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Loss of presynaptic inhibition for step initiation in parkinsonian individuals with freezing of gait

Jumes Leopoldino Oliveira Lira[1], **Carlos Ugrinowitsch**[2], **Daniel Boari Coelho**[3,4], **Luis Augusto Teixeira**[4], **Andrea Cristina de Lima-Pardini**[5], **Fernando Henrique Magalhães**[1], **Egberto Reis Barbosa**[6], **Fay B. Horak**[7], **Carla Silva-Batista**[1]

[1]Exercise Neuroscience Research Group, School of Arts, Sciences and Humanities, University of São Paulo, SP, Brazil;

[2]Laboratory of Strength Training, School of Physical Education and Sport, University of São Paulo, SP, Brazil;

[3]Biomedical Engineering, Federal University of ABC, São Bernardo do Campo, SP, Brazil;

[4]Human Motor Systems Laboratory, School of Physical Education and Sport, University of São Paulo, SP, Brazil;

[5]Centre for Neuroscience Studies, Queen's University, Kingston, Canada;

[6]Movement Disorders Clinic, Department of Neurology, School of Medicine of the University of São Paulo, SP, Brazil;

[7]Department of Neurology, Oregon Health and Science University, Portland, Oregon, USA.

Abstract

Freezing of gait (FoG) in Parkinson's disease involves deficient anticipatory postural adjustments (APAs) resulting in cessation of step initiation due to supraspinal dysfunction. Individuals with FoG (freezers) may require functional reorganization of spinal mechanisms to perform APAs. As presynaptic inhibition (PSI) is centrally modulated to allow execution of supraspinal motor commands, here we hypothesized a loss of PSI in freezers during APA for step initiation, which would be associated with FoG severity. Seventy individuals (27 freezers, 22 non-freezers, and 21 age-matched healthy controls [HC]) performed a GO-commanded step initiation task on a force platform under 3 conditions: 1) without electrical stimulation; 2) test Hoffman reflex (H-reflex); and 3) conditioned H-reflex. They also performed a control task (quiet stance). In the step initiation task, the H-reflexes were evoked on the soleus muscle when the amplitude of the APA

Corresponding to: Carla Silva-Batista, PhD, School of Arts, Sciences and Humanities of University of São Paulo, St. Arlindo Béttio, 1000, 03828-000, Vila Guaraciaba, São Paulo, Brazil, Tel: +55 11 999475935, csilvabatista@usp.br.

Author contributions

All authors contributed to the design of the study. J.L.O.L., D.B.C., A.C.L.P., F.H.M., E.R.B., C.S.B. collected the data. J.L.O.L., D.B.C., A.C.L.P., F.H.M., C.U., L.A.T., E.R.B., C.S.B. analysed the data, and all authors contributed to the interpretation of the data. J.L.O.L. and C.S.B. prepared the first draft of the manuscript. All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Competing interests

Fay B. Horak has a significant financial interest in APDM, a company that may have a commercial interest in the results of this research and technology. Fay B. Horak also consultants with Biogen, Neuropore, Sanofi, Adamus, Abbott, and Takeda. This potential individual conflict has been reviewed and managed by Oregon Health & Science University.

exceeded 10–20% of the mean of the baseline mediolateral force. PSI was quantified by the ratio of the conditioned H-reflex relative to the test H-reflex in both the tasks. Objective assessment of FoG severity (FoG-ratio) was performed. Freezers presented lower PSI levels during quiet stance than non-freezers and HC ($P<0.05$). During step initiation, freezers presented loss of PSI and lower APA amplitudes than non-freezers and HC ($P<0.05$). Significant correlations were only found for freezers between loss of PSI and FoG-ratio ($r=0.59$, $P=0.0005$) and loss of PSI and APA amplitude ($r=-0.35$, $P<0.036$). Our findings suggest that loss of PSI for step initiation in freezers may be due to FoG.

Keywords

freezers; H-reflex; spinal inhibitory mechanism; step initiation; sensorimotor integration; inhibition

Introduction

Freezing of gait (FoG) is one of the most debilitating features of Parkinson's disease (PD) and one of the major reasons for falls and reduced quality of life (Moore *et al.*, 2007; Giladi & Nieuwboer, 2008; Kerr *et al.*, 2010; Nonnekes *et al.*, 2015). This disabling clinical phenomenon is characterized by brief episodes of inability to step or by extremely short steps that typically occur when initiating gait or when turning (Nutt *et al.*, 2011). FoG has been associated with small and prolonged anticipatory postural adjustments (APAs) during step initiation (Tard *et al.*, 2014; Cohen *et al.*, 2017; Schlenstedt *et al.*, 2018; Heilbronn *et al.*, 2019).

Taking a step is a challenging task given the abrupt transition from bipedal stance posture to an unstable, unipedal gait in which the center of body mass is moved beyond the base of foot support, both forward and toward the initial stance leg (Burleigh *et al.*, 1994; Horak & Macpherson, 1996; Horak, 2006). The sagittal component of the APA pushes the body forward, while the mediolateral component shifts left-right leg support (Burleigh *et al.*, 1994; Horak & Macpherson, 1996). Previous findings have shown that individuals with FoG (freezers) delayed step initiation associated with prolonged APAs (Jacobs & Horak, 2007; Jacobs *et al.*, 2009b; Tard *et al.*, 2014; Cohen *et al.*, 2017).

Deficient APAs in step initiation (Jacobs *et al.*, 2009a; de Lima-Pardini *et al.*, 2017) has been related to disorders of frontocortical areas, which may be more affected in freezers than non-freezers because freezers have smaller activity of the supplementary motor area than non-freezers (Butler *et al.*, 2017). Dysfunction of the supplementary motor area may require functional reorganization of spinal circuitry, given the abnormal projections from this area through reticulospinal tract, which is involved in APA regulation (Schepens & Drew, 2004; Takakusaki, 2013; Takakusaki, 2017). As the reticulospinal tract connects to spinal interneurons that mediate one of the most powerful spinal inhibitory mechanisms, presynaptic inhibition (PSI) (Sirois *et al.*, 2013), it is possible that PSI during APAs may be deficient in freezers compared to non-freezers and age-matched healthy controls (HC).

