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Cognitive and emotional factors influence specific domains of postural control in individuals with moderate-to-severe Parkinson's disease

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ABSTRACT

Introduction: Cognition and emotional state are domains that highly interfere with postural control in individuals with Parkinson's disease (PD). This study aims to find associations between executive function, anxiety, depression, and reactive and anticipatory postural control domains in individuals with moderate-to-severe Parkinson's disease.
Methods: In this study, 34 individuals with PD while on medication were thoroughly assessed for postural control in perturbed, quiet standing and stepping. We performed multiple linear stepwise regressions using postural variables as dependent and cognitive/emotional as independent variables.
Results: The results showed that cognitive flexibility explained 23 % of anticipatory postural adjustments (APA) duration, inhibitory control explained 42 % of instability on a malleable surface, anxiety explained 21 % of APA amplitude, and 38 % of reactive postural response amplitude.
Conclusion: Our results highlight the impact of emotional and cognitive states on particular domains of postural control in individuals with PD while on medication. These results may have significant implications for future treatments, mainly considering the predictors for postural control domains, which were consistent with the assumption that impairments in affective and executive domains underlie posture. As we have shown that cognitive and emotional states influence postural control domains in individuals with PD, this should be taken into account in rehabilitation protocols

1. Introduction

Postural control's integrity depends on different domains working adequately to account for internal and external demands changes. Reactive postural responses are triggered to adjust the body against unpredictable disturbance, requiring fast and less flexible responses than anticipatory mechanisms [1]. Anticipatory postural adjustments (APA) during self-initiated steps are known to involve control by high-order levels [2]. Living in a constantly changing environment, the integrity of both domains is fundamental. The integrity of postural control depends not only on a sound sensorimotor system but also on cognitive and emotional processes [3,4], even during quiet standing [5].

Reactive postural response (PR), even occurring in less than 100 ms, is influenced by cognition [6] and emotional states such as anxiety [7] and fear of falling [8]. The involvement of cognitive processing in APA is evident. Studies have associated the performance of APA during step initiation (SI) and executive function abilities such as inhibitory control [2,9,10]. The emotional state has also been demonstrated to change the

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characteristics of the APA. The overall mood state measured by the level of anxiety, depression, hostility, vigor, fatigue, and confusion, for example, was associated with the latency and amplitude of APA [11]. Therefore, cognition and emotional state modulate sensory, visual, and vestibular inputs to maintain balance.

Parkinson's disease (PD) individuals suffer from multiple disorders that affect postural control, cognitive and emotional domains. A high incidence of PD intermingles motor, cognition, and emotional aspects is called Freezing of Gait (FoG). FoG is described as a brief, episodic absence or marked reduction in the anterior progression of the feet, despite the intention to walk, having a significant impact on the quality of life [12] and postural control [13] of PD individuals. Although not fully elucidated, FoG can be triggered by various situations, including walking through narrow passages, turning, dual tasks, and changes in mood and anxiety [14]. To alleviate FoG, individuals are often forced to rely on cognitive-behavioral strategies that temporarily improve their gait pattern [15]. In addition, PD individuals show a higher level of reactive and anticipatory postural control disorders than healthy subjects. The association among those postural disorders with cognitive and emotional problems is a topic of high scientific interest [6,7].

An open question is whether each domain of postural control in individuals with PD is affected by specific domains of cognition and emotion. This study aims to find associations between executive function, anxiety, depression, and reactive and anticipatory postural control domains in individuals with moderate-to-severe Parkinson's disease. Thus, the findings of this study could be helpful to improve rehabilitation in the three domains: cognitive, emotional, and postural control, given that the specific rehabilitation of postural control might be beneficial to treat the associated cognitive/emotional disorder and vice-versa.

