Automated mechanical peripheral stimulation and postural control in subjects with Parkinson's disease and freezing of gait: a randomized controlled trial

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Summary

Individuals with Parkinson's disease (PD) and freezing of gait (FOG) have impaired postural control. Recent studies using foot sensory stimulation delivered by means of automated mechanical peripheral stimulation (AMPS) have demonstrated improvements of gait in individuals with PD.
This study aimed to investigate the effects of AMPS on postural control in individuals with PD and FOG. Thirty-three subjects participated in this randomized controlled trial.
Participants were allocated to two groups: AMPS and AMPS SHAM. Subjects underwent eight sessions of real (AMPS) or placebo AMPS (AMPS SHAM) once every three/four days. Postural control was assessed by means of posturography before the first and after the eighth session of treatment. We did not find positive effects of AMPS on center of pressure parameters. Thus, it seems that AMPS has no positive effect in terms of improving static postural control in individuals with PD and FOG.

KEY WORDS: Parkinson's disease, postural balance, postural equilibrium, rehabilitation, touch Senses.

Introduction

Parkinson's disease (PD) is a progressive neurological disorder characterized by four cardinal features represented by the acronym TRAP: tremor rest, rigidity, akinesia (or bradykinesia), and postural instability (Patel et al., 2014). Almost one third of individuals with PD present freezing of gait (FOG) (Perez-Lloret et al., 2014; Forsaa et al., 2015). FOG is defined as a brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk (Nonnekes et al., 2015).
Freezing of gait is considered an important clinical problem, and it is related to postural instability and the risk of falls (Chiari et al., 2000; Błaszczyk and Orawiec, 2011; Pelykh et al., 2015; Vervoort et al., 2016). It is also associated with limitations in performing daily life activities and with reduced quality of life (Perez-Lloret et al., 2014). Studies that analyzed balance in quiet standing have shown that center of pressure (CoP) measures are increased in individuals with PD and FOG compared with those without FOG (Pelykh et al., 2015; Schlenstedt et al., 2015). These CoP alterations include increased CoP velocity in the anteroposterior (AP) and mediolateral (ML) directions, as well as a greater sway amplitude in the ML direction (Nantel and Bronte-Stewart, 2014). This balance deficit may be worsened in the absence of visual information (Błaszczyk and Orawiec, 2011; Pelykh et al., 2015).
Increasing evidence also relates poor postural control to sensory disturbances in subjects with PD and FOG (Tan et al., 2011). A dopaminergic deficit in the basal ganglia is probably responsible for high tactile and proprioceptive thresholds and for sensorimotor disruption in subjects with PD (Conte et al., 2013). It is recognized that postural problems become increasingly severe as the disease progresses, despite treatment with levodopa (Jankovic, 2008; Vaugoyeau et al., 2011). Considering that dopaminergic treatment can improve some cardinal signs but does not robustly improve postural instability (Roberts-Warrior et al., 2000; Maurer et al., 2003), other non-dopaminergic pathways would seem to be involved in postural control of individuals with PD (Campbell et al., 2003). Thus, new treatment approaches have been continuously investigated.
Considering the sensory deficits presented by subjects with PD, automated mechanical peripheral stimulation (AMPS) has been investigated as a potential rehabilitation strategy (Galli et al., 2008; Kleiner et al., 2015a; Quattrocchi et al., 2015; Stocchi et al., 2015; Kleiner et al., 2018; Pagnussat et al., 2018; Pinto et al., 2018). AMPS can be delivered using a commercial device

(Gondola™, Gondola Medical Technologies SA, Switzerland) and consists of mechanical pressure stimulation applied, in sequence, in two areas of each foot (four areas in total). Our previous research into the benefits of AMPS for individuals with PD has shown positive effects of this therapy in terms of reducing motor fluctuations (Galli et al., 2008) and improving functional mobility and gait parameters (Galli et al., 2008; Kleiner et al., 2015b; Stocchi et al., 2015; Kleiner et al., 2018; Pinto et al., 2018). Recently, we demonstrated effects of AMPS on biomarkers related to neuroplasticity (Pagnussat et al., 2018).

Bearing in mind the importance of static postural control for the performance of several daily activities and its relationship with sensory deficits in individuals with PD and FOG, we proposed to investigate the long-term effects of AMPS treatment on postural control in this population. We hypothesized that AMPS would induce positive effects on postural control in individuals with PD and FOG.