PSI is required in the execution of supraspinal motor commands, as it is modulated centrally during and at onset of voluntary movements (Hultborn *et al.*, 1987a; Katz *et al.*, 1988; Rudomin & Schmidt, 1999). Hoffman reflex (H-reflex) has been used to measure PSI levels, which is quantified by the ratio of the conditioned H-reflex relative to the test H-reflex (Baudry *&* Duchateau, 2012; Magalhaes *et al.*, 2015; Silva-Batista *et al.*, 2017). Several studies have demonstrated increased PSI in young healthy individuals during 1) acquisition of a novel visuomotor skill (Perez *et al.*, 2005), 2) co-contraction of antagonist muscles (Nielsen & Kagamihara, 1993), 3) automatic activation of soleus muscles during gait (Dietz *et al.*, 1984; Morin *et al.*, 1984; Faist *et al.*, 1996), and 4) at onset of voluntary movements (Hultborn *et al.*, 1987b). PSI may be involved during APAs, as a recent study has observed larger H-reflex amplitudes in older than in younger and middle-aged individuals during a self-perturbing arm swing (indirectly indicating APAs) (Hortobagyi *et al.*, 2018).

PSI has been assessed only at rest in individuals with PD, with evidence that PSI is smaller in non-freezers than HC (Roberts *et al.*, 1994; Morita *et al.*, 2000; Silva-Batista *et al.*, 2017). PSI has been also negatively correlated with gait speed in non-freezers (Morita *et al.*, 2000). However, PSI remains unexplored in APAs for step initiation in freezers, non-freezers and HC. As FoG may be due to an inability to inhibit postural preparation and initiate voluntary stepping (Nutt *et al.*, 2011; Cohen *et al.*, 2014), we hypothesized that lack of central inhibition of postural preparation to allow stepping to commence would be reflected in loss of PSI in freezers (i.e., higher ratio of the conditioned H-reflex relative to the test H-reflex), which would be associated with FoG severity. We also hypothesized that loss of PSI would be related to lower amplitude and longer duration of APAs in freezers. Thus, the aims of this study were threefold: 1) to compare PSI during APA among freezers, non-freezers and HC; 2) to determine whether PSI correlated with the amplitude and duration of APAs; 3) to determine if PSI and APA amplitudes were correlated with FoG severity. We also measured PSI during quiet stance as a control task.

Methods

Ethical approval—The study was approved by University's Ethical Committee (School of Physical Education and Sport - ref. 2011/12), registered at the National Clinical Trial (RBR-83VB6B), and performed in accordance with the Declaration of Helsinki. All individuals provided written informed consent.

Participants

The individuals with PD (freezers and non-freezers) were recruited from the Movement Disorders Clinic in the School of Medicine at University of São Paulo. HC were also recruited from the surrounding University area. Individuals with PD were diagnosed by a movement disorders specialist in accordance with the UK Parkinson's Disease Society Brain Bank diagnostic criteria (Hughes *et al.*, 1992). The eligibility criteria for individuals with PD were: 1) Hoehn and Yahr stage range 2–4; 2) to be on stable dopaminergic therapy; 3) age range 49–80 years; 4) to be able to walk safely for 20 m without walking aids; 5) absence of neurological disorders (other than PD); 6) absence of significant arthritis, musculoskeletal or vestibular disorders, and severe tremor; 7) Mini-Mental State Examination (MMSE) score

>23 (Folstein *et al.*, 1975); and 8) lack of regular physical training in the period of 3 months preceding our data collection. Eligibility criteria for the HC included items 3 to 8. A movement disorders specialist assessed probable FoG by using videos of objective tests (e.g., step-over obstacles, turning clockwise and counter clockwise, and walking through a doorway) and the New Freezing of Gait Questionnaire (NFoGQ) (Nieuwboer *et al.*, 2009). Thus, individuals with PD who were defined as having FoG in the videos and scoring >3 on the NFoGQ (Fling *et al.*, 2013) were classified as freezers. The presentation of a short (30 s) video to illustrate FoG was performed at the beginning of the questionnaire application.

Experimental procedures

After explaining the study and obtaining consent, a physical therapist assessed the motor disability with the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) (Fahn & Elton, 1987) and clinical severity of FoG from the individual's experience with NFoGQ (Nieuwboer *et al.*, 2009) in individuals with PD. Afterwards, FoG severity was also objectively assessed by a 360 degree turning task (FoG-ratio) (Mancini *et al.*, 2017) only in freezers. On the second day, before all of the participants (freezers, non-freezers, and HC) performed the step initiation task, they performed the quiet stance task. H-reflexes were measured during quiet stance on the force platform (AMTI ORG-7) as a control task. We also adjusted the stimulation parameters in quiet stance (Figure 1A) so that the size of the test H-reflex was similar to the H-reflex measured during APA. We matched the size of the H-reflex because it is more susceptible to inhibition/facilitation depending on the size of the test H-reflex relative to maximal motor response (M_{max}) (Crone *et al.*, 1990). We evoked the soleus H-reflex in the left leg (the same leg required during initiation of APA), given that the individuals started the step with the right leg and applied the mediolateral force with the left support leg (de Lima-Pardini *et al.*, 2017). The soleus H-reflex was evoked at an intensity corresponding to 20–25% of M_{max}, resulting in a soleus H-reflex on the ascending portion of its recruitment curve, and in most individuals a small motor response. Afterwards, all individuals performed the step initiation task on the force platform in 3 conditions, as it follows: 1) without stimulus; 2) test H-reflex; and 3) conditioned H-reflex. Order of conditions was counterbalanced across individuals. Fifteen trials were performed in each condition, with a 10-s interval between trials. Intervals between conditions and tasks (quiet stance and step initiation) lasted 5 minutes. For each condition, a warning luminous stimulus was presented, and 2 s later a verbal imperative signal "GO!" was given. This imperative signal prompted individuals to initiate the step (Figure 1A). Individuals with PD performed both the tasks in the clinically "on" state (fully medicated) within 1.5 hours from taking their morning dose of anti-parkinsonian medication. As levodopa treatment improves APAs (Burleigh-Jacobs *et al.*, 1997; Smulders *et al.*, 2016) and the excitability of the H-reflex in PD (McLeod & Walsh, 1972), individuals with PD remained sat for 20 min in the laboratory after taking their normal dose of levodopa medication.This time window has been considered as appropriate for improvement of their motor state following medication consumption (Colosimo *et al.*, 1996).

Assessments

Presynaptic inhibition (PSI)—*Test H-reflex.* The soleus H-reflex was induced by stimulating the posterior tibial nerve in the left leg via a monopolar stimulating electrode (1

ms rectangular pulse) over the popliteal fossa using a constant-current stimulator (Nicolet® Viking Quest portable electromyography [EMG] apparatus, CareFusion, Wisconsin, USA). The anode was placed proximally to the patella. H-reflexes were recorded using two self-adhesive surface disc surface EMG electrodes (1-cm diameter) placed on the soleus muscle, below the insertion of the gastrocnemius muscles, with inter-electrode distance of 3–4 cm. Reflex responses were measured as the peak-to-peak amplitude of the H-reflex. H-reflexes were evoked with 10-s intervals. Stimulus intensities were increased in steps of 0.05 mA, starting below H-reflex threshold and increasing up to supramaximal intensity to measure the M_{max}. Sensitivity of the H-reflex to inhibitory and facilitatory effects depends critically on its size (Crone *et al.*, 1990). H-reflex was adjusted to 20–25% of M_{max} in all conditions (Crone *et al.*, 1987). The value of M_{max} was obtained when no further increase in the peak-to-peak amplitude of the M response with increasing stimulation intensity was observed.