2. Methods

2.1. Participants

Participated in this study 34 individuals with idiopathic PD and FoG. The diagnosis was confirmed by a movement disorders specialist and FoG based on question 1 of the New Freezing of Gait Questionnaire (NFoG-Q) [16]. Inclusion criteria were the following: Hoehn & Yahr (H&Y) stage 3, regular medication use, able to walk 20 m without the use of mobility aids, not presenting neurological disorders (other than PD) or significant arthritis, musculoskeletal or vestibular disorder, and being able to understand basic instructions. The School of Physical Education and Sport ethics committee at the University of São Paulo approved the study protocol.

2.2. Procedures

Participants were assessed in two laboratory visits in the same order and time of the day. All individuals were evaluated in the clinically "on" state (fully medicated) within 1.5 h after taking their first morning dose of dopaminergic medication [17]. On the first visit, the following scales were applied: New Freezing of Gait Questionnaire (NFOGQ), Unified Parkinson's Disease Rating Scale part III (UPDRS-III), Fall Efficacy Scale-International (FES-I), Montreal Cognitive Assessment (MoCA), Frontal Assessment Battery (FAB), Stroop test part III (Stroop-III), Digit Symbol Substitution Test (DSST), Trail Making Test B (TMTB), Hospital Anxiety and Depression Scale (HADS) subdivided in the Hospital Anxiety Scale (HAS) and the Hospital Depression Scale (HDS). A physical therapist trained in administering the questionnaires conducted these assessments in a quiet room without distractions. On the second visit, the participants performed postural tasks such as response to external perturbation, step initiation (SI), and quiet standing (QS). All postural tasks were performed barefoot, feet parallel hip-width apart, holding arms crossed over the chest (in quiet standing and postural response tasks) or arms along the body (step initiation task), gazing at a fixed spot on a monitor positioned 1 m away approximately at the eye's height.

A force plate (AMTI OR6–7) measured the center of pressure (CoP). A reflective marker attached to the right lateral malleolus was tracked through four optoelectronic cameras (Vicon, Model T10) to evaluate step length. The moving platform was custom-built, and the displacement was controlled using LabVIEW (National Instruments) software. Force plate, moving platform, and kinematic signals were synchronized through a Vicon Nexus system. Feet positions were marked on the ground with tape to maintain the same place throughout evaluations. CoP position and kinematic data were measured at a sampling frequency of 200 Hz and filtered with a 10-Hz low-pass Butterworth filter. Data processing was performed using Matlab software (MathWorks). Fig. 1 shows curves representing the displacement of the force platform, the mediolateral CoP in the perturbation task and the experimental setup, and the mediolateral CoP in the step initiation task.

To measure the postural response (PR), participants had to recover balance in response to backward translation of the support base, with a displacement range of 7 cm and a maximum velocity of 30 cm/s. Participants were instructed to keep their balance without stepping in response to perturbations. The amplitude of CoP displacement was calculated as the difference between the maximum amplitude of the first peak CoP displacement after the perturbation and the mean position on the anteroposterior axis in the 200 ms before the perturbation. These values were normalized by the length of each participant's foot. We analyzed the first trial to evaluate the most revealing information about reactive postural control, excluding learning effects [18].

The balance during QS was measured by asking participants to stand upright in bipedal support on either rigid (RS) or malleable (MS) surfaces under the full vision for 30 s. The malleable surface corresponded to a 9-cm-thick viscoelastic piece of high-density foam (Tempur, Soft D3110) placed upon the platform surface. Analysis of balance was based on the normalized CoP area, where the CoP signal in both directions was divided by the foot's length versus the distance between the malleoli.

Participants took a step by moving their right foot after a beep to measure the step initiation. After each step, they were instructed to return to the starting position on the force platform. Participants performed 20 trials. The following variables were analyzed: (a) APA amplitude - defined as the difference between the maximum amplitude of mediolateral CoP displacement and the mean position on the mediolateral axis in the 200 ms before the step; (b) APA duration - considered to be the time between APA onset (2 standard deviations above the baseline) and the beginning of the step (when the malleolus marker moved 2 mm above the resting position); and (c) step length - based on heel position, defined as the linear anteroposterior distance between step initiation and heel contact with the floor. APA amplitude and step length were normalized by each participant's foot length.