Materials and methods

Study design

This is a randomized, double-blinded, placebo-controlled interventional study with concealed allocation and intention-to-treat analysis. The trial was registered online at ClinicalTrials.gov (identifier: NCT02594540) and approved by the Ethics Committee of the Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA) (protocol 1.333.131). The randomization, performed using the tool available at https://www.random.org, was done by an investigator who was not involved in the recruitment process or assessments.

The first researcher determined whether subjects were eligible to be included in the trial. A second researcher, who has considerable experience in posturography, acquired postural control data. Both these examiners were unaware of the group allocations. The randomization list was drawn up by a third researcher, who did not know the participants. An independent researcher performed the clinical evaluation before the start of the procedures. A further researcher checked each participant's allocation according to the randomization list and applied the AMPS treatment in both groups. Participants were also unaware of their allocated arm.

This study lasted from April to September 2016, and all procedures were performed at the Movement Analysis and Rehabilitation Laboratory at UFCSPA. Written informed consent was obtained from all the participants before the start of the procedures.

Participants

Thirty-three subjects with PD were recruited using the convenience sampling method, advertising for participants through hospitals, associations and other entities in the city of Porto Alegre, Brazil. We included male and female subjects, aged between 50 and 85 years, diagnosed with idiopathic PD, according to the London Brain Bank Criteria (NICE, 2006). To be included, they needed to be able to walk 25 feet unassisted or with minimal assistance; present regular FOG episodes as shown by the Freezing of Gait Questionnaire (FOG-Q); and have a minimum score of 20 on the Mini-Mental State Examination (MMSE). The exclusion criteria were: the presence of deep brain stimulation devices and any secondary musculoskeletal disorder involving the lower limbs, such as chondral injuries, ligament injuries and ankle sprains which, causing pain or impaired motion, could impede the gait evaluation.

Clinical characterization procedures also included the Motor Section of the UPDRS (UPDRS III) and the Hoehn & Yahr Scale (H&Y). Both scales were evaluated during the OFF-levodopa phase (at least 12h after the last medication dose).

The included subjects were randomly allocated to two treatment groups, real AMPS (AMPS) or placebo AMPS (AMPS SHAM), and accordingly underwent eight sessions of real or placebo AMPS (one session every three/four days). The experimental period lasted four weeks in total. All subjects were evaluated and treated during the OFF medication phase. We chose to evaluate participants in the OFF phase in order to avoid dopamine effects on FOG (Nonnekes et al., 2015). The participants continued to follow their routine rehabilitation or physiotherapy, but they were not allowed to start any new treatment during the study. After the end of the study, participants continued their regular treatments.

Intervention

AMPS: AMPS was delivered using a commercial device (Gondola™). This system consists of foot supports with electric motors that activate metallic stimulators. Each of these has a round end with a diameter of 2 mm. The AMPS treatment consisted of the application of pressure-based stimulation via the stimulators in four target areas (two per foot, corresponding to the head of the big toe and the base of the first metatarsal bone, between the sesamoid bones). Stimulation was applied in a pressure range of 0.3-0.9 N/mm^2, twice at each point, in succession. The stimulation pressure was set for each subject and corresponded to the level that caused the appearance of the tibialis anterior withdrawal reflex, identified by detection of a threshold contraction. Once the pressure value had been set, the value was recorded for administration of the AMPS treatment in the subsequent sessions.

AMPS SHAM: placebo stimulation was delivered using the same device used for real AMPS, following the same stimulation protocol and therapy cycle. However, a rigid plastic disk with a diameter of 12 mm was used in place of the round-ended stimulators. The pressure applied was therefore lower as the surface contact was bigger. All the other steps of the treatment were the same as for the real AMPS, as described above.

During the interventions, the subjects lay supine on a stretcher. The overall treatment session lasted about 15 minutes, including preparation (approx. 10/13 minutes) and stimulation (approx. 2 minutes). At the end of the treatment, both units of the device were removed, and the subject was instructed to stand up. The operator asked the subject to take two very long steps immediately after getting up. This strategy was used in all sessions, for both the AMPS group and the AMPS SHAM group. Thereafter, all participants completed three walk trials of 10 m distance, after being instructed to: "take a first step a little bit longer than usual" (this same instruction was given to all the subjects during the pre-treatment measurements). No adverse event or undesirable effect was seen during the study.