Conditioned H-reflex.: PSI of the soleus H-reflex was evoked by the conditioning stimulation (Capaday *et al.*, 1995; Patikas *et al.*, 2004; Magalhaes *et al.*, 2015; Silva-Batista *et al.*, 2017) (1 ms rectangular pulses) of the common peroneal nerve through bipolar surface electrodes (0.5 cm diameter) placed 1–3 cm distal to the neck of the fibula in the left leg. Motor responses were recorded using two self-adhesive surface disk electrodes (1-cm diameter) placed on the tibialis anterior muscle. Care was taken to ensure that the conditioning stimulus was applied at a position where the threshold for an motor response (motor threshold) in the tibialis muscle was lower than the motor threshold in the peroneal muscle (1.1 × motor threshold), preventing vigorous contractions of the tibialis anterior muscle, which could be monitored throughout the experiments. The specificity of this stimulation was checked several times during experiment. A stimulation intensity of 1.1 × motor threshold is submaximal for activation of all inhibitory interneurons, allowing that both facilitatory and inhibitory effects be observed (Hultborn *et al.*, 1987a; Crone *et al.*, 1990; Patikas *et al.*, 2004; Geertsen *et al.*, 2008). Thus, to measure PSI during quiet stance and step initiation, a interval of 100ms was used between the conditioned H-reflex and the test H-reflex. At a conditioning-test interval of 100 ms, stimulation of the common peroneal nerve evokes an inhibition that is attributed to PSI on the terminals of Ia afferents to soleus motor neurons (Capaday *et al.*, 1995; Iles, 1996; Earles *et al.*, 2001; Patikas *et al.*, 2004). It has been shown that long latencies of 100–120 ms between activation of tibialis muscle and its antagonist (soleus muscle) strongly inhibit soleus H-reflexes during quiet stance and in the early part of the stance phase of walking (Capaday *et al.*, 1995). This effects indicates that a significant portion of the inhibition occurs at a premotoneuronal level, likely via PSI. Several different subsets of interneurons transmit PSI to Ia terminals projecting to several motoneuron pools (see more details in Knikou, 2008). Thus, the average values of 15 test H-reflexes and 15 conditioned H-reflexes for each task (quiet stance and step initiation) were considered for further analysis. Changes in PSI in both the tasks were quantified by the ratio of the conditioned H-reflex relative to the test H-reflex, with lower ratio indicating higher PSI levels (Baudry & Duchateau, 2012; Magalhaes *et al.*, 2015; Silva-Batista *et al.*, 2017). In addition, rectified and averaged EMG (raEMG) recordings during the tasks were measured over a 100 ms epoch that preceded tibial nerve stimulation (test H-reflex) or the common peroneal nerve stimulation (conditioned H-reflex). An epoch of 100 ms was selected to obtain raEMG values that represented the muscle activation at the time of stimulation

(Baudry & Duchateau, 2012). A co-contraction ratio was calculated to express the raEMG amplitude for tibial anterior muscle relative to the raEMG for soleus muscle.

Identification of PSI during APAs.: To trigger H-reflexes (test and conditioned) during APAs for step initiation, we used the force platform (AMTI ORG-7) to detect the abrupt increase of mediolateral force amplitude. When the APA amplitude exceeded 10–20% of the mean of the mediolateral force (corresponding to 2 standard deviations above the mean of the baseline force) an electrical stimulus was automatically triggered (Figure 1B). The baseline force threshold was calculated through LabVIEW software.

Anticipatory postural adjustments (APAs)—APAs were quantified during step initiation as described previously (de Lima-Pardini *et al.*, 2017). Onset of the APA was defined as the time between the abrupt increase of the mediolateral force amplitude (i.e., 2 standard deviations above the mean of the baseline force) and the onset of step. The duration of APA was calculated as the time between the onset of APA and the onset of the step. Step onset was identified by the marker on the right malleolus (2 standard deviations above the mean of the baseline foot displacement in the anteroposterior direction). Mediolateral force amplitude during the step task was normalized by the distance between the malleoli of the individual (unit in N/cm). To quantify step length, a kinematic analysis system (four cameras - Vicon brand, model T10) provided three dimensional coordinates of the foot by tracking the spherical reflective (passive) marker attached to the ankle (14 mm diameter). Amplitude and duration of the APA from condition 1 (without electrical stimulation) were used to compare APAs among the freezers, non-freezers, and HC groups.

Severity of freezing of gait (FoG)—Objective FoG measure (FoG-ratio) was calculated during a 2-minute turning task, in which individuals made 360° turns on the spot, alternating between clockwise and anti-clockwise turns as fast as they could do safely. Inertial sensors (Physilog, Gait Up, Lausanne, Switzerland) were placed on the shins and at the lumbar level. Data were sampled at 128Hz and stored for offline analysis using Matlab 2016b (Mathworks Inc.). Analysis was based on power spectral density from the anteroposterior acceleration data. The FoG-ratio was then calculated as the ratio between the square of the total power in the frequency band corresponding with freezing episodes (3–8 Hz) and the total power in the frequency band corresponding to locomotion (0.5–3 Hz). Higher FoG-ratio scores indicate greater FoG severity (see more details in Mancini *et al.*, 2017).

Subjective FoG measure was performed by NFoGQ that is a useful and comprehensive tool to subjectively assess the severity of FoG and its impact on activities of daily living and quality of life (Nieuwboer *et al.*, 2009). The NFoGQ consists of three parts. Part I detected the presence of FoG using a dichotomous item in which patients were classified as freezers or non-freezers, based on the occurrence of freezing episodes in the past month. Parts II and III were designed for freezers only, providing a score between 0 and 28. Part II (items 2–6, scoring range 0–19) rated the severity of FoG based on its duration and frequency (during turning and initiation of gait). Part III rated the impact of FoG on daily life (items 7–9, scoring range 0–9). Higher NFoGQ scores indicate greater FoG severity (Nieuwboer *et al.*, 2009).