2.3. Statistical analysis

Shapiro-Wilk and Levene's tests were used to assess data normality and variance. In cases of non-normal data, the choice of data normalization method was selected from the Pearson P statistical function divided by the degrees of freedom (P/df); this ratio can be compared between the different forms of normalization and indicate which of them the data follow the distribution closest to the normal (ratio close to 1). Next, we performed multiple linear regressions using the bi-directional stepwise method to explain the variance of dependent variables (postural tasks: SI APA duration, SI APA amplitude, SI step length, PR amplitude, QS RS area, and QS MS area). First, the univariate analyses were used to test which factors (clinical scales: MoCA, FAB, Stroop-III, TMTB, DSST, TMTB, HAS, and HDS) would be associated with the dependent variables (postural tasks: SI APA duration, SI APA amplitude, SI step length, PR amplitude, QS RS area, and QS MS area). Afterward, to explain the variance of the dependent variables, we included the factors in the linear multivariate analysis using the stepwise model if they presented a P value ≤ 0.10 and a correlation of lower than 0.6 between

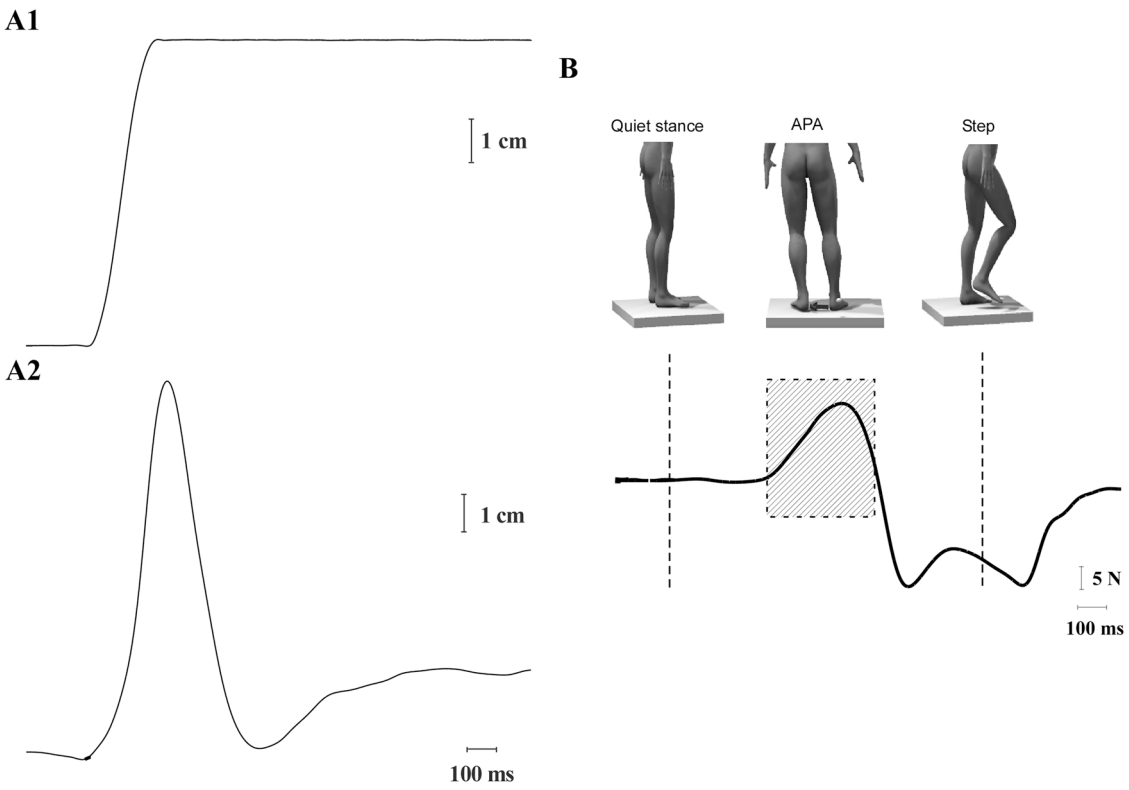

Fig. 1. Experimental setup and respective signals from the (A) perturbation and (B) step initiation tasks. The left panels show the characteristics of displacement of (A1) platform translation and (A2) center of pressure (CoP), while dashed vertical lines represent the onset of platform displacement. The right panels show the step initiation task with the participant starting in a quiet standing, performing a step initiation task with lateral weight shift associated with the anticipatory postural adjustment (APA) and stepping. The arrow shows the shifting of body weight before moving the opposite foot forward. The hatched area are APAs (time from the displacement of mediolateral CoP to the step onset).