Outcome measures

Postural control data were acquired using a single force platform (BTS P-6000, BTS Bioengineering, Quincy, USA). All participants were under treatment with antiparkinsonian medication, but they all performed the analysis after a medication withdrawal period of at least 12 hours. Balance was measured at baseline (PRE) and after the eighth session of treatment (POST 8th). Participants stood barefoot on a force platform with their feet placed over outlines representing the feet, at an angle of 30º with respect to the AP direction. They were instructed to keep their arms hanging naturally at the sides of the body.

They were instructed to stand still for 30 seconds with their eyes open (EO) (Del et al., 2015) and then for 30 seconds with their eyes closed (EC) (Scoppa et al., 2013). We recorded a series of three trials in each condition, with a rest period of approximately one minute between the two series (Mazaheri et al., 2010). We performed the analysis using the average of the three trials in each condition (EO and EC). In the EO trials, subjects were instructed to look at a target positioned at 1.5 m in front of them.

Data analysis

An algorithm developed in Matlab software (Mathworks Inc., Natick, USA) was used to filter the raw data and to calculate the CoP descriptors. These procedures are detailed below.

Data filtering. During the data collection, the force platform signals were sampled at 100 Hz and the cutoff frequency of the low-pass filter was chosen after a residual analysis (Kleiner et al., 2015ab). A low-pass second order Butterworth digital filter at 4 Hz was applied. The first and the last 5 s of the 30 s acquisition time were discarded for the data analysis (Del Din et al., 2015). These periods were considered adaptation and fatigue periods, respectively.

Data normalization. Variables were normalized to the participant's height in mm. CoP displacements were computed in the AP and ML directions. A complete description of the algorithms appears in a previous study (Duarte et al., 2000; Rigoldi et al., 2013). The following variables were calculated and normalized to the body height: (a) Total path length [mm]: size or length of CoP trajectory on the base of support; this index is related to the energy consumption (Kantner et al., 1991; Duarte et al., 2000; Duarte and Freitas, 2010); (b) CoP area (mm^2): this variable estimates the dispersion of the CoP data through the statokinesigram area calculation, and it is related to the energy consumption; (c) Sway range of the CoP in the AP and ML directions [mm]: the difference between the maximum and minimum CoP displacement in each direction (Kantner et al., 1991; Duarte and Freitas, 2010); (d) Root mean square (RMS) for the AP and ML directions [mm]: dispersion of CoP displacement from the mean position during a time interval. The higher the RMS is, the higher the internal perturbation and thus the greater the need for postural adjustments (Kantner et al., 1991; Duarte and Freitas, 2010); (e) Mean velocity for the AP and ML directions [mm/s]: to determine how fast the CoP displacements were in the AP and ML directions. These variables were calculated to quantify the direction of the perturbation (Duarte and Freitas, 2010); (f) Total mean velocity for AP and ML directions [mm/s]: this is calculated through the displacement of the total sway of the CoP in both directions divided by the total duration of the trial. The higher the velocity, the higher the postural perturbation and thus the greater the risk of falls (Kantner et al., 1991; Duarte and Freitas, 2010). The total mean velocity was set as the primary outcome.

Statistical analysis

The sample size was determined on the basis of a previous study (Schlenstedt et al., 2015) (https://www.stat.ubc.ca/~rollin/stats/ssize/n2.html). A sample size of at least 16 participants in each group was calculated as necessary in order to detect a difference of 4.7 mm/s in the anteroposterior CoP mean velocity, with a deviation of 4.1 mm/s, two-sided 5% significance level and power of 90% (Schlenstedt et al., 2015). As the data met the criteria of normality and equal variance (determined by means of the Shapiro-Wilk and Levene tests, respectively), parametric statistical tests were applied. Two-way ANOVA was used to compare the intervention effects and interactions between group (AMPS and AMPS SHAM) and evaluation time (PRE and POST 8th) for the EO and EC conditions. IBM SPSS Statistics 24 was used for the statistical analysis. The level of significance was set at $\alpha < 0.05$.

Results

Thirty-six subjects were screened for eligibility and 33 met the inclusion criteria and were randomized. Figure 1 shows the flowchart of the recruitment process, participant selection and dropouts. The groups displayed similar baseline demographic, clinical characteristics and CoP variables ($p > 0.05$) (Table I).

Two-way ANOVA showed no interaction of time x group for any of the CoP variables ($p > 0.05$). Tables II and III show the p-values and data of static postural control measurements before (PRE) and after the eighth session of treatment (POST 8th).

Discussion

This is the first study investigating the effects of long-term AMPS treatment on postural balance during quiet standing in individuals with PD and FOG. Contrary to our hypothesis, we did not identify any difference in CoP parameters when real AMPS was compared with placebo AMPS.