Statistical analyses

Data normality was checked by the Shapiro–Wilk test and non-normal data (conditioned H-reflex relative to the test H-reflex and co-contraction ratio during quiet stance and step initiation) were log transformed. After checking data normality to test for the effects of both tasks on dependent variables (conditioned H-reflex relative to the test H-reflex, test H-reflex amplitude normalized to its corresponding M_{max}, raEMG of the soleus muscle, raEMG of the tibial anterior muscle, and co-contraction ratio), a linear mixed model for repeated measures was employed using groups (freezers, non-freezers, and HC) and tasks (quiet stance and step initiation) as fixed factors and subjects as a random factor. Whenever a significant *F*-value was obtained, a post hoc test with a Tukey's adjustment was performed.

To compare amplitude and duration of the APAs (condition without electrical stimulation) among the three groups (freezers, non-freezers, and HC), a one-way analysis of variance (ANOVA) was used. In addition, we used disease severity (UPDRS-III) as a covariate (ANCOVA) for this analysis.

To compare the MMSE score, demographic and anthropometric characteristics among the three groups (freezers, non-freezers, and HC), we used an one-way ANOVA.

To compare clinical characteristics between freezers and non-freezers, we used independent *t*-tests.

Two-tailed Spearman's rank correlation coefficients were calculated between the PSI levels with amplitude and duration of APA in all individuals, between the PSI levels with the FoG-ratio in freezers, and between APA amplitude with the NFoGQ scores in freezers.

The level of statistical significance was set at $P < 0.05$ for all comparisons. Results are expressed as means ± SD. SAS 9.2 software (SAS Institute, Cary, NC) was used to perform the statistical analyses.

Results

Participants

Seventy individuals (27 freezers, 22 non-freezers, and 21 HC) participated in the study. The demographic, anthropometrical, and clinical characteristics of the individuals in each group are presented in Table 1.

Loss of PSI in the step initiation in freezers

Figure 1C shows examples of test and conditioned soleus H-reflexes for the freezer, non-freezer, and healthy control during quiet stance (A1) and during APA for step initiation (A2).

Figure 2 shows the values of ratio of the conditioned H-reflex relative to the test H-reflex (i.e., PSI) in both the tasks for each group. The linear mixed model showed a significant group × task interaction for PSI levels ($F_{[2, 67]} = 203.39$, $P<0.0001$). The non-freezer and HC groups presented higher PSI levels (i.e., lower ratio of the conditioned H-reflex relative to the test H-reflex) in the step initiation than in the quiet stance (mean difference [MD]:

−7.1%; 95% confidence interval [CI]: −12.1 to −2.0; P=0.001; and MD: −22.8%; CI: −23.9 to 17.7 to; *P*<0.0001, respectively), whereas the freezer group presented loss of PSI in the step initiation (i.e., higher ratio of the conditioned H-reflex relative to the test H-reflex), but presented PSI levels in the quiet stance (MD: 23.1%; CI: 18.5 to 27.6; P<0.0001). Post hoc comparisons revealed that the non-freezer and HC groups presented higher PSI levels in the quiet stance than the freezer group (MD: −5.8%; CI: −10.8 to −0.7; P=0.014; and MD: −40.6%; CI: −45.7 to −35.5; P<0.0001, respectively), whereas in the step initiation, the freezer group presented higher ratio of the conditioned H-reflex relative to the test H-reflex (i.e., loss of PSI) than the non-freezer and HC groups (MD: 35.9%; CI: 30.9 to 41.0; P<0.0001; and MD: 63.7%; CI: 58.5 to 68.8; P<0.0001, respectively). The HC group presented higher PSI levels than the non-freezer group in the quiet stance (MD: −11.9%; CI: −17.2 to −6.5; P<0.0001) and in the step initiation (MD: −27.7%; CI: −33.1 to −22.3; P<0.0001) (Figure 2).

Test H-reflex amplitude (%M_{max})

There were no significant differences for the test H-reflex amplitude normalized to its corresponding M_{max} (P=0.963) neither among groups nor tasks (Table 2.

raEMG recordings

There were no significant differences for the raEMG of the soleus muscle (P=0.810), raEMG of the tibial muscle (P=0.154), and co-contraction ratio (P=0.218) neither among groups nor tasks (Table 2).

APA amplitude and duration

The freezers did not present with any episodes of FoG associated with “trembling of the knees” and multiple APAs (Jacobs *et al.*, 2009b) during the step initiation tasks in this study. In addition, single APAs were observed in all trials of freezers, non-freezers, and HC individuals. The ANOVA showed that the freezer group presented smaller APA amplitudes than the non-freezer group (MD = −0.46N/cm; IC = −0.80 to −0.12; P=0.005; Figure 3A) and the HC group (MD = −0.87N/cm; IC = −1.21 to −0.52; P<0.0001). The non-freezer group showed lower APA amplitudes than the HC group (MD = −0.40N/cm; IC = −0.76 to −0.04; P=0.02; Figure 3A). In addition, the freezer group showed longer APA durations than the HC group (MD = 75.9ms; IC = −30.03 to 121; P=0.0005), and the non-freezer group showed longer APA durations than the HC group (MD = 84.0ms; IC = 36.02 to 132; P=0.0002; Figure 3B). There was no significant difference in APA duration between the freezer and non-freezer groups (MD = −8.15ms; IC = −53.2 to −36.9; P=0.90; Figure 3B).

Correlational analysis

Significant correlations were observed only for freezers between the loss of PSI in the step initiation and APA amplitude (P<0.05), between the loss of PSI in the step initiation and the FoG-ratio (P<0.05), and between the NFoGQ scores and the APA amplitude (P<0.05) as shown in Figure 4. For non-freezers and HC, no significant correlations were found between PSI level and any APA related variable as shown in Table 3.

Discussion

The current study is the first to identify spinal reflex involvement during an important functional task for freezers (step initiation), as well as the importance of PSI to prevent freezing. Our main findings were the following: 1) Freezers presented loss of PSI (i.e., higher ratio of the conditioned H-reflex relative to the test H-reflex) whereas non-freezers and HC presented PSI during APAs, and 2) Significant correlations were found between loss of PSI and FoG-ratio and small APA amplitude for freezers. Our data provide novel insights about the important role of central and spinal inhibitory mechanisms to manage the transition from standing to walking.

