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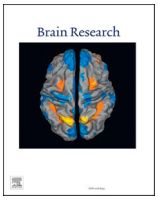

Temporal dynamics of cortical activity and postural control in response to the first levodopa dose of the day in people with Parkinson's disease

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ABSTRACT

Background: Our understanding of how balance control responds to levodopa over the course of a single day in people with Parkinson's disease (PD) is limited with the majority of studies focused on isolated comparisons of ON vs. OFF levodopa medication.
Objective: To evaluate the temporal dynamics of postural control following the first levodopa dose of the day during a challenging standing task in a group of people with PD.
Methods: Changes in postural control were evaluated by monitoring cortical activity (covering frontal, motor, parietal and occipital areas), body sway parameters (force platform), and lower limb muscle activity (tibialis anterior and gastrocnemius medialis) in 15 individuals with PD during a semi-tandem standing task. Participants were assessed during two 60 second trials every 30 minutes (ON-30 ON-60 etc.) for 3 hours after the first matinal dose (ON-180).
Results: Compared to when tested OFF-medication, cortical activity was increased across all four regions from ON-60 to ON-120 with early increases in alpha and beta band activity observed at ON-30. Levodopa was associated with increased gastrocnemius medialis activity (ON-30 to ON-120) and ankle co-contraction (ON-60 to ON-120). Changes in body sway outcomes (particularly in the anterior-posterior direction) were evident from ON-60 to ON-120.
Conclusions: Our results reveal a 60-minute window within which postural control outcomes may be obtained that are different compared to OFF-state and remain stable (from 60-minutes to 120-minutes after levodopa intake). Identifying a window of opportunity for measurement when individuals are optimally medicated is important for observations in a clinical and research setting.

1. Introduction

Postural instability is one of the most disabling motor symptoms of Parkinson's disease (PD) – it increases fall risk and ultimately falls, which in turn lead to a higher number of hospitalizations and deaths (Balash et al. 2005). Examples of maladaptive postural responses in people with PD (pwPD) include an inability to modulate postural responses, a delay in initiating corrective and anticipatory postural responses, reduced limits of stability and greater oscillation of the center of pressure (CoP) (Carpenter 2004). Maintaining postural equilibrium is reliant on the contribution of multiple sensory systems relaying information to the brain to co-ordinate postural adjustments. One method of measuring brain activity during postural tasks is electroencephalography (EEG; Jacobs and Horak 2007). Interestingly, pwPD demonstrated reduced beta band cortical activity compared to controls particularly during complex movements (Shirahige et al. 2020). This is relevant because beta band activity is related to motor control and planning (Kilavik et al. 2013).

Prescription of levodopa remains the most common pharmaceutical strategy for managing and alleviating motor symptoms in pwPD. Levodopa influences cortical activity by: (1) ameliorating beta-band power in the local field potentials of the subthalamic nucleus (reducing the

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UPDRS-III score by ~ 53% on average) (Kühn et al. 2006); (2) restoring oscillatory coupling between the prefrontal cortex and pre-motor areas (Herz et al. 2014; Orcioli-Silva et al. 2020); and (3) enhancing motor automaticity due to a reduction in striatal functioning and cerebellar compensations (Gilat et al. 2017) in pwPD. In addition, dopamine-replacement drugs lead to higher muscle synergies and anticipatory postural adjustments (Falaki et al. 2017), as well as reduced muscle co-contraction in the proximal and distal lower limb joints due to large antagonist muscle activation (Dimitrova et al. 2004). However, cortical activity is likely to be influenced by task complexity (Orcioli-Silva et al. 2020), which may offer some explanation for the contradictory effects of levodopa on postural instability reported in the literature (Curtze et al. 2015; Di Giulio et al. 2016; Nova et al. 2004) whereby a variety of postural tasks have been utilized.

Increased body sway has been observed in pwPD during a static standing task (feet side by side; trial duration: 35–60 s) following the administration of levodopa (Bonnet et al. 2017; Rocchi 2002). In addition, when assessed using a challenging standing balance task (tandem stance), postural asymmetry is reduced in pwPD when tested ON-levodopa (compared to OFF-medication) (Barbieri et al. 2016). Generalizing the effect of levodopa on body sway in pwPD is difficult. For example, while levodopa reduces passive stiffness at the ankle (Rocchi 2002), the effect levodopa has on other postural control mechanisms is minimal (Bonnet et al. 2017) (e.g., the amplitude of proximal muscle activity is unchanged following administration of levodopa (Burleigh et al. 1995). Conversely, evidence suggests that the administration of levodopa alters postural control strategy (e.g., less reliance on an ankle strategy when optimally medicated) (Baston et al. 2016), and can attenuate PD-specific postural abnormalities such as a stooped posture (Kataoka and Ueno 2017).

One important factor which may explain the disparity across these studies is the lack of protocol standardization, particularly the timing of postural assessment with respect to medication intake (i.e., 0.5–2 h). Most studies (Bloem et al. 1996; Bonnet et al. 2017; Rocchi 2002) evaluate postural control one hour after levodopa intake (usual dose), but this is not always consistent. Other studies have modified the dose (up to 125% of usual dose) and/or assessment time (Baston et al. 2016; Bonnet et al. 2017; Revilla et al. 2013). Defining the window within which levodopa effects are optimal is important for evaluating best performance. Documenting changes in postural control periodically in the hours following medication will help to elucidate the dynamic role of levodopa on postural control in pwPD.