Subjects with PD and FOG present postural control impairments which increase their risk of falling (Nantel and Bronte-Stewart, 2014; Pelykh et al., 2015; Schlenstedt et al., 2015). Static posturography data show that individuals with PD and FOG present large ML CoP sway amplitudes and high CoP velocity in the ML and AP directions compared with subjects without FOG (Nantel and Bronte-Stewart, 2014). Individuals with PD and FOG were also found, in a previous study, to show impaired control in weight shifting, swaying with a larger radius and displaying low adaptability of the postural sway process. These CoP characteristics may lead to an increased risk of falls (Pelykh et al., 2015). The high risk of falls caused by postural instability leads to decreased independence and a lower quality of life in af-

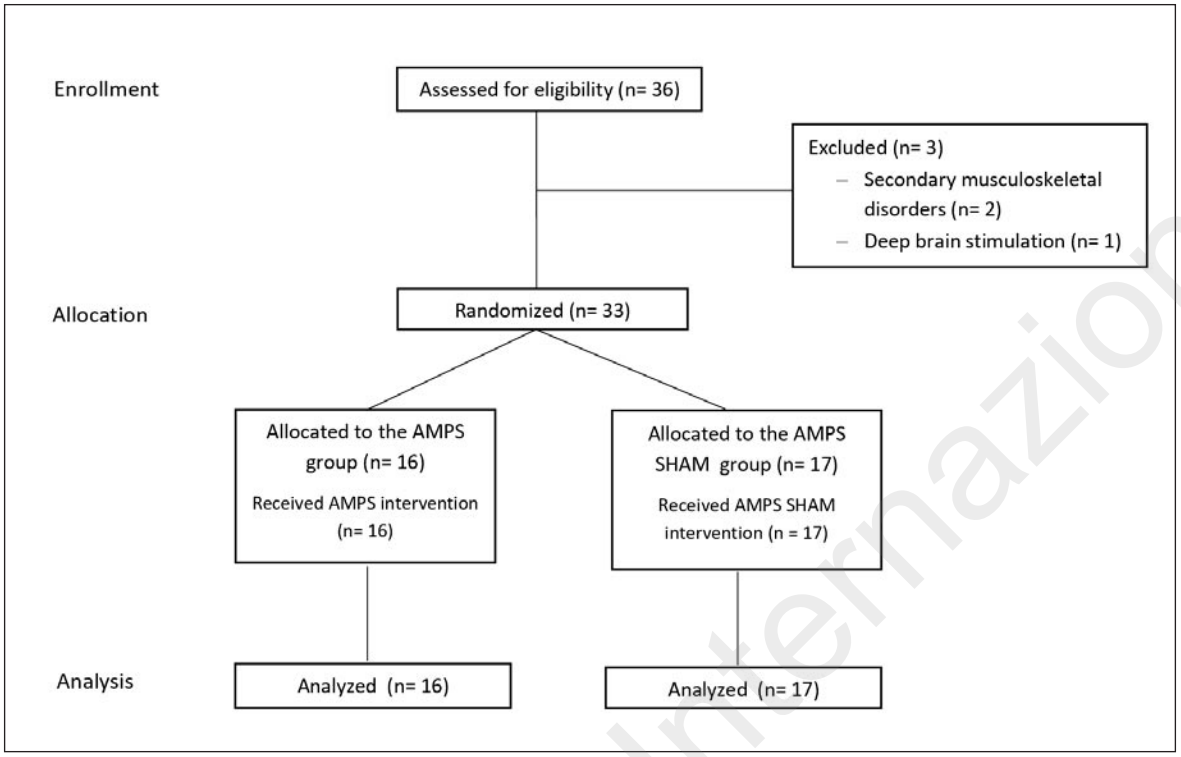

Figure 1 - Recruitment and selection flow chart.

Table I - Demographic characteristics of the included participants.