them to avoid collinearity [19]. Spearman's correlation coefficients (two-tailed) were calculated between the clinical scales and postural tasks, controlled by disease duration and levodopa dosage. Statistical procedures were performed using SAS 9.2 (Institute Inc., Cary, NC, USA), and the significance level was set at $p < 0.01$.

3. Results

No participant had a freezing of gait episode during the experimental tasks. The anthropometric and clinical characteristics of the individuals are presented in Table 1. Fig. 2 shows the dispersion of data from the clinical scales and postural task variables.

Table 2 shows the postural control variables that were statistically significant to explain the measurements of postural tasks. The multiple regression analysis showed that TMTB explains 23 % of APA duration variability. HAS explains 21 % of APA amplitude and 38 % of PR amplitude. The performance in Stroop-II explains 0.42 of the quiet standing area on an unstable surface.

Fig. 3 show the scatter plot between the clinical scales and postural tasks variables. The generalized Spearman correlation and rank matrix with the levels of significance (p-value) between the clinical scales and postural task variables are shown in Fig. 4. UPDRS-III showed a significant correlation with APA duration (rho = 0.47, $p = 0.007$) and amplitude of PR (rho = 0.44, $p = 0.011$). FES-I showed a significant correlation with amplitude of PR (rho = 0.38, $p = 0.031$) and area of QS in RS (rho = 0.41, $p = 0.019$). Stroop-III showed a significant correlation with APA duration (rho = 0.46, $p = 0.009$) and area of QS in RS (rho = 0.48, $p = 0.005$) and MS (rho = 0.63, $p < 0.001$). HAS showed a significant correlation with time (rho = 0.51, $p = 0.003$) and amplitude (rho = 0.45, $p = 0.011$) of APA, amplitude of PR (rho = 0.61, $p < 0.001$) and area of QS in MS (rho = 0.38, $p = 0.033$). HDS showed a

Table 1
Mean and standard deviation [minimum–maximum] of anthropometrical and clinical characteristics of the patients.

	Characteristics
Men/women (n)	22/12
Age (years)	66.32 (9.38) [55.00–79.00]
Height (m)	1.64 (0.09) [1.40–1.80]
Weight (kg)	70.20 (11.7) [49.00–100.00]
Educational level (years)	11.56 (5.87) [4.00–20.00]
Disease duration (years)	8.21 (4.17) [2.00–25.00]
H&Y 3 (n)	30
Mini-Mental State Examination (score)	26.24 (1.67) [24.00–30.00]
NFOGQ (score)	22.50 (5.60) [11.00–28.00]
UPDRS-III (score)	51.62 (12.35) [30.00–79.00]
PIGD (score)	8.50 (2.36) [4.00–13.00]
FES-I (score)	28.60 (14.30) [3.00–57.00]
L-Dopa equivalent units (mg day^{-1})	811.51 (264.55) [200.00–1000.00]

NFOGQ: New Freezing of Gait Questionnaire. UPDRS-III: Unified Parkinson's Disease Rating Scale part III. PIGD: Postural instability and gait disorders. FES-I: Fall Efficacy Scale-International.