Our understanding of how balance control responds to levodopa over the course of a single day in pwPD is limited, with the majority of studies focused on isolated comparisons of ON vs OFF levodopa medication (Bloem et al. 1996; Bonnet et al. 2017; Rocchi 2002), often evaluated on two separate days. More than 60% of pwPD display motor fluctuations in response to levodopa regime, including delay in the “off–on” phenomenon and decline in dose duration (McColl et al. 2002). In particular, a delayed response to the first (matinal) levodopa dose of the day has been noted (Chana 2004). Previous studies have already evidenced that motor fluctuations due to levodopa occur during walking (Moore et al. 2008) and finger-tapping movements (Contin et al. 2001). This study aimed to evaluate the temporal dynamics of cortical activity, muscle activity and body sway in response to the first levodopa dose by conducting repeated measurements every 30 minutes from OFF-medication to 180 minutes post levodopa intake during a challenging semi-tandem standing task. Standing with the feet semi-tandem is likely to challenge medial–lateral (ML) sway the most (Di Fabio and Emasithi 1997; Polastri et al. 2019). This task was chosen as ML sway is considered to be more sensitive than anterior-posterior (AP) sway when detecting balance impairments during static standing in pwPD (Mancini et al. 2012), as it involves control of hip and trunk muscles, which may be more affected by PD (Wright et al. 2007). Considering that cortical activity is reduced in pwPD (compared to healthy adults) and levodopa can increase cortical activity (Herz et al. 2014; Nettersheim et al. 2019; Orcioli-Silva et al. 2020), we hypothesized that the following changes would be observed 60 minutes post levodopa intake: (1) an increase in cortical activity (e.g., prefrontal and motor areas (Herz et al. 2014; Nettersheim et al. 2019; Orcioli-Silva et al. 2020)); (2) an increase in body sway (e.g. higher amplitude of CoP and its variability (Baston et al. 2016; Bonnet et al. 2017)); (3) an increase in lower limb muscle activity; and (4) a reduction in ankle muscle co-contraction (Dimitrova et al. 2004) during a semi-tandem standing task. In addition, we expect the effects of levodopa on cortical activity, body sway and muscle activity would last >2 hours after intake (Pahwa et al. 2014).

2. Results

2.1. Participant characterization, clinical measures and medication feedback (Visit 1)

Participants were of mild-moderate disease stage (H&Y I-III) and considered cognitively intact when assessed on levodopa medication (MMSE $\geq$ 24/30) (Table 1).

All participants had been prescribed levodopa for >6-months, but many used a combination of other dopaminergic medications to treat PD symptoms (Table 1). The majority of participants (80%) reported feeling in an ON-state at the ON-60 assessment, which was maintained until ON-150 before reducing to only 40% reported feeling in an ON-state at ON-180 (Fig. 1A). In addition, one participant reported feeling in an ON-state of medication at all time intervals (from ON-30 to ON-180) and one participant reported feeling in an OFF-state of medication at all time intervals.

The total UPDRS-III score and BBS score were evaluated in an OFF-state and at 60 minutes post levodopa (Table 1; Full evaluation). The UPDRS-III score reduced by 11.7% and the BBS score increased by 1.9% at 60 minutes ($z = 10.50$, $p < 0.01$ and $z = 48.5$, $p < 0.03$, respectively). There were no significant changes in disease stage classification from OFF-state to ON-60 (H&Y; $z = 2.50$, $p = 0.78$) (Table 1).

A selection of items from the UPDRS-III and BBS were evaluated at each time interval. There were no significant changes in UPDRS-III items in the time intervals following levodopa intake ($z = 3.04$, $p = 0.69$; Fig. 1B). Conversely, BBS items improved following intake of levodopa indicating larger differences at ON-90 and ON-120 vs ON-30 ($z = 10.1$, $p < 0.04$ and $z = 15.02$, $p < 0.02$ respectively; Fig. 1C).

2.2. Temporal dynamics of cortical activity, muscle activity and body sway parameters in response to levodopa during a postural task (Visit 2)

Results from the multivariate analysis revealed a significant effect of medication status on cortical activity across all four areas, muscle activity and body sway parameters. A summary of the statistical analysis (Table S1), ensemble averages (Tables S2 and S3) and multivariate analysis statistical values (Table S4) are provided in the Supplementary material. None of the participants experienced difficulty or loss of balance during the standing task.

When evaluating differences between OFF vs ON-time intervals, early increases in cortical activity were observed in frontal (beta; $d = 1.4$ - *large*), parietal (alpha; $d = 0.6$ - *moderate*) and occipital (alpha; $d = 0.9$ - *large*) regions (OFF vs ON-30; $p < 0.002$). The majority of changes in cortical activity occurred between OFF vs ON-60 and OFF vs ON-120. Changes in cortical activity across the delta band occurred across the motor region only ($F_{6,66} = 4.23$, $p < 0.01$, $\eta^2 = 0.27$). In comparison, changes in cortical activity across the theta band occurred across the parietal ($F_{6,66} = 5.50$, $p < 0.0001$, $\eta^2 = 0.33$) and occipital ($F_{6,66} = 5.27$, $p < 0.002$, $\eta^2 = 0.32$) regions. Alpha band activity was altered across parietal ($F_{6,66} = 3.30$, $p < 0.03$ $\eta^2 = 0.23$) and occipital ($F_{6,66} = 5.31$, $p < 0.006$, $\eta^2 = 0.32$) regions. Lastly, beta band cortical activity changes occured in both frontal ($F_{6,66} = 4.38$, $p < 0.01$, $\eta^2 = 0.28$) and parietal ($F_{6,66} = 3.60$, $p < 0.004$, $\eta^2 = 0.24$) regions (Fig. 2C and 2D).