		AMPS (n= 16)	**AMPS SHAM (n= 17)**
Age (years)		65.31 (10.04)	64.19 (8.42)
Gender (M/F)		13 / 3	11/ 6
Height (m)		1.64 (0.11)	1.64 (0.10)
Body mass (kg)		75.88 (18.30)	77.69 (20.57)
Disease duration (years)			10.31 (5.06)
7.44 (4.54)			
H&Y	H&Y stage 1	0	1
	H&Y stage 1.5	0	2
	H&Y stage 2	2	1
	H&Y stage 2.5	6	6
	H&Y stage 3	4	5
	H&Y stage 4	4	2
UPDRS III		24.69 (7.80)	25.13 (10.31)
FOG-Q		15.69 (4.17)	13.31 (4.22)
MMSE		26.38 (3.70)	26.38 (3.46)

Abbreviations: AMPS=group of participants receiving automated mechanical peripheral stimulation treatment; AMPS SHAM= group of participants receiving placebo treatment; M=males; F=females; m=meters; kg= kilograms; H&Y=Hoehn & Yahr Scale; UPDRS III= Motor Section of the Unified Parkinson's disease Rating Scale score in OFF-Levodopa phase; FOG-Q: Freezing of Gait Questionnaire score; MMSE: Mini-Mental State Examination score. Data are mean values and standard deviations.

fected subjects (Perez-Lloret et al., 2014). It is therefore clinically important to investigate the effects of strategies designed to improve balance in this population.

Previous research has shown that foot sensory stimulation, though textured insoles, may allow individuals with PD to obtain improved ML postural sway when standing on firm or smooth surfaces with their eyes open or closed (Qiu et al., 2013). The lack of effect found in our study may be related to the fact that the AMPS stimulated only two areas of each foot. Maybe a greater stimulation area would be required to induce positive effects on postural balance during quiet standing. The absence

Table II - Center of pressure variables acquired with eyes open.

		Evaluations		
Variables	**Groups**	**PRE**	**POST 8**	**Two-Way ANOVA and p-value between groups**
Total path length	AMPS AMPS SHAM	76.98 (51.99 - 101.98) 115.10 (91.02 - 139.18)	73.96 (48.97 – 98.95) 100.30 (74 – 122.16)	F1,49=.213; p= .647
CoP Area (mm)	AMPS AMPS SHAM	.048 (.010 - .086) .104 (.066 - .142)	.041 (.003 - .079) .096 (.057 - .134)	F1,47=.267; p= .608
Sway range of CoP in AP	AMPS AMPS SHAM	.029 (.019 - .039) .043 (.033 - .052)	.028 (.018 - .038) .038 (.028 - .048)	F1,49=.176; p= .677
Sway range of CoP in ML	AMPS AMPS SHAM	.017 (.011 - .022) .024 (.018 - .029)	.014 (.009 - .020) .020 (.014 - .025)	F1,46=.072; p= .790
Root mean square for AP	AMPS AMPS SHAM	.005 (.003 - .006) .007 (.005 - .008)	.005 (.003 - .006) .006 (.005 - .008)	F1,49=.067; p= .797
Root mean square for ML	AMPS AMPS SHAM	.003 (.002 - .004) .004 (.003 - .005)	.002 (.001 - .003) .003 (.002 - .004)	F1,47=.009; p= .923
Mean velocity for AP (s)	AMPS AMPS SHAM	.030 (.014 - .047) .049 (.033 - .064)	.027 (.011 - .044) .047 (.031 - .062)	F1,46=.003; p= .960
Mean velocity for ML (s)	AMPS AMPS SHAM	.015 (.007 - .023) .024 (.016 - .032)	.013 (.005 - .021) .019 (.011 - .027)	F1,44=.125; p= .725
Total mean velocity (s)	AMPS AMPS SHAM	.037 (.017 - .057) .053 (.045 - .073)	.033 (.013 - .053) .057 (.038 - .076)	F1,45=.188; p= .667

Abbreviations: AMPS=group of participants receiving automated mechanical peripheral stimulation treatment; AMPS SHAM= group of participants receiving placebo treatment; M=males; F=females; m=meters; kg= kilograms; H&Y=Hoehn & Yahr Scale; UPDRS III= Motor Section of the Unified Parkinson's disease Rating Scale score in OFF-Levodopa phase; FOG-Q: Freezing of Gait Questionnaire score; MMSE: Mini-Mental State Examination score. Data are mean values and standard deviations.

of an effect of AMPS on postural control may also be explained by the idea that individuals with PD and FOG might depend more on proprioceptive feedback than on tactile inputs in order to achieve appropriate static balance control. Balance control depends on somatosensory, proprioceptive and vestibular inputs. There exists evidence indicating that subjects with PD exhibit tactile and proprioceptive threshold changes even early in the course of the disease (Conte et al., 2013). Impaired plantar sensitivity may result from dopaminergic deficits of the basal ganglia (Prätorius et al., 2003), and it is related to the disease severity. Moreover, subjects with PD have proprioceptive deficits, characterized by spatial disorientation and impaired perception of the body's motion in space (Conte et al., 2013). Impaired integration of sensory feedback from vestibular, visual and proprioceptive sensory systems leads to a decrease in balance and gait control (Patel et al., 2014).