Loss of PSI during the APA in freezers

Three possible explanations for the loss of PSI during the APA in freezers include abnormal alterations in some mechanisms that underlying FoG in PD, such as abnormal supraspinal motor commands, abnormal proprioceptive inputs, and or a combination of both alterations (*i.e.*, deficits in sensorimotor integration). APAs are thought to be generated by the supplementary motor area, as lesions in supplementary motor area result in absent APAs in humans (Gurfinkel *et al.*, 1988; Viallet *et al.*, 1992). Additionally, inhibition of supplementary motor area via repetitive low frequency transcranial magnetic stimulation of the pre-supplementary motor area prolongs APAs, especially in individuals with PD (Jacobs *et al.*, 2009a). The supplementary motor area and the peduncolopontine nucleus have significant inputs to pontomedullary reticular formation, in addition to the spinal cord (Keizer & Kuypers, 1989; Matsuyama & Drew, 1997; Schepens & Drew, 2004). The pontomedullary reticular formation has neurons related to APAs, different neurons related to stepping, and a third set of neurons related to both APAs and stepping (Schepens & Drew, 2004). In freezers, both the supplementary motor area and peduncolopontine nucleus may send abnormal motor commands to the reticulospinal tract, which may coordinate APAs with step initiation (Schepens & Drew, 2004; Takakusaki, 2013; van Lith *et al.*, 2018). Alternatively, the supplementary motor area may forward programs of precise leg-foot movement to the primary motor cortex, which, in turn, sends motor command via the corticospinal tract (Hoshi & Tanji, 2007; Takakusaki, 2013). Recently, corticospinal involvement during the APA has been observed, as corticospinal excitability of the erector spinae muscle increased 40 ms prior to rapid shoulder flexion in healthy individuals (Chiou *et al.*, 2018). Both the reticulospinal and corticospinal tracts project to the spinal motoneuron pool (Takakusaki, 2013; Takakusaki, 2017), which send drive to excitatory and inhibitory interneurons that mediate PSI during voluntary movements (Lundberg & Voorhoeve, 1962; Iles, 1996; Meunier & Pierrot-Deseilligny, 1998; Sirois *et al.*, 2013). Therefore, an intact drive from frontocortical and subcortical areas to spinal circuits controlling PSI may be important for flexible modulation of APAs.

In fact, the small APA amplitude of freezers was inversely correlated with loss of PSI (i.e., higher ratio of the conditioned H-reflex relative to the test H-reflex), with smaller APAs related to more loss of PSI (Figure 4A). In addition, smaller APAs were negatively correlated with higher NFoGQ scores (Figure 4C). Freezers showed smaller APA amplitudes than the other groups (Figure 3A), corroborating findings from previous studies (Schlenstedt

et al., 2018). Thus, our results would suggest that reticulospinal and corticospinal tracts send irregular or no drive to interneurons mediating PSI of the soleus muscles during deficient APA in freezers. In addition, FoG has been hypothesized be due to an inability to inhibit stance postural control and initiate stepping (Jacobs & Horak, 2007; Jacobs *et al.*, 2009b; Nutt *et al.*, 2011; Cohen *et al.*, 2014). Furthermore, freezers show loss of white matter in the inhibition pathway between the right supplementary motor area and right subthalamic nucleus, as well as between the right supplementary motor area and right peduncolopontine nucleus (Fling *et al.*, 2013). This right-sided pathway has been implicated in cognitive inhibition in healthy control individuals (Coxon *et al.*, 2012). Thus, we believe that lack of central inhibition of stance posture to allow stepping to commence is reflected in loss of PSI in freezers. However, other possible explanations for loss of PSI include proprioceptive deficits and/or abnormal sensorimotor integration.

Abnormal proprioception may also contribute to the observed loss of PSI in freezers, given that freezers may present greater proprioceptive deficits than non-freezers and HC (Tan *et al.*, 2011). These proprioceptive deficits might interfere negatively with APAs prior to a step, since presynaptic proprioceptive signals may also project to the sensorimotor cortex and cerebellum to coordinate posture and movement (Morita *et al.*, 1998). However, further studies should determine if greater proprioceptive deficits are related to loss of PSI during APAs in freezers. Evidence has suggested that even non-freezers have deficits in sensorimotor integration (Lewis & Byblow, 2002). It might interfere negatively in the reorganization of PSI during APA, given that the APA motor program can be adjusted during its execution (Delval *et al.*, 2018). This process might involve rapid and direct sensorimotor integration, such as reorganization of the supraspinal and spinal motor systems and proprioceptive afference for the ongoing APA (Takakusaki, 2013; Takakusaki, 2017). We hypothesize that abnormal sensorimotor integration may also contribute to loss of PSI during APA in freezers. Further studies are necessary to confirm this hypothesis.

Correlation between loss of PSI and FoG-ratio

Loss of PSI was associated with higher FoG severity (FoG-ratio values) (Figure 4B). The FoG-ratio is based on the assumption that the high frequency weight shift represent “trembling of the knees” and the lower frequencies represent the gait cadence. So although there was no clinically apparent FoG during the study the freezers demonstrated prefreezing characteristics involving rapid left-right weight shifts during APAs that delayed onset of a step (prolonged APAs). Although APAs were small and prolonged none step initiation trials in freezers resulted in FoG, including multiple APAs (trembling of the knees) (Jacobs *et al.*, 2009b) in this study. The lack of freezing is likely because individuals were tested in the clinically “on” levodopa state and freezing is usually reduced in the “on” state (Nutt *et al.*, 2011). In addition, the step initiation on our study was triggered by an external cue, a verbal “GO” command. It is well known that freezing can be overcome with these types of external cues (Ginis *et al.*, 2018). We calculated the FoG-ratio during 360 degree turns. Evidence has suggested that continuous turning for 2 min with direction reversals every 360 degrees is the best way to induce FoG events, because it imposes temporal and spatial asymmetry between steps (Plotnik *et al.*, 2008; Snijders *et al.*, 2012; Mancini *et al.*, 2017). Temporal and spatial asymmetry between steps are associated with problems in rhythmic movement coordination

(Plotnik *et al.*, 2008), which also is controlled by a spinal cord network (Takakusaki, 2013; Takakusaki, 2017). As PSI is important for modulating muscles' coordination by adjusting both supraspinal motor commands and sensory feedback at the spinal level (Nielsen, 2004), the loss of PSI found in freezers may contribute to FoG severity.