GM muscle activity was significantly increased at ON-60 vs OFF

Table 1
Participant demographics, clinical outcomes, and medication status

	Sex (m/f)	Age (y)	Body mass (kg)	Height (m)	Disease duration (y)	MMSE (score/30)	H&Y stage OFF	H&Y stage ON	UPDRS-III OFF (score /132)	UPDRS-III ON (score /132)	BBS OFF (score/56)	BBS ON (score /56)	Levodopa (Morning dose) (mg/day)	Levodopa (Daily dose) (mg/day)	Medicine class
P1	m	68	88.2	1.68	7	29	2	2	20	13	53	55	391	1564	D/COMT I/DA
P2	m	69	72.5	1.65	3	24	2	2	48	46	54	54	100	500	D
P3	m	65	95.4	1.76	15	29	2.5	2	43	25	48	52	350	1650	D/A/MAO-B I/DA
P4	m	72	72.6	1.72	12	28	2	2	24	24	52	55	200	1005	D
P5	m	65	74.8	1.70	10	29	1	1	17	14	56	56	325	1075	D/A/DA
P6	m	72	69.0	1.56	3	27	2	2	42	41	50	52	100	300	D
P7	f	55	69.7	1.52	8	27	2	2	25	26	53	54	100	500	D
P8	f	63	73.9	1.70	1	28	2	2	20	19	56	56	125	450	D/A/DA
P9	f	80	65.4	1.56	2	30	2	2	22	26	54	54	50	150	D
P10	m	83	57.3	1.73	7	28	3	2	36	27	51	52	175	550	D
P11	m	70	73.1	1.70	2	29	3	3	40	36	52	50	100	500	D
P12	f	61	88.4	1.65	6	26	2	2	55	54	52	53	100	700	D/A
P13	f	66	49.1	1.58	6	26	2	2	20	16	54	54	325	875	D/A/DA
P14	m	74	86.4	1.67	8	27	1.5	1.5	20	20	53	54	230	930	D
P15	f	71	70.4	1.60	3	29	2	2	29	20	54	56	140	530	D
Average		**69**	**73.7**	**1.70**	**6**	**27.7**	**2.1**	**2.0**	**30.7**	**27.1**	**52.8**	**53.8**	**187.4**	**751.9**	**-**
SD		**7**	**12.1**	**0.10**	**4**	**1.6**	**0.5**	**0.4**	**12.2**	**12.0**	**2.1**	**1.7**	**110.6**	**432.8**	**-**
Amplitude		**55-83**	**49.1-95.4**	**1.52-1.76**	**1-15**	**24-30**	**1-3**	**1-3**	**17-55**	**13-54**	**48-56**	**50-56**	**50-391**	**150-1564**	**-**
Median		**69**	**73.0**	**1.67**	**6**	**28**	**2**	**2**	**25**	**25**	**53**	**54**	**140**	**550**	
IQR		**7**	**16.8**	**0.11**	**5**	**2**	**0**	**0**	**21**	**12**	**2**	**2.5**	**177.5**	**467.5**	

Abbreviations: Hoehn & Yahr disease stage (H&Y); Mini-Mental State Exam (MMSE); Unified Parkinson Disease Rating Scale Part III Motor Symptoms (UPDRS-III); Berg Balance State (BBS); Dopaminergic (D); Catechol-O-methyltransferase inhibitor (COMT I); Amantadine (A); Dopaminergic agonist (DA).

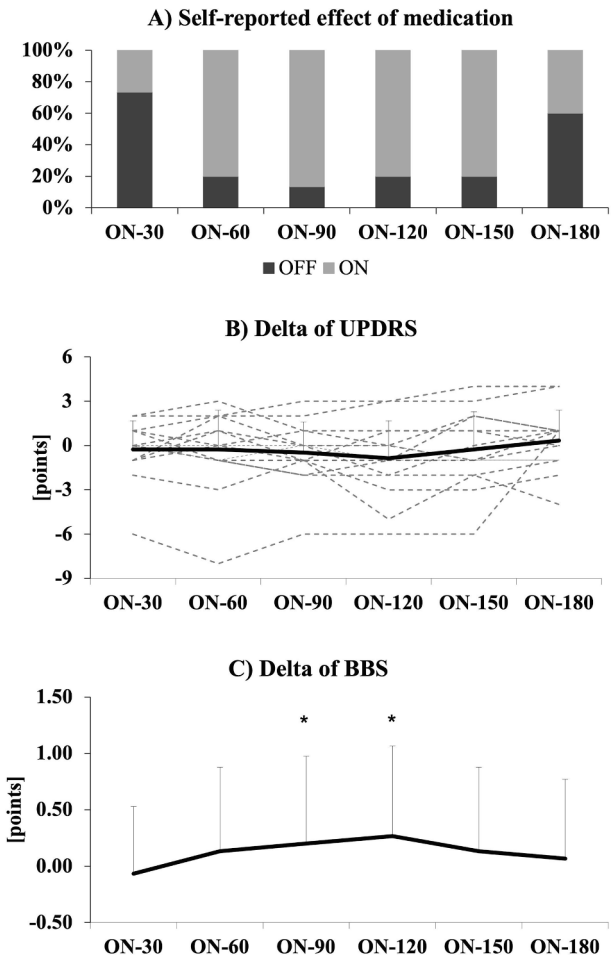

Fig. 1. A) Percentage of individuals that reported ON or OFF levodopa at each time interval. B) Means and standard deviations of Unified Parkinson's Disease Rating Scale-III (UPDRS III- Items 20 22 and 26) delta values at each time interval. C) Means and standard deviations for the Berg Balance Scale (BBS) at each time interval. Dashed lines represent individual participant data. Dashed lines are not included for the BBS for clarity as the differences observed were small. * denotes significant difference compared to ON-30.

($F_{6,84} = 8.19$, $p < 0.001$, $\eta^2 = 0.40$) and this was maintained until ON-180 (d-values from 1.8 to 2.1 - *large*) (Fig. 3B). Similarly, the co-contraction index significantly increased at ON-90 vs OFF-medication ($F_{6,84} = 7.28$, $p < 0.001$, $\eta^2 = 0.34$) and this was maintained until ON-120 (d-values from 1.1 to 1.8 - *large*) (Fig. 3C). TA muscle activity ($F_{6,84} = 0.31$, $p = 0.822$, $\eta^2 = 0.02$) was unchanged over the 3 hours post levodopa intake (Fig. 3A).

Body sway parameters increased over time, in particular AP CoP amplitude ($F_{6,84} = 2.56$, $p < 0.04$, $\eta^2 = 0.15$), which increased at ON-60 and this was maintained until ON-120 (d-values from 0.6 to 0.9 – *moderate to large)* (Fig. 4A). Also, AP and ML CoP RMS ($F_{6,84} = 2.97$, $p < 0.02$, $\eta^2 = 0.17$ and $F_{6,84} = 2.99$, $p < 0.03$, $\eta^2 = 0.14$, respectively) increased at ON-90 (d = 1.2 and 0.9, respectively – *large*) compared to OFF-medication (AP CoP RMS at ON-120 was also higher than OFF-medication – $p < 0.002$; d = 1.2 – *large*). No significant changes in ML CoP amplitude (Fig. 4A), mean velocity (Fig. 4B) or DFA (Fig. 4E) were observed during the 3 hours post levodopa medication. None of the outcomes recorded at ON-150 and ON-180 were significantly different to when recorded OFF-medication except for GM muscle activity.

