a threshold in the favorable effects of PA on obstacle negotiation performance. The crossing phase involves single leg support and balance, a skill that might require specific training of dynamic balance. Clinically relevant, being physically reduced the PD-related impairments in gait control during obstacle negotiation at baseline (before rSTS) and also reduced the effects of muscle fatigability on approaching the obstacle, underlying the favorable effects of PA on gait control in PwPD (Mirelman et al., 2019).

4.2. PA and fatigue effects on gait

Of the four subgroups, the fatigue state had the greatest effect on obstacle negotiation in inactive PwPD. After rSTS, inactive PwPD increased stride length and velocity by 23–34% and reduced step width and duration by 10–21% (Figs. 3a-d and 4a). Because increased velocity might increase forward velocity of extrapolated center of mass during obstacle negotiation (Hak et al., 2019), increase in stride length might be a reactive and safety strategy to reduce the margim of stability and maintain the dynamic balance during the task under fatigued state. This strategy might be an attempt to minimize a loss in neuromuscular control induced by muscle fatigability (Barbieri et al., 2016, 2014).

Curiously, increases in step length and velocity in inactive PwPD during approach were accompanied by reductions in step width, while active PwPD and CGs increased width after rSTS. The data imply that active PwPD and CGs increased the mediolateral margin of stability and kept the center of mass displacement stable during walking (Hof et al., 2007, 2005). Therefore, a reduction in step width after rSTS in inactive PwPD might accentuate the risk of balance loss in the mediolateral direction during the obstacle approach. However, alternatively increasing stride/step length and velocity in inactive PwPD might compensate for the reduction in width (Barbieri et al., 2014) and avoid forward fall by reducing the magnitude of the negative anterior margin (Hof et al., 2007). Alternatively, increasing the gait velocity might reduce the time available to perform adjusts and recovery the postural control in case of an unexpected trip and/or slip during obstacle negotiation.

Another new observation was that adaptations in strides outcomes to fatigability during approach phase and in velocity during obstacle crossing were evident mainly in inactive PwPD. Such PA-effects on PD-related gait adaptation to muscle fatigability differ from previous studies that reported muscle fatigability effects on gait independent of PA in healthy younger adults (Barbieri et al., 2013) and PwPD during level walking (Santos et al., 2016). It is also peculiar that, since inactive PwPD performed the rSTS for the fewest number of rSTS trials (Table 1), this group would reasonably show less muscle fatigability and its effect on gait. Possibly, due to a reduced PA, inactive PwPD exhibited pronounced PD symptoms on gait such as bradykinesia and hypokinesia, executed the rSTS task cautiously, maybe to spare the knee muscles from becoming dysfunctional, and adjusted gait to guarantee the success in negotiating with an obstacle. An alternative explanation is that instead of interfering, rSTS facilitates with walking, similar to the effects of

acute exercise on gait in PwPD (Fernández-Lago et al., 2019). This observation may explain why the adaptation to muscle fatigability in approach phase minimized, or even inhibited, subgroups differences observed before rSTS.

Analyzing the data pooled across approach and crossing phases, we interpret that rSTS did not limit participants' internal resources. This interpretation stems from the observation that increased, instead of decreased, in spatial stride outcomes and gait speed during obstacle negotiation are characteristics of adults who have a low fall risk (Creaby and Cole, 2018; Galna et al., 2010) and positively respond to an exercise stimulus (Intzandt et al., 2018; Tollár et al., 2018). Thus, rSTS indicated to have limitations as a perturbation model to examine gait adaptations. Because gait requires a fraction of maximal voluntary force, the ~ 7% reductions in MVC after rSTS (Fig. 1) would only limit minimal, if any, mechanical adjustments in one's gait, an idea supported by a lack of correlation between changes in MVC and changes in approach and crossing phases outcomes (Table 3).

4.3. Limitation

Study limitation includes a lack of EMG and kinetic measurements during obstacle negotiation to understand the underlying neuro-mechanical mechanisms of gait adaptations to fatigability. Although rSTS is a highly demanding task (Bryanton and Bilodeau, 2017), rSTS does not target specific aspects of gait control (e.g., rhythm/temporal). Therefore, further studies should focus on fatigue protocols that target key elements of gait (e.g., incremental/long-distance walking) and verify their association with adaptation in target tasks. Age and body mass differences would interfere with fatigability effects on gait. However, given the slight and not statistically significant lower age and BMI in actives vs. inactive, any effect on the result is unlikely/improbable.

4.4. Conclusion

Our results suggested new insights in terms of the benefits of PA in PwPD, indicating that physically active PwPD have less difficulty in adapting their gait to negotiate with an obstacle and endure less muscle fatigability interference during obstacle negotiation. We also observed that higher fatigue trait was associated with PD-typical shorter limb placements to the obstacle, but not with changes induced by muscle fatigability. In conclusion, PA minimizes PD-typical gait impairments during obstacle negotiation and affords a protective effect against fatigue-effects on obstacle negotiation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authorship contribution

Conception and design of the study: Paulo C. R. Santos; Fabio A. Barbieri, Lilian T. B. Gobbi; *Acquisition of data:* Paulo C. R. Santos, Fabio A. Barbieri; Diego Orcioli-Silva, Victor S. Beretta; *Analysis:* Paulo C. R. Santos, Fabio A. Barbieri, Diego Orcioli-Silva, Victor S. Beretta; *Interpretation of data:* Paulo C. R. Santos, Fabio A. Barbieri, Diego Orcioli-Silva, Victor S. Beretta, Tibor Hortobágyi, Lilian T. B. Gobbi; *Drafting the article:* Paulo C. R. Santos; *Revising the manuscript critically for important intellectual content:* Paulo C. R. Santos, Fabio A. Barbieri, Diego Orcioli-Silva, Victor S. Beretta, Tibor Hortobágyi, Lilian T. B. Gobbi; *Final approval of the version:* Paulo C. R. Santos, Fabio A. Barbieri, Diego Orcioli-Silva, Victor S. Beretta, Tibor Hortobágyi, Lilian T. B. Gobbi.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbiomech.2021.110568.

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