Methodological care

We took care to prevent two methodological possibilities to facilitation, instead of inhibition, following a conditioning stimulus to the tibialis anterior muscle. First, the conditioning stimulation depolarizes Ia afferents from peroneal muscles that have facilitatory effects on the soleus muscle (Meunier *et al.*, 1993). Second, the H-reflex is more susceptible to inhibition/facilitation depending on the size of the test H-reflex (Crone *et al.*, 1990). To minimize these two factors, contraction of the peroneal muscle was highly controlled in the present study to isolate activation of the tibialis anterior muscle with stimulation. We checked that the stimulation evoked a motor response in the tibialis anterior muscle without a motor response in the peroneal muscles. In addition, the size of the test H-reflex was maintained constant throughout the experiments, thus reducing the bias in the amount of inhibition (PSI), as it depends on the size of the test H-reflex. Since the soleus H-reflex is often depressed in the quiet stance (Katz *et al.*, 1988; Capaday *et al.*, 1995; Baudry & Duchateau, 2012), and mainly in the early part of the stance phase of walking (Capaday *et al.*, 1995), the test stimulus intensity during the APA was adjusted so that the reference (unconditioned) H-reflex attained the same size as in the quiet stance. In fact, we also observed that all freezers had PSI during quiet stance in which the size varied by group: freezers < non-freezers < age-matched healthy controls (Figure 2). Thus, loss of PSI during the APA in the freezers may be due to FoG.

Possible influences on loss of PSI during APAs

If the APAs are reduced in step initiation, but tibial muscle activity is not inhibited, one may suggest that cocontraction and/or prolonged activation of tibialis muscles during APAs could also be another possible explanation. PSI is known to increase during cocontraction of ankle muscles (Nielsen & Kagamihara, 1993). Freezers have more cocontraction than non-freezers (Schlenstedt *et al.*, 2018) and non-freezers have higher cocontraction levels than HC (Dimitrova *et al.*, 2004; Horak, 2006), even so, we found that non-freezers presented lower PSI levels than HC, whereas freezers did not present PSI at all. Thus, cocontraction may not have interfered. In addition, using the co-contraction ratio at the time of stimulation, there were no between-group differences (Table 2). Moreover, there was no correlation ($P > 0.09$) between the co-contraction ratio with loss of PSI in freezers and with the PSI leves in non-freezers and HC (data not shown). On the other hand, evidence has demonstrated that in individuals with PD, during stepping, the freezing events are anticipated by early with prolonged activation of tibialis muscles (Nieuwboer *et al.*, 2004) that may reflect unsuccessful compensatory attempts to facilitate PSI in the soleus muscle. This may be a possible explanation for the loss of PSI during deficient APAs in freezers. However, freezers did not present any freezing events in the present study. Moreover, there were no between-group differences for the arEMG of the tibial muscle at the time of stimulation. Thus, further studies should investigate if prolonged activation of tibialis muscles during APAs in freezing events may be related with loss of PSI.

Clinical Implications

FoG is a disabling clinical phenomenon that is thought to involve defective APAs resulting in difficulty or cessation of step initiation. Our findings show that loss of PSI is associated with both small APAs and FoG severity. Therefore, this study has implications for informing the design of treatment methods to focus on restoring PSI levels and improving APA amplitude, which could improve FoG severity. As the loss of PSI during APAs observed in freezers may also be explained by deficits in sensorimotor integration, treatment strategies to enhance sensorimotor integration may be helpful. Spinal cord stimulation is a recent, semi-invasive method that may enhance the sensorimotor integration in freezers. It activates multiple structures along the somatosensory pathway and desynchronizes the pathological cortico-striatal oscillations responsible for the manifestation of Parkinson's disease symptoms (Fuentes *et al.*, 2009; Yadav & Nicolelis, 2017). In addition, proprioceptive signals run primarily through some of the largest myelinated axons that comprise the dorsal columns of the spinal cord during electrical stimulation (Fuentes *et al.*, 2009; Yadav & Nicolelis, 2017). Although spinal cord stimulation has improved APA duration (de Lima-Pardini *et al.*, 2018) and FoG episodes (de Lima-Pardini *et al.*, 2018; Samotus *et al.*, 2018), evidence is still inconclusive as these findings were recorded in a small number of individuals.

Alternatively, exercise strategies that require high levels of sensorimotor integration may be helpful for restoring PSI and improving APAs to reduce FoG severity. In fact, we recently demonstrated that three months of challenging exercise with high levels of sensorimotor integration (i.e., resistance training with instability) improved PSI levels at rest (Silva-Batista *et al.*, 2017) and improved APAs by a clinical scale (Silva-Batista *et al.*, 2018). Future studies should investigate the effects of this type of exercise program in freezers.

Conclusion

The current study demonstrates that freezers consistently show loss of PSI, unlike non-freezers and HC during their APAs. Furthermore, the loss of PSI was associated with small APA size and worse FoG severity. From these observations, we suggest that loss of PSI of stance posture in preparation for a step may be due to FoG.

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Key Points

- Individuals with freezing of gait (FoG) due to Parkinson's disease (PD) have small and long anticipatory postural adjustments (APA) associated with delayed step initiation.
- Individuals with FoG (freezers) may require functional reorganization of spinal mechanisms to perform APAs due to supraspinal dysfunction. As presynaptic inhibition (PSI) is centrally modulated to allow execution of supraspinal motor commands, it may be deficient in freezers during APAs.
- We show that freezers presented PSI in quiet stance (control task), but they presented loss of PSI (i.e., higher ratio of the conditioned H-reflex relative to the test H-reflex) during APAs prior to step initiation (functional task), whereas non-freezers and healthy control individuals presented PSI in both the tasks.
- The loss of PSI in freezers was associated with both small APA amplitudes and FoG severity.
- We hypothesize that loss of PSI during APA for step initiation in freezers may be due to FoG.