When evaluating differences in all postural task outcomes (cortical activity, muscle activity and body sway) between ON-time intervals, significant increases across parietal (theta), motor (delta), and occipital (theta) regions were observed between ON-30 and ON-60 (Fig. 2A and B). No other differences in cortical activity, muscle activity or body sway parameters were observed.

3. Discussion

To our knowledge this is the first study to investigate the temporal dynamics of postural control (cortical activity, muscle activity and body sway) in response to levodopa during a challenging standing task (semi-tandem stance) in pwPD. As expected, in general cortical activity, muscle activity (GM and ankle co-contraction) and body sway all increased following levodopa intake. Increased cortical and muscle activity, as well as greater body sway, were generally observed after 60 minutes and were stable (unchanged) for a further 60 minutes (ON-120).

3.1. Increased cortical activity, muscle activity and body sway in response to levodopa

Interpreting changes in body sway is complex. Reduced body sway may reflect a more rigid system or conversely a controlled state of equilibrium. Certainly, some magnitude of body sway is necessary to adjust and control the movement of the centre of mass to maintain upright stance, however a large magnitude of body sway may reflect an uncontrolled state of equilibrium. In pwPD, postural responses are slow, delayed and inflexible resulting from symptomatic impairments affecting rigidity, stiffness, an inability to scale movements, increased muscle co-contraction and reduced force production (Romero and Stelmach 2003). Evidence suggests that increased body sway is associated with falls in pwPD (Revilla et al. 2013). Our findings are in agreement with the literature reporting an increased body sway when assessed ON-levodopa medication compared to an OFF-state despite different protocols being utilized (Baston et al. 2016; Bonnet et al. 2017; Revilla et al. 2013). For example, Revilla et al. (2013) assessed participants (on average) 110 minutes post levodopa intake. In the study by Bonnet et al. (2017), participants were asked to take 150% of their usual morning dose and assessed 45–60 minutes post intake depending upon the neurologist's judgment of medication effectiveness. In comparison, Baston et al. (2016) evaluated participants 1 hour after taking 125% of their usual morning dose. The findings of the present study may be used to inform standardized protocols that can be used in clinic evaluations and research laboratories when assessing postural control.

Motor symptom severity was significantly reduced at 60 minutes post levodopa intake compared to OFF-medication (lower UPDRS-III total scores). We consider that the increased body sway observed in response to levodopa in the present study reflects reduced axial rigidity in response to levodopa medication (Baston et al. 2016; Bonnet et al. 2017). In support, Bonnet et al. (2017) demonstrated that increased body sway in pwPD when tested ON levodopa was associated with greater movement of the lower back. Conversely, reduced body sway observed when tested OFF-medication was associated with reduced movement of the lower back (Bonnet et al. 2017). Greater movement at the lower back when tested ON levodopa will necessitate greater muscle activity at the hip and the reliance on a hip strategy to maintain equilibrium (compared to an ankle strategy) (Baston et al. 2016). Increased body sway observed during the semi-tandem standing task occurred in parallel to an increased cortical activity across brain areas and frequencies. Cortical activation is related to task complexity with more challenging tasks requiring increased cortical activation (Stuart et al. 2018).

An increased cortical activity was coupled with increased muscle activity following levodopa. Levodopa replacement increases the availability of dopamine in the system and reestablishes the thalamo-cortical pathway by improving basal ganglia function (Obeso et al. 2008), and increases excitatory signaling to other cortical areas including motor and cognitive areas (Obeso et al. 2008; Orcioli-Silva et al. 2020). Increased cortical activity across the frontal, parietal and motor cortex is associated with a reduction in striatal functioning and