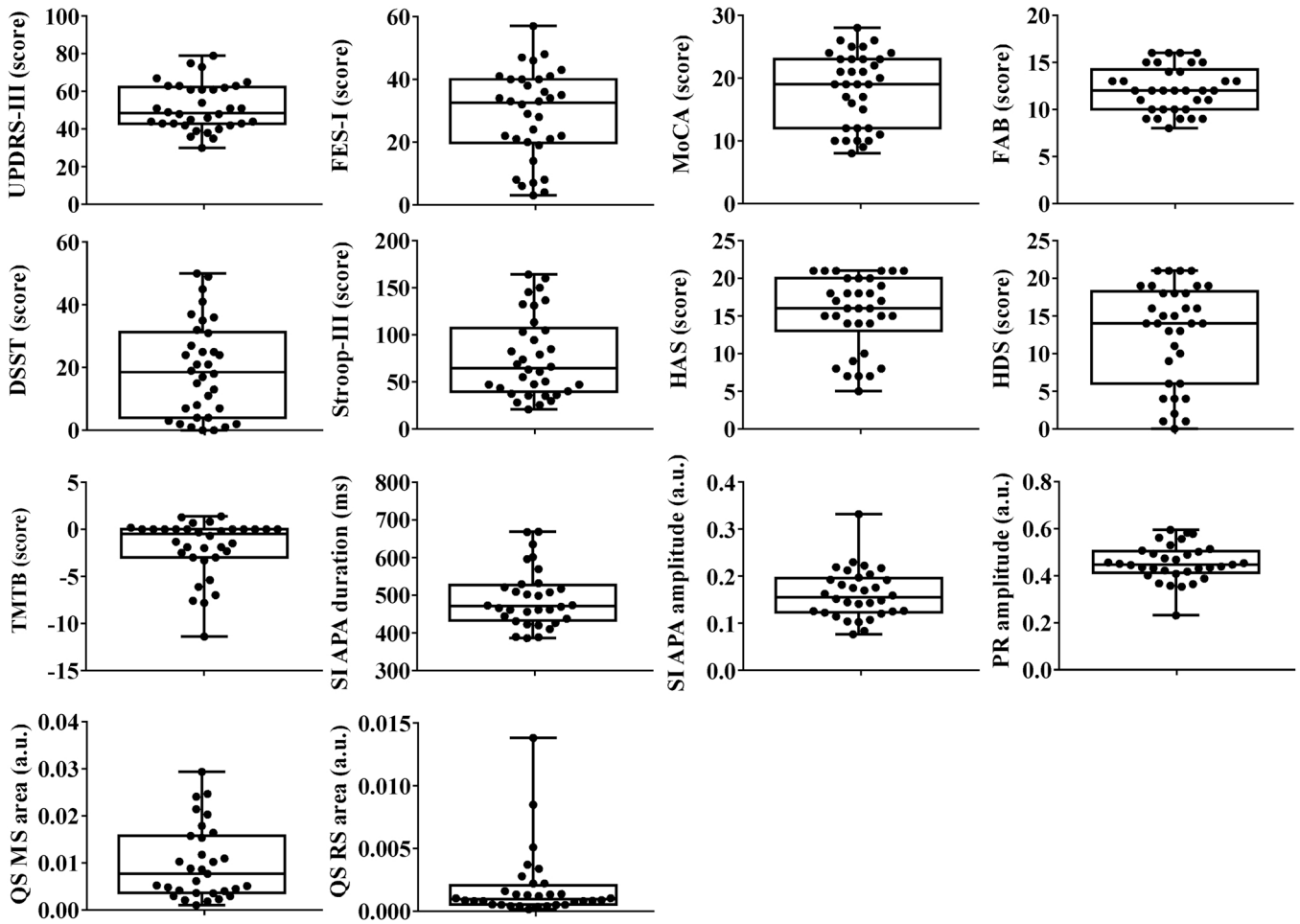

Fig. 2. Boxplot of variables used to measure clinical scales and postural tasks. UPDRS-III: Unified Parkinson's Disease Rating Scale part III. FES-I: Fall Efficacy Scale-International. MoCA: Montreal Cognitive Assessment. FAB = Frontal Assessment Battery. Stroop-III: Stroop test part III. DSST: Digit Symbol Substitution Test. HAS = Hospital Anxiety Scale. HDS = Hospital Depression Scale. TMTB = Trail Making Test B. APA = anticipatory postural adjustments in step initiation. PR = postural response. QS = quiet standing. RS = rigid surface. MS = malleable surface.