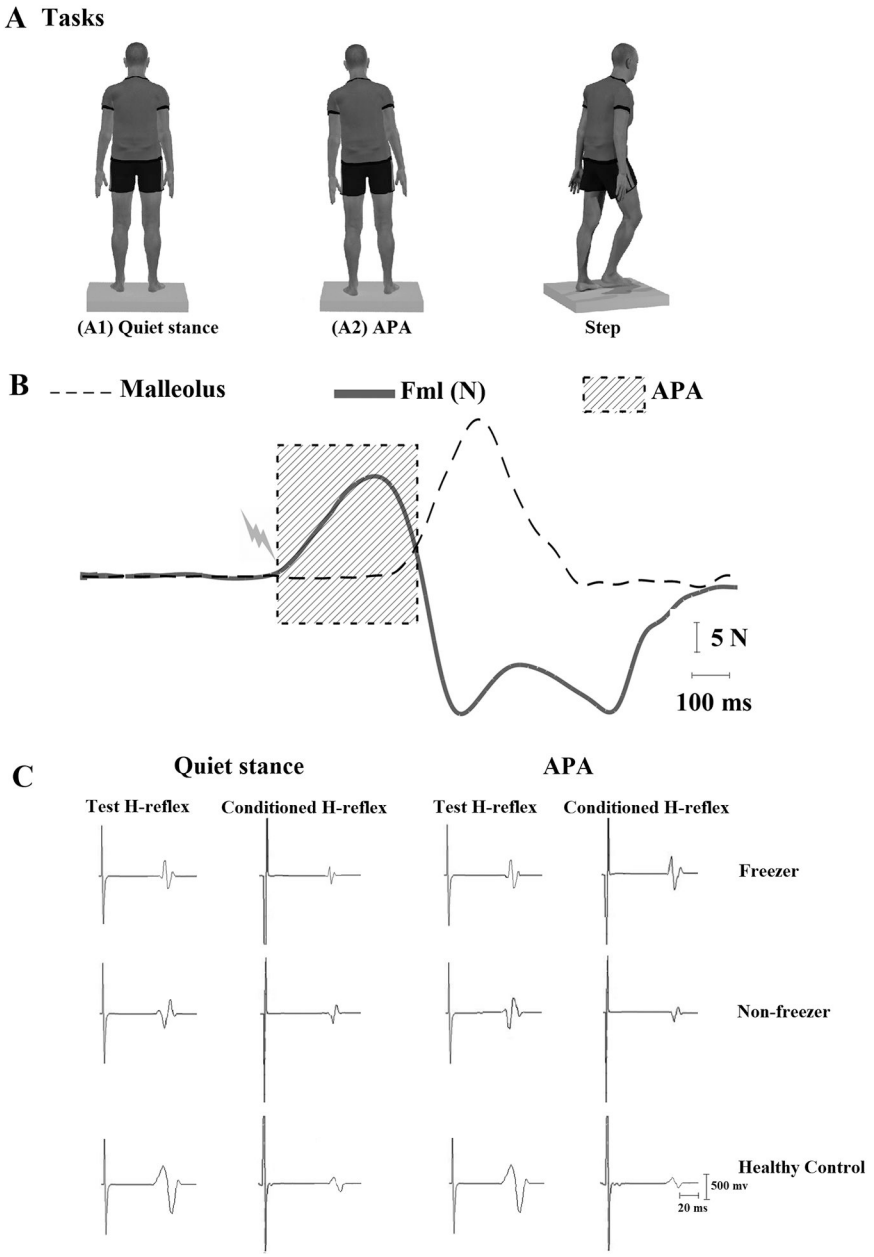

Figure 1.

Experimental setup and respective signals. (A) Task examples: (A1) quiet stance; (A2) performing step initiation task with lateral weight shift associated with the anticipatory postural adjustment (APA) after a verbal imperative “GO” signal and stepping. H-reflexes (test and conditioned) were triggered during quiet stance (A1) and during APAs for step initiation (A2). (B) Example of an H-reflex triggered at the onset of APA (duration shaded). Solid line shows mediolateral force (Fml) amplitude during the APA and dashed line shows forward displacement of the reflective marker attached to the ankle during the step. (C) Representative traces of test and conditioned H-reflexes (average over 15 responses) for a freezer, non-freezer, and age-matched healthy individual during quiet stance and in APA for step initiation.

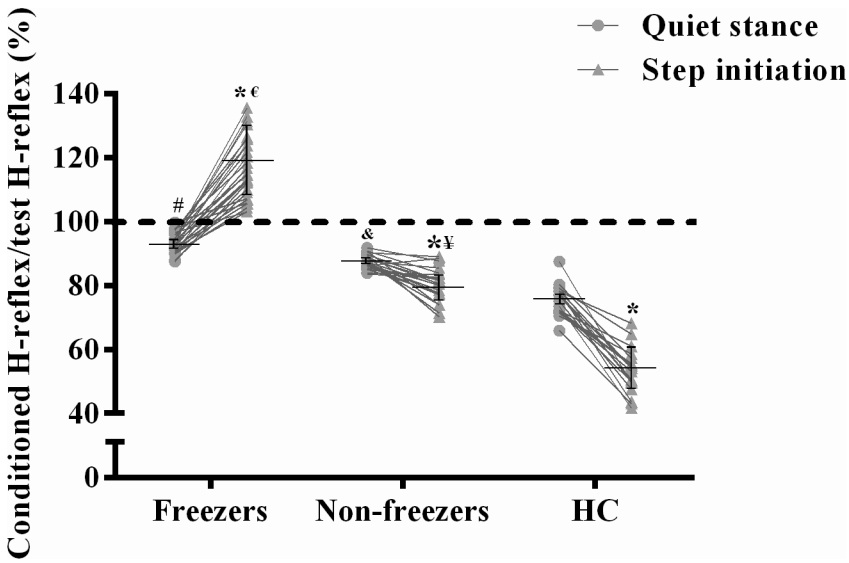

Figure 2.

Means ± SD for the ratio of the conditioned H-reflex relative to the test H-reflex (i.e., presynaptic inhibition [PSI]) during quiet stance and step initiation. As can be seen, every freezer showed loss of PSI (i.e., higher ratio of the conditioned H-reflex relative to the test H-reflex) during APA in the step initiation (above the dashed line), but presented PSI levels during quiet stance, whereas every non-freezers and age-matched healthy individuals (HC) showed PSI in both the tasks.

*Different from quiet stance values ($P<0.05$).

#Different from quiet stance values of the non-freezer and HC groups ($P<0.05$). &Different from quiet stance values of the HC group ($P<0.05$).

€Different from step initiation values of the non-freezer and HC groups ($P<0.05$). ¥Different from step initiation values of the HC group ($P<0.05$).

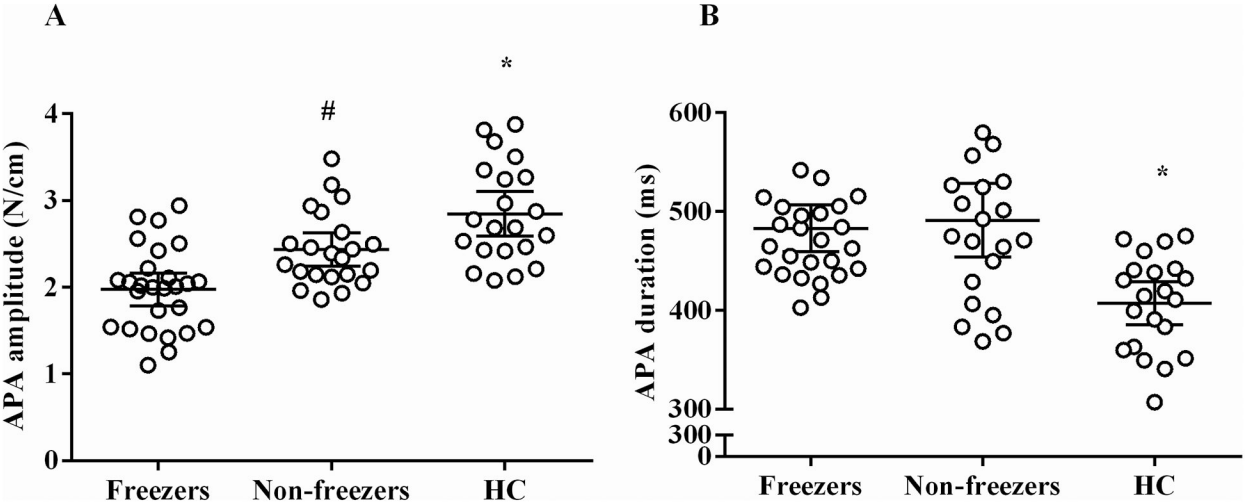

Figure 3.