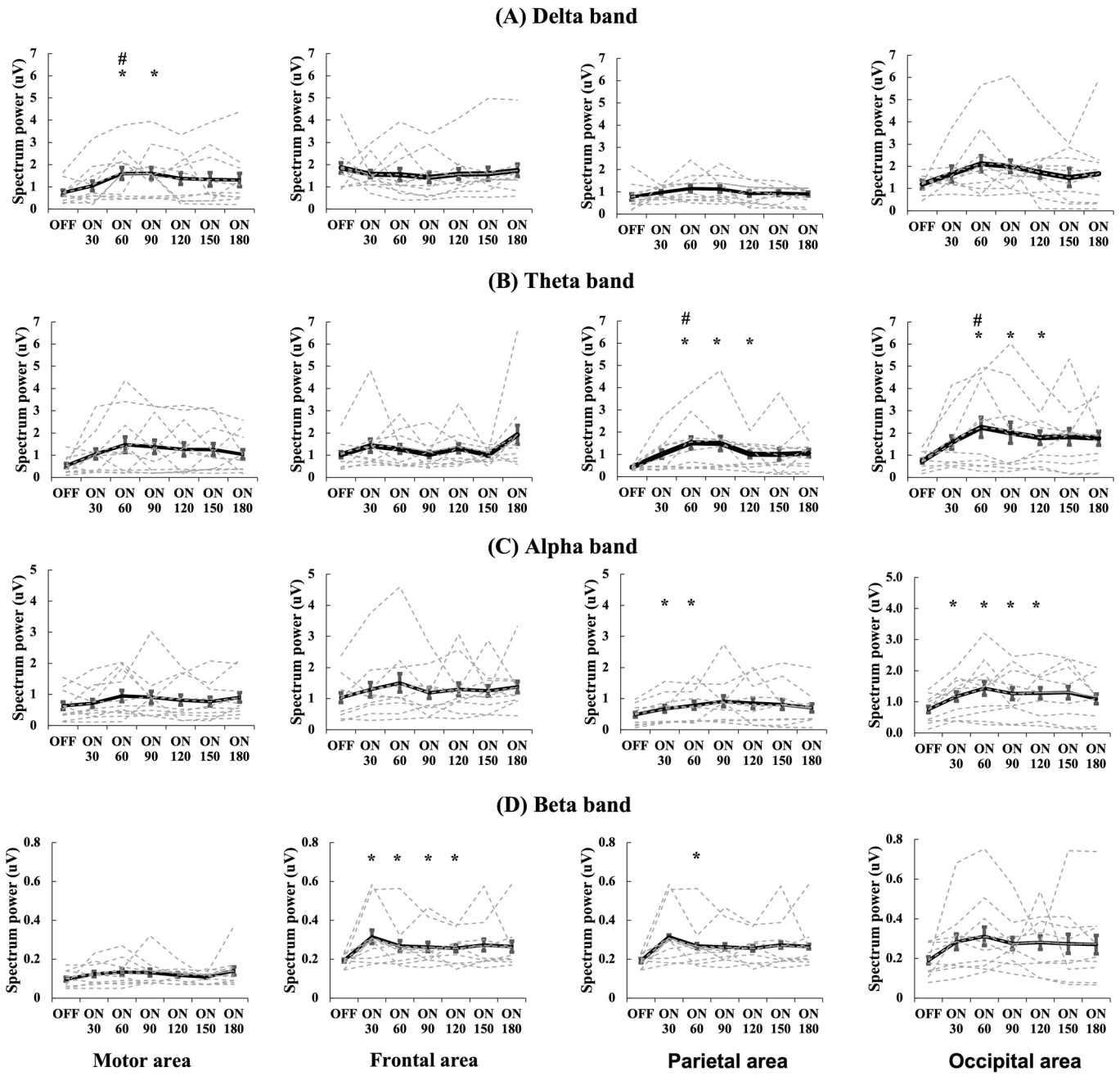

Fig. 2. Mean and standard errors of cortical activity according to cortical areas and frequency bands (A – Delta band, B – Theta band, C – Alpha band, and D – Beta band) during levodopa temporal dynamics. Grey lines represent individual participants. The black solid line represents the group average. * denotes significant differences compared to OFF-state. # denotes significant difference compared to ON-30.

cerebellar compensations restoring oscillatory coupling between pre-frontal cortex and pre-motor areas (Herz et al. 2014; Nettersheim et al. 2019). This increased activity leads to reduced attentional motor control, lower orbitofrontal-striatal limbic interference and enhanced automatic postural responses (Gilat et al. 2017). It is noteworthy that variability in EEG signals across the group were large which is in agreement with previous studies (Cozac et al. 2016; Näpflin et al. 2007). To reduce the influence of large variability within EEG signals, it is recommend that the relative power calculated as the power in a given frequency band (i.e., alpha, beta, etc.) divided by the sum of all power measurements across all frequencies (Cozac et al. 2016).

PwPD demonstrate an inability to activate and inhibit antagonist muscles when responding to balance perturbations (Lang et al. 2019). In the present study, increased GM activity and co-contraction of the ankle muscles were observed in pwPD during a semi-tandem standing task, resulting in increased ankle joint stiffness. This may compromise and/or limit available postural responses and contribute to overall balance impairment in pwPD. Changes in body sway were noted particularly in the AP direction (CoP amplitude and RMS), which may have prompted the muscle response observed, particularly, co-contraction of the TA and GM.

Bonnet et al. (2017) evaluated changes in postural control during a challenging task whereby participants were required to perform gaze-shifts while standing still. They reported that when pwPD were tested in an ON-state (45–60 minutes post levodopa), participants were able to increase the absolute contribution of postural control mechanisms (i.e., transfer of body weight distribution from one foot to the other relocation of the CoP) particularly in response to the challenging balance task

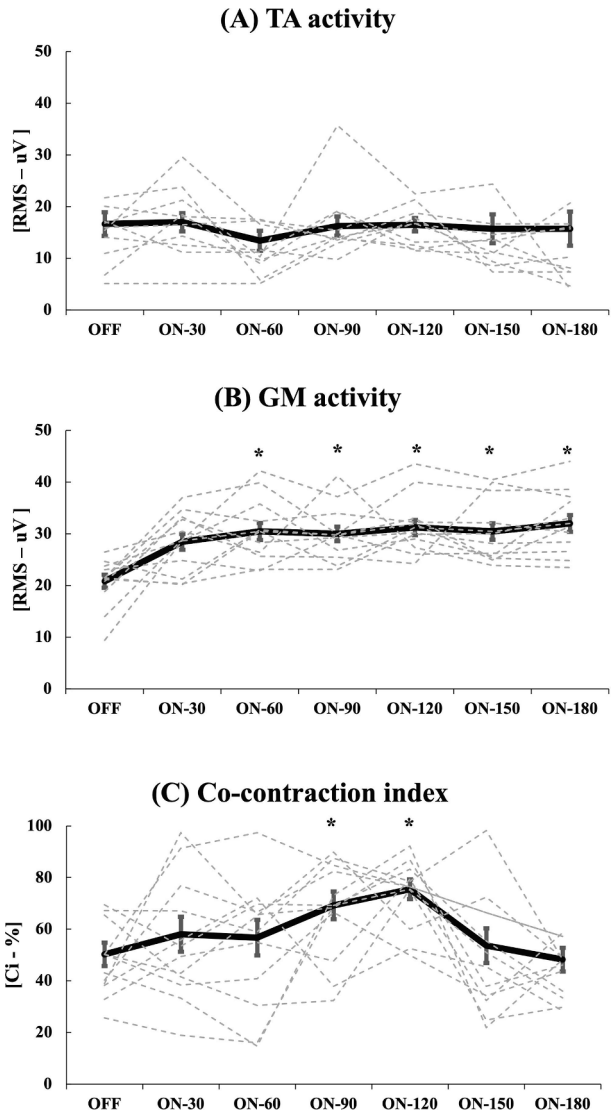

Fig. 3. Means and standard errors of muscle activity. A) tibial anterior activity B) gastrocnemius medialis activity and C) co-contraction index. Grey lines represent individual participants. The solid black line represents the group average. * denotes significant differences compared to OFF-state.

(gaze-shift) compared to the stationary gaze task. Thus, we could speculate that the effects of levodopa on postural control mechanisms are related to the complexity of the task. Body sway was evaluated during a single semi-tandem standing task in the present study. Evaluating postural control while completing a range of standing balance tasks of varying complexity is required to determine which are most sensitive to pathology and how performance during these tasks changes in response to medication. An alternative explanation could be related to the tradeoff between stability and maneuverability (Huang et al., 2011). Workman and Thrasher (2019) demonstrated that levodopa resulted in increased body sway (ellipsis) in pwPD, which they attributed to an increase in maneuverability without compromising stability. This was in contrast to increased rigidity/bradykinesia when assessed OFF medication, which resulted in a smaller ellipsis. Retaining some degree of maneuverability is essential for executing postural response strategies to perturbations in balance and maintaining upright stance. Changes in body sway in PD likely reflect primary pathology (i.e., rigidity and stiffness) but also other secondary factors such as co-contraction of muscles as a voluntary response to counter the fear of falling (Romero and Stelmach 2003).