Table 2
Stepwise multiple regression analysis results with clinical scales and postural tasks variables as dependent variables.

Postural tasks variables	Clinical scales	Partial (r^2)	*P*-value
APA duration	TMTB	0.23	0.006
APA amplitude	HAS	0.21	0.010
PR amplitude	HAS	0.38	0.001
QS MS area	Stroop-III	0.42	0.001

APA = anticipatory postural adjustments in step initiation. PR = postural response. QS = quiet standing. MS = malleable surface. Stroop-III: Stroop test part III. HAS = Hospital Anxiety Scale. TMTB = Trail Making Test B.

significant correlation with time (rho = 0.38, $p = 0.034$) and amplitude (rho = 0.39, $p = 0.029$) of APA and amplitude of PR (rho = 0.62, $p < 0.001$). The correlation matrix between the clinical scales and postural tasks variables is presented in the Supplementary material.

4. Discussion

This study analyzed whether cognitive and emotional states can explain the performance in postural control of individuals with PD while on this on state of medication. Our main findings showed that TMTB accounts for part of the APA duration, anxiety explained the amplitude of both APA and PR, and Stroop-III helped explain quiet standing on unstable surfaces. Additionally, our results show that emotional factors such as anxiety as well as inhibiting executive functions are strongly correlated with reactive and anticipatory postural control domains.

APA timing and amplitude are affected in PD individuals [20]. Previous studies have found evidence that APA requires high-order processing involved with executive functions [9,21]. PD individuals show brain function and connectivity alterations during APA [22]. Cognitive flexibility is one of the executive functions essential for the coupling between preparation and step initiation. Immediately before stepping, the body weight is shifted toward the support leg, bearing the body weight during the transition from quiet standing to locomotion. This control must be well-timed to avoid the premature release of the foot and needs to account for the unpredictability of the environment. Timing and selection are two executive domains that comprise cognitive flexibility, assessed by part B of the TMT [23]. TMTB is a strong predictor of FOG [24]. The overlapped contribution of the supplementary motor area in both TMTB [25] processing and APA [22], specifically the APA timing [20], supports our findings.

Inhibitory control has been shown to influence profoundly challenging postures and is more affected in individuals with FOG than those PD individuals without FOG [26]. Our analysis showed that the performance in the Stroop test explains 42 % of the variance of CoP area during standing on a malleable surface. Redfern et al. [5] found an inverse association between performance on inhibitory control and the performance on an unstable surface in healthy elderly subjects. Possibly, inhibitory control is involved in the resolution of sensorimotor conflict, as during the diminished role of proprioception when standing on a