Even though the effects of AMPS on postural control have never been investigated, its effects on dynamic parameters have recently been explored. Studies have reported improvements in spatiotemporal parameters, such as stride length and walking velocity, as well as restoration of the rhythmicity of gait and reduction of bradykinesia (Kleiner et al., 2015b; Stocchi et al., 2015; Kleiner et al., 2018). AMPS therapy has also been shown to enhance functional mobility, as assessed by the Timed Up and Go test, and to improve kinematic parameters (Galli et al., 2008; Pinto et al., 2018). AMPS also seems to improve walking stability, leading to improved dynamic balance (Kleiner et al., 2015b; Stocchi et al., 2015). Quattrocchi et al. (2015) reported acute effects of AMPS on brain activity, showing an increase in the resting state functional connectivity of regions related to visuospatial integration and processing, sensorimotor integration and anticipation of body position during movements. All these improvements were seen in dynamic movements of PD subjects without FOG.

In conclusion, it seems that AMPS has no effect on postural control as assessed by instrumented posturography. The present study has some limitations that should be considered, for example, the lack of sensory assessments and dynamic balance evaluations and the absence of a group of PD subjects without FOG. In addition, even though posturography is considered the safest and most widely applied method to assess postural balance (Piirtola and Era, 2006), the lack of a clinical measure of balance must be considered another

Table III – Center of pressure variables acquired with eyes closed.

		Evaluations		
Variables	**Groups**	**PRE**	**POST 8**	**Two-Way ANOVA and p-value between groups**
Total path length	AMPS AMPS SHAM	92.558 (61.974 - 123.141) 136.404 (108.089 - 164.718)	86.138 (56.755 - 115.522) 114.013 (84.630 - 143.397)	$F_{1,48}$=.219; p= .642
CoP Area (mm)	AMPS AMPS SHAM	0.066 (0.026 - 0.105) 0.079 (0.038 - 0.121)	0.054 (0.016 - 0.092) 0.095 (0.056 - 0.135)	$F_{1,44}$=.397; p= .532
Sway range of CoP in AP	AMPS AMPS SHAM	0.037 (0.026 - 0.048) 0.049 (0.039 - 0.060)	0.034 (0.023 - 0.044) 0.046 (0.035 - 0.056)	$F_{1,49}$=.001; p= .978
Sway range of CoP in ML	AMPS AMPS SHAM	0.020 (0.014 - 0.026) 0.020 (0.014 - 0.026)	0.017 (0.011 - 0.023) 0.023 (0.017 - 0.029)	$F_{1,45}$=.911; p= .345
Root mean square for AP	AMPS AMPS SHAM	0.006 (0.004 - 0.008) 0.008 (0.006 - 0.010)	0.006 (0.004 - 0.007) 0.007 (0.006 - 0.009)	$F_{1,48}$=.039; p= .844
Root mean square for ML	AMPS AMPS SHAM	0.003 (0.002 - 0.004) 0.004 (0.002 - 0.005)	0.003 (0.002 - 0.004) 0.004 (0.003 - 0.005)	$F_{1,45}$=.389; p= .536
Mean velocity for AP (s)	AMPS AMPS SHAM	0.045 (0.027 - 0.062) 0.052 (0.035 - 0.070)	0.038 (0.021 - 0.056) 0.053 (0.035 - 0.070)	$F_{1,48}$=.134; p= .716
Mean velocity for ML (s)	AMPS AMPS SHAM	0.017 (0.008 - 0.026) 0.023 (0.014 - 0.031)	0.014 (0.006 - 0.023) 0.020 (0.011 - 0.028)	$F_{1,43}$=.000; p= .989
Total mean velocity for AP and ML (s)	AMPS AMPS SHAM	0.049 (0.029 - 0.068) 0.054 (0.035 - 0.074)	0.044 (0.026 - 0.063) 0.053 (0.033 - 0.072)	$F_{1,45}$=.020; p= .888

Abbreviations: CoP=center of pressure; AP=anterioposterior direction; ML=mediolateral direction; AMPS= automated mechanical peripheral stimulation; AMPS SHAM: placebo automated mechanical peripheral stimulation. Data are mean values and 95% confidence intervals.

limitation. Further studies should investigate the effects of longer periods of treatment on static and dynamic balance control, and explore sensory improvements in individuals with PD and FOG after AMPS treatment.

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