3.2. *Temporal dynamics of postural control in response to levodopa*

Increased response latency to levodopa has been reported for the first levodopa dose in particular (Olanow and Stocchi 2018) due to reduced levodopa plasma and striatum levels and late gastric emptying (Chana 2004). Food intake was monitored, especially protein content, as it affects the uptake of levodopa in the brain, diminishing response to the drug and increasing motor fluctuations after levodopa intake (Wang et al. 2017). Motor fluctuations have been reported particularly in response to the first levodopa dose of the day (Chana 2004; Contin et al. 2001; Moore et al. 2008). Overall parameters of cortical activity, body sway and muscle activity increased at 60 minutes post levodopa dose (compared to OFF-state) and were stable for 60 minutes (until ON-120). This window coincided with the majority of the sample reporting that they felt in an ON-state of medication. However, increases in some parameters of cortical activity (alpha, beta and theta band activity across frontal, parietal and occipital areas) were noted earlier (30 minutes post levodopa). Conversely, increases in some parameters of body sway were not observed until 90 minutes post levodopa (CoP RMS in both AP and ML directions) and were stable until 150 minutes post levodopa. The findings of the present study enhance our understanding of the temporal dynamics underpinning postural responses and affirm the need for standardized balance protocols with respect to timing post levodopa dose.

Compared to when assessed in an OFF-state, an increased ankle muscle co-contraction was observed at ON-60 and this was maintained until ON-120. This was contrary to our hypothesis. Greater ankle muscle co-contraction indicates increased ankle joint stiffness and may reflect efforts to increase ankle rigidity and resist increases in body sway. This may consequently result in postural demands diverted towards the larger proximal muscles at the hip; however, this was not measured in the present study. These findings corroborate previous studies that demonstrate improved posture and sagittal joint range of motion in the ON-state, permitting more flexible movements (Benninger et al. 2015). The GM and soleus muscles are important anti-gravity muscles for maintaining postural control. Muscle activity measured during quiet stance reflects postural tone, which is larger in pwPD, and reflects rigidity, which can make it difficult for patients to respond to postural perturbations and execute movements to relocate the centre of mass (Frank et al. 2000; Horak et al. 1996). Further work is required to understand the relationship between muscle contractile properties and levodopa during challenging standing tasks.

No significant changes were observed in the score recorded for the UPDRS-III items (limb tremor, rigidity and agility) across each of the time intervals. Repeating the entire UPDRS-III assessment would not have been possible within the time constraints of the current protocol. Thus, assessing a select number of items from the UPDRS-III enabled repeated assessments to be conducted in a timely manner. With only a small variation in score for the three items (score out of 12), changes in response to medication were not detected. Consequently, measures that are sensitive to subtle changes and that can be obtained continuously over time are required. There were few significant differences between the time intervals post levodopa (i.e., ON-30 vs ON-60 ON-60 vs ON-90 etc.) suggesting that once outcomes (cortical activity, muscle activity and body sway) increased they remained stable. Utilizing shorter time intervals to detect subtle changes, individual levodopa response time may be identified and used to inform medication regimes.

The present findings indicate that conducting assessments of postural control while optimally medicated are not advised after 120 minutes post levodopa or before 1 hour post the first levodopa dose due to similarities in performance compared to an OFF-state. Our results reveal a 60 minute window within which measures may be obtained that are different compared to OFF-state and remain stable. It is considered that this 60 minute window may represent when pwPD may be considered to be optimally medicated. Observations outside of this window, particularly pertaining to the evaluation of postural control, may reflect altered