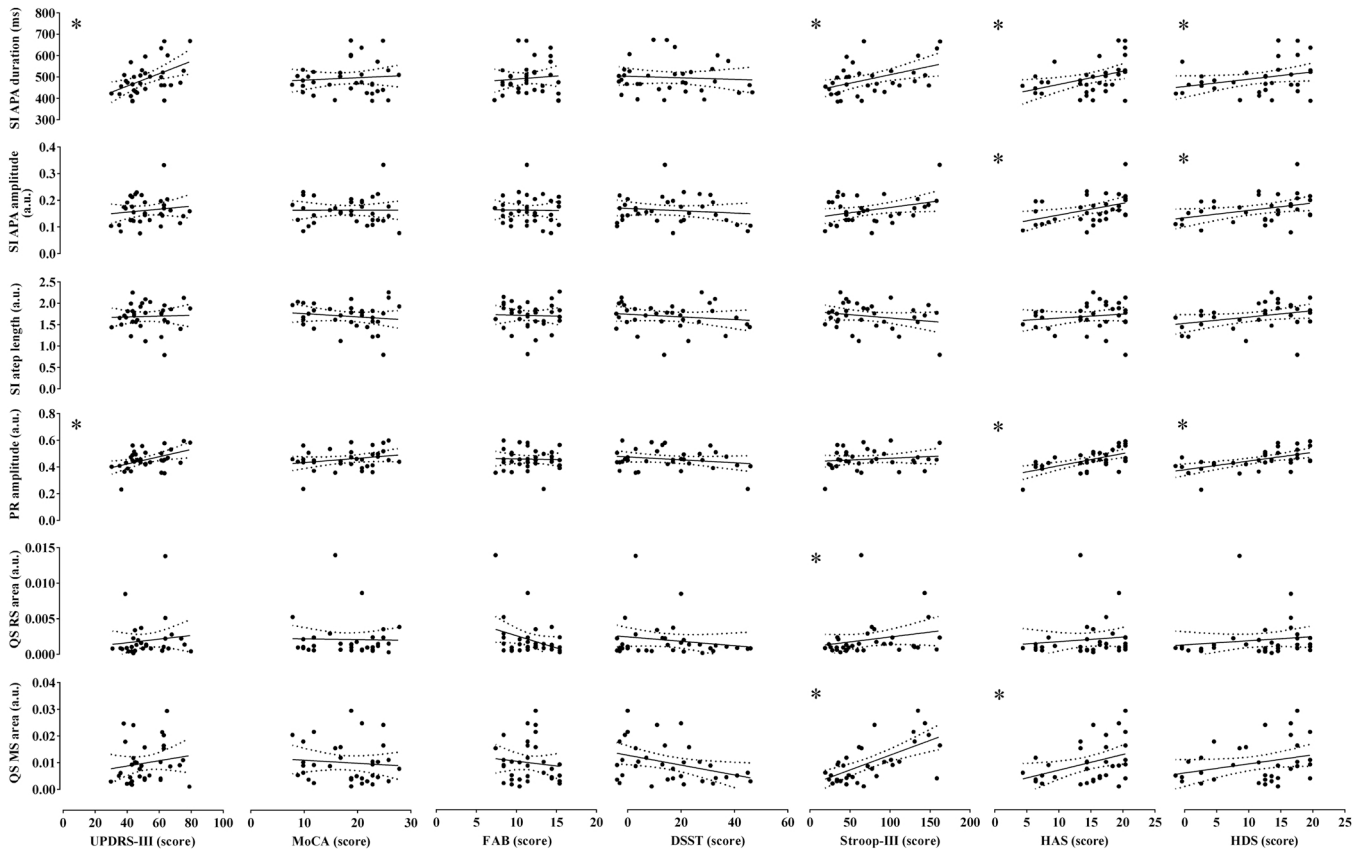

Fig. 3. Scatter plot between the clinical scales and postural tasks variables. UPDRS-III: Unified Parkinson's Disease Rating Scale part III. FES-I: Fall Efficacy Scale-International. MoCA: Montreal Cognitive Assessment. FAB = Frontal Assessment Battery. Stroop-III: Stroop test part III. DSST: Digit Symbol Substitution Test. HAS = Hospital Anxiety Scale. HDS = Hospital Depression Scale. SI – step initiation. APA = anticipatory postural adjustments in step initiation. PR = postural response. QS = quiet standing. RS = rigid surface. MS = malleable surface. * indicates significant correlation.