Means ± SD for the amplitude (A) and duration (B) of the anticipatory postural adjustments (APA) in the step initiation for the freezer, non-freezer, and age-matched healthy controls (HC) groups.

*HC presented higher APA amplitudes and shorter APA durations than the individuals with PD ($P<0.05$).

#Non-freezer presented higher APA amplitudes than the freezers ($P<0.05$).

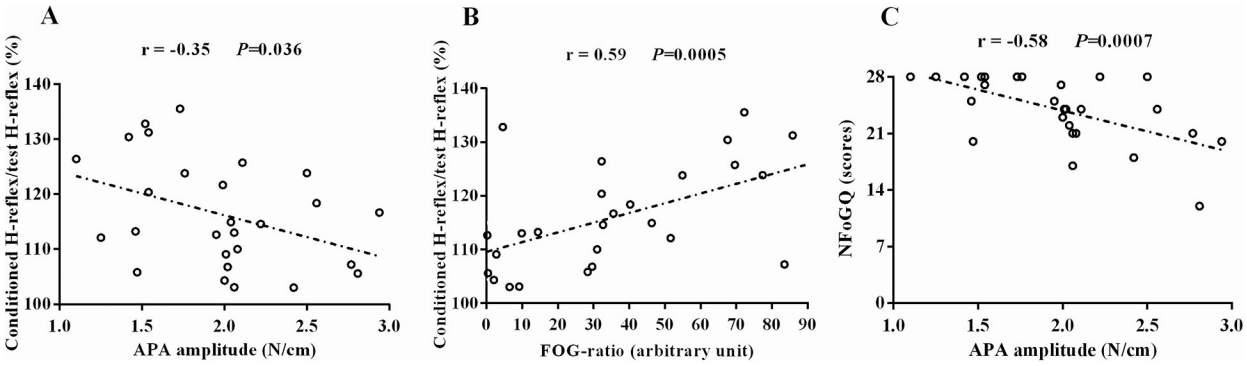

Figure 4.

Correlation of loss of presynaptic inhibition (i.e., higher ratio of the conditioned H-reflex relative to the test H-reflex) with anticipatory postural adjustment (APA) amplitude (A) and with freezing severity (FoG-ratio) (B), and correlation of the subjective severity of freezing (New Freezing of Gait Questionnaire [NFoGQ] scores) with APA amplitude (C). Spearman's r-values and P-values are shown.

Table 1.

Characteristics of the freezers, non-freezers, and age-matched healthy controls (HC) (mean±SD).

Characteristics	Freezers	Non-freezers	HC	P-values
Demographic				
Men/women (n)	18/9	18/4	18/3	
Age (yr)	66.7±9.7	65.6±9.8	67.3±8.5	0.778
Anthropometrical				
Body mass (kg)	69.5±12.3	68.7±9.1	70.1±10.8	0.362
Heigth (m)	1.6±0.2	1.7±0.1	1.6±0.1	0.515
Clinical				
MMSE (score)	26.0±1.9	26.9±2.0	28.0±1.7	0.851
Years since diagnosis	8.7±4.5	8.1±5.1	-	0.648
Hoehn & Yahr Scale (a.u.)	3.1±0.6	2.7±0.5	-	**0.023**
$_{L}$-Dopa equivalent units (mg/day)	834.2±226.1	747.8±241.4	-	0.206
UPDRS-III (score)	49.7±12.5	35.1±14.5	-	**<0.001**
PIGD (score)	8.7±2.0	4.2±1.8	-	**<0.001**
NFoGQ (score)	23.9±4.1	-	-	-
FoG-ratio (a.u.)	37.6±29.6	-	-	-

MMSE = Mini-Mental State Examination; UPDRS-III = Unified Parkinson's Disease Rating Scale part III; PIGD = Postural Instability and Gait Disturbance; NFoGQ = New Freezing of Gait Questionnaire; FoG-ratio = Freezing of gait ratio.

Table 2.

Test H-reflex amplitude normalized to its corresponding maximal motor response (M_{max}), rectified and averaged electromyography (raEMG) recordings, and co-contraction ratio during quiet stance and step initiation for each group (mean±SD).

Variables	Tasks	Freezers	Non-freezers	HC
Test H-reflex amplitude (%M_{max})	Quiet stance	32.26 ± 5.76	33.24 ± 8.86	35.85 ± 6.54
	Step Initiation	32.47 ± 7.97	33.96 ± 7.16	35.79 ± 5.71
raEMG of the soleus (mV)[&]	Quiet stance	0.07 ± 0.04	0.08 ± 0.05	0.07 ± 0.03
	Step Initiation	0.08 ± 0.02	0.07 ± 0.04	0.06 ± 0.04
raEMG of the tibial (mV)[&]	Quiet stance	0.04 ± 0.03	0.06 ± 0.03	0.04 ± 0.04
	Step Initiation	0.05 ± 0.04	0.05 ± 0.03	0.07 ± 0.05
Co-contraction (%)[&]	Quiet stance	0.76 ± 0.58	0.90 ± 0.59	0.73 ± 0.57
	Step Initiation	0.63 ± 0.51	0.79 ± 0.44	0.96 ± 0.54

[&]measured over a 100 ms epoch that preceded stimulation of each nerve.

Table 3.

Spearman's rank correlation coefficients between conditioned H-reflex relative to the test H-reflex (cond-H/test-H) and amplitude and duration of the anticipatory postural adjustment (APA) for each group, and between cond-H/test-H and severity of freezing of gait (FoG) for freezers.

	Freezers		Non-freezers		HC	
	Cond-H/test-H (%)		Cond-H/test-H (%)		Cond-H/test-H (%)	
Variables	***r***	***P value***	***r***	***P value***	***r***	***P value***
APA amplitude (N/cm)	−0.35	0.036	−0.16	0.226	−0.05	0.401
APA duration (ms)	0.15	0.225	0.19	0.188	0.21	0.170
FoG-ratio (a.u.)	0.59	0.0005				

HC = age-matched healthy controls.