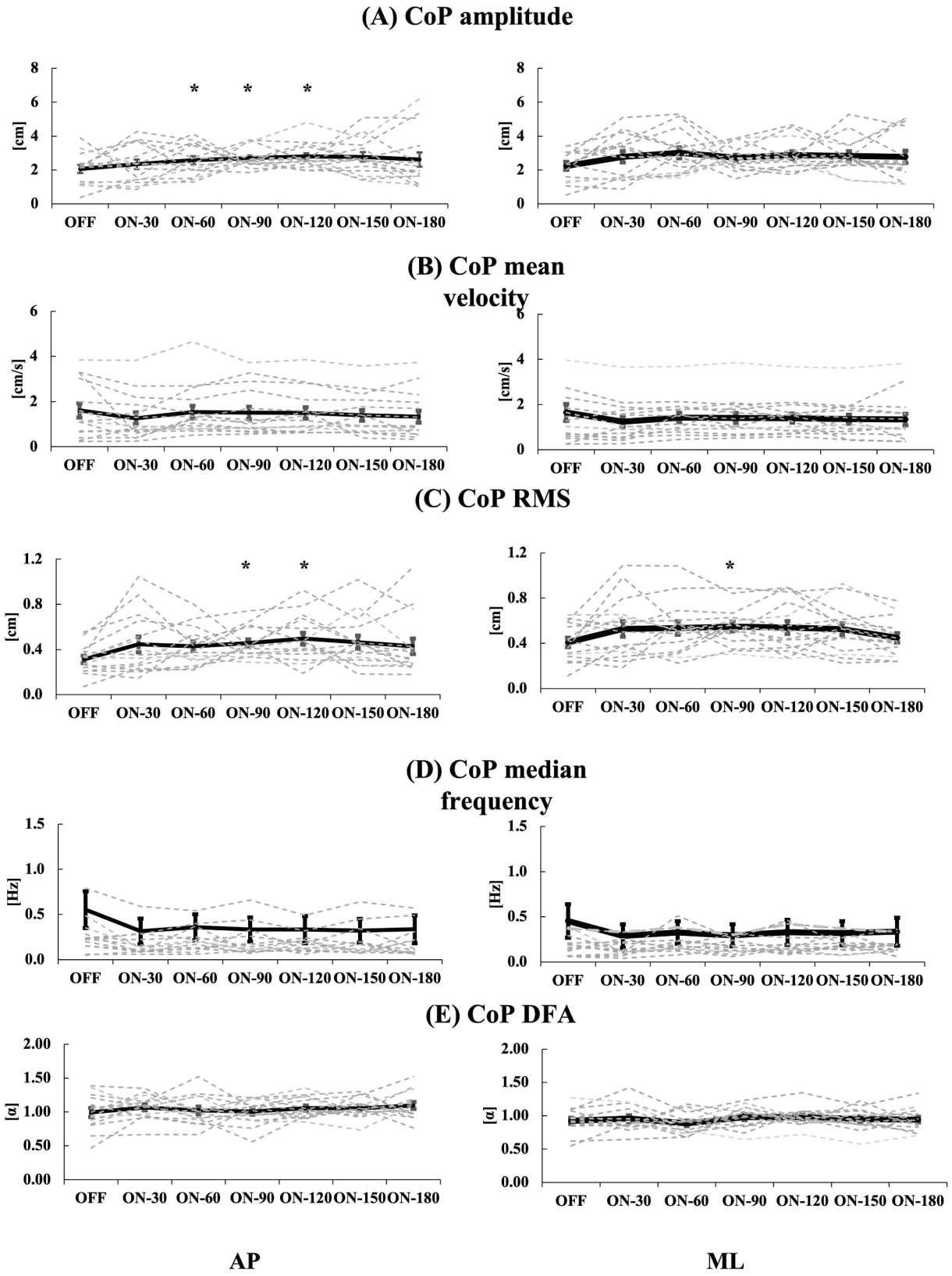

Fig. 4. Means and standard errors of body sway parameters. A) Center-of-pressure (CoP) amplitude B) CoP mean velocity C) Root-mean-square (RMS) D) CoP median frequency and E) Detrended Fluctuations Analysis (DFA). Grey lines represent individual participants. The solid black line represents the group average. * denotes significant differences compared to OFF-state.

responses due to suboptimal medication. Identifying a window of opportunity for measurement when individuals are optimally medicated is important for observations in a clinical and research setting. Often multiple measures (clinical evaluations and mobility outcomes such as gait and postural control) are obtained and reviewed collectively to evaluate an individual's state at a given time. This is particularly important when evaluating the progression of PD symptoms through longitudinal assessment and operating within this window for repeated assessments will ensure consistency.

There are some limitations that must be considered when interpreting the findings of the present study. The postural task was chosen to represent a challenging task for pwPD (compared to standing with feet side-by-side) (Mancini et al. 2012). To fully appreciate the role of task complexity in response to levodopa, future research should incorporate tasks of graded difficulty. Second, our sample of pwPD was restricted to mild-to-moderate disease severity with the majority of participants Hoehn & Yahr I-II. The stage of disease is an important aspect that warrants further investigation. PwPD in the moderate to advanced stages of the disease (i.e. H&Y III) may respond to PD medication differently and show altered temporal dynamics (McColl et al. 2002). Consequently, the protocol may need to be less challenging to ensure that the tasks may be completed safely. In addition, motor phenotype was not quantified in the present study (Stebbins et al. 2013). Compared to the tremor dominant phenotype, the postural instability and gait difficulty phenotype has been associated with suboptimal response to dopamine replacement therapy (Mohl et al. 2017) which may differentially affect postural control. We provide a comprehensive evaluation of postural control (cortical activity, muscle activity and body sway outcomes) every 30 minutes. It is possible that the significant changes in response to levodopa happened between assessments (within a 30 minute window). Investigating subtle changes in postural control that occur more frequently (e.g., every 10 minutes) may offer further insight into the temporal dynamics of the response to levodopa. However, including more frequent assessments is problematic due to increased fatigability in pwPD and possible practice effects associated with protocols involving repeated measures. Finally, we only measured muscle activity from the ankle due to its prominent role in maintaining postural equilibrium. Future efforts should include monitoring proximal leg muscles (acting about the hip joint) and axial muscles (at the torso) to fully appreciate muscle synergies and postural strategies.

We can conclude that i) body sway, cortical activity and muscle activity (including ankle muscle co-contraction) all increase in response to levodopa when measured during a semi-tandem postural task; ii) generally these changes occurred 60 minutes post levodopa and were stable until 120 minutes post levodopa. Therefore, assessments of postural control while optimally medicated are recommended within a 1–2 hour window post levodopa. Measurements before 1 hour post the first levodopa dose and beyond a 2 hour window following levodopa are more likely to reflect a sub-optimal medication state. Future studies should investigate how postural control responds to levodopa during a variety of postural tasks of graded difficulty to fully appreciate the role of task complexity.

4. Experimental procedure

4.1. Participants

To determine the required sample size for the present study, we conducted a power analysis (G*power©) based on the CoP velocity parameter reported in Rocchi (2002) which demonstrated an effect size = 0.69 (critical t = 1.761). Considering a statistical power of 80% and α of 0.05, a total sample of 14 participants was required. Thus, we recruited 15 individuals with PD (Table 1) to account for potential data loss and increase statistical power. Written informed consent was obtained from all participants according to the protocol approved by the University Ethical Committee Board (CAAE #78660517.2.0000.5398).

Participants were eligible providing they: were aged > 55 years; had a diagnosis of idiopathic PD (Hughes et al. 1992) with mild-moderate disease severity (Hoehn & Yahr I-III) (Hoehn and Yahr 1967; Schenkman et al. 2001); had been prescribed dopaminergic treatment for a minimum of 6 months prior to assessment (with a maximal matinal dose of 450 mg and daily equivalent dose of ≤2350 mg (Tomlinson et al. 2010); had normal or corrected to normal vision and hearing; and were capable of following instructions. Participants were excluded if they self-reported memory problems or cognitive impairment, or orthopedic or neurological condition other than PD.

4.2. Experimental procedures

Fig. 5 presents the experimental design of two visits separated by a minimum of 7-days and maximum of 14-days. For both visits, participants came to the laboratory OFF-medication which was defined as a minimum of 12 hours since intake of levodopa. They were instructed not to consume protein on the day of the assessment (Wang et al. 2017). For both visits, participants were evaluated in the OFF-state prior to taking levodopa medication. Participants were assessed every 30 minutes (ON-30, ON-60, ON-90, ON-120, ON-150, ON-180) for 3 hours after the first matinal dose (until ON-180).

During the first visit, demographic, anthropometric and clinical outcomes were obtained. The motor portion of Unified Parkinson's Disease Rating Scale (UPDRS-III) (Fahn and Elton 1987) and the Berg Balance Scale (BBS) (Berg et al. 1995) were assessed in an OFF-state and at ON-60 (full evaluation). The MMSE was evaluated at ON-60. Items 20, 22 and 26 of the UPDRS-III (rest tremor rigidity and agility) and items 7 and 13 of BBS (static standing with narrow and tandem stance) were assessed at each time interval. UPDRS-III and BBS items took 4-minutes to evaluate. Selecting to assess items of the UPDRS-III and BBS was important to reflect motor and balance symptoms at each of the repeated time intervals and ensured the assessments could be achieved within the protocol. Consequently the total range in scores for the UPDRS-III and BBS items were from 2 to 13 and from 6 to 8 pts, respectively. Delta values (OFF-state minus ON-state) were computed for each time interval for the sum of the selected items.

During the second visit, participants performed a standing postural task during which cortical activity, body sway and muscle activity were measured. At each time interval: i) participants were asked to report whether they felt in an ON or OFF-state and the percentage of participants in ON and OFF-state were calculated; and ii) the standing postural task was performed.

4.3. Standing task protocol

Participants stood quietly and barefoot in an upright position with their arms relaxed and down by their sides for 60-s. Participants were asked to fixate on a target that was positioned at eye level approximately 1-metre away. The position of participants' feet were organized in a semi-tandem stance by placing the least affected limb in front of the other with a heel-to-toe distance of 10 cm (Barbieri et al. 2019; Barbieri et al., 2016) and ML distance of approximately 5 cm. The least and most affected limbs were determined based on the difference between of the right and left limb for UPDRS items 20–23 and 25–26 in an OFF-state (Stewart et al. 2009). The boundary of the feet was marked on a sheet of paper to ensure consistent foot positioning and orientation across the repeated trials. Two 60 second standing trials were completed at each time interval.

4.4. Data analysis

All measured signals (CoP, muscle and cortical activity) were synchronized electronically and analyzed in MATLAB® (R2016b Mathworks USA). The first 10 s of each recording was removed to account for postural adjustments.

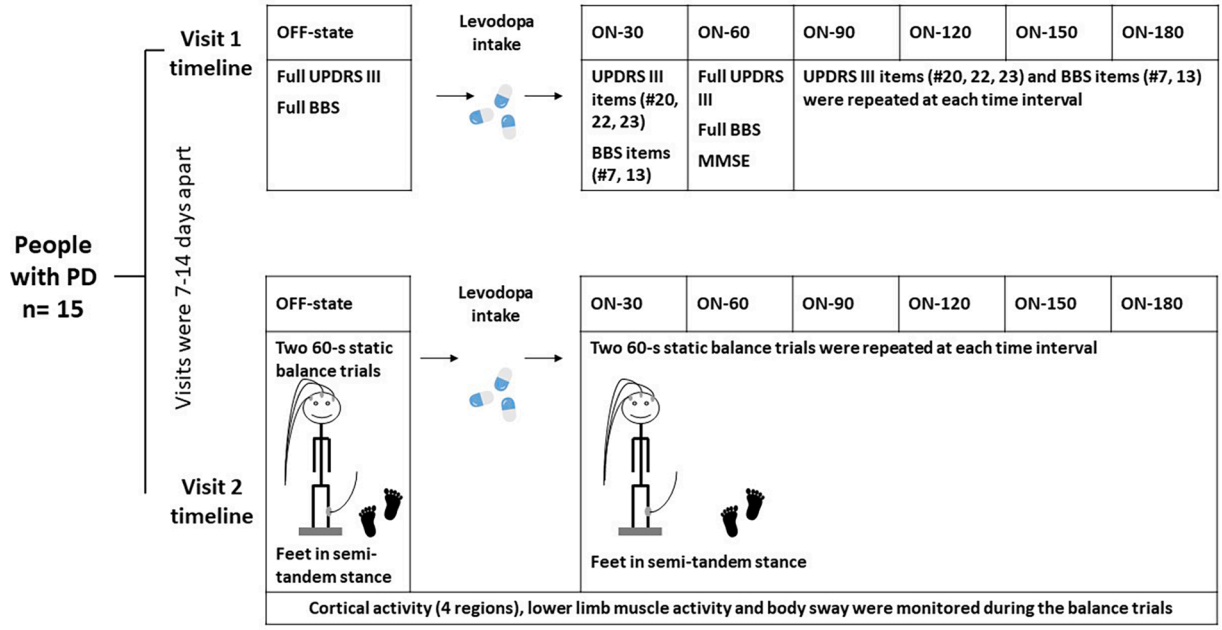

Fig. 5. Experimental design of the study. Parkinson's Disease (PD); Unified Parkinson's Disease Rating Scale (UPDRS); Berg Balance Scale (BBS); Mini-Mental State Exam (MMSE); CoP signal (GRF); electromyography (EMG); electroencephalogram (EEG); items 20 22 and 26 of the UPDRS-III evaluating rest tremor rigidity and agility; items 7 and 13 of BBS evaluating the ability to stay in an upright position without support and the feet in a narrow stance and in a tandem position.

The CoP signal was calculated from the force and moment recorded by a force platform (AccuGait – 50 × 50 cm Advanced Mechanical Technologies USA; 100 samples/s). The data was filtered with a low-pass Butterworth filter of 4th order with a cut-off frequency of 5 Hz determined by residual analysis. The following CoP parameters in both AP and ML directions were calculated: amplitude mean velocity and root mean square (RMS). In addition, we calculated the median frequency of the CoP using spectral power density (Welch periodogram separately for each direction) and performed Detrended Fluctuation Analysis (DFA) using scaling exponent alpha (α) (white noise $\alpha = 0.5$; pink noise $\alpha = 1$; and Brownian noise $\alpha = 1.5$) (Peng et al. 1995).

Surface electromyography (EMG) was used to measure lower limb muscle activity (MIOTEC – MioTool