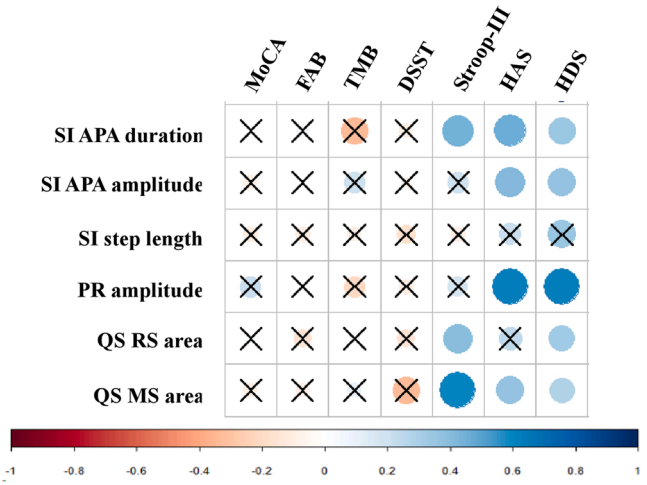

Fig. 4. Correlation matrix and generalized Spearman rank correlation with significance levels (p-value) between the clinical scales and postural tasks variables. UPDRS-III: Unified Parkinson's Disease Rating Scale part III. FES-I: Fall Efficacy Scale-International. MoCA: Montreal Cognitive Assessment. FAB = Frontal Assessment Battery. Stroop-III: Stroop test part III. DSST: Digit Symbol Substitution Test. HAS = Hospital Anxiety Scale. HDS = Hospital Depression Scale. SI – step initiation. APA = anticipatory postural adjustments in step initiation. PR = postural response. QS = quiet standing. RS = rigid surface. MS = malleable surface.

malleable surface. To our knowledge, this is the first study showing a relationship between inhibitory control and reactive balance in individuals with FOG. Our results are consistent with previous studies from our team that showed impairments in APA amplitude in individuals with FoG being associated with loss of presynaptic inhibition and alterations in brain networks comprising areas that control inhibitory control [27]. Together, our results and previous findings suggest that inhibition explains the control of automatic postural responses under more challenging situations like walking and postural perturbation [28–30].

Level of anxiety was shown to explain 21 % of the APA amplitude and 38 % of the postural response. The instability of bearing the body weight on one leg during step initiation and equilibrium recovery after postural perturbation are challenging situations influenced by the anxiety level. A recent study reported that PD individuals with a high level of anxiety showed an increased amplitude of center of gravity sway, which was not attenuated with dopamine. Other studies have also demonstrated the increased influence of anxiety on the postural control of PD individuals [31–34]. Jazaeri et al. [35] show that anxiety influences balance control in quiet-standing individuals with PD, particularly those with high anxiety levels. In particular, individuals with FOG are more influenced by the severity of anxiety than those without FOG [36], which could explain why the regression analysis showed a prominent role of anxiety in explaining postural control variance in FOG individuals in our study.

Limitations of this study include: a) the absence of a control group and a condition without antiparkinsonian medication. The absence of a control group and similar studies in other populations does not allow us to differentiate our results found in individuals with PD in relation to other groups. Our study does not discriminate and differentiate the

cognitive/emotional correlates of postural control in Parkinson's disease in relation to other populations. However, as an area of difficulty for individuals with PD is executive function [37], we can hypothesize that the results would differ in other groups; b) Another limitation is that the step initiation was always performed with the right foot. Depending on which side is more affected, there might be a difference in length between a step with the right and the left leg; c) Considering the addition of two covariates, we decided not to correct multiple comparisons, which might lead to false negatives [38]; d) its cross-sectional nature preventing the determination of a cause-and-effect relationship. Further longitudinal studies are needed to confirm the suggested relationships. Therefore, the results should be interpreted with caution. Despite these limitations, this study is the first to identify cognitive and emotional predictors of postural control domains. This result is interesting for two reasons. First, our results underscore the importance of assessing how specific aspects of cognition, emotion, and postural control relate to individuals with PD. Second, the present study's findings could help handle postural/cognitive/emotional rehabilitation more accurately. Although this is a cross-sectional study and we could not establish cause-effect relationships between independent and dependent variables, future studies should test the effectiveness of treatment strategies to improve affective and executive domains that might positively impact postural control domains in individuals with moderate-to-severe PD. Despite there is still no consensus about the optimal rehabilitation for individuals with PD, mainly for those who suffer from FOG, rehabilitations that require situations with greater challenge and complexity might be important for improving postural control.

Conflict of interest statement

Authors declare to have no actual or potential conflict of interest including financial, personal or other relationships which might influence results and their interpretation.

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Conflict of interest statement

The authors declare that there is no interest or relationship, financial or otherwise, which might be considered as a potential conflict of interest influencing the interpretation and conclusions drawn from the current results.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.gaitpost.2023.02.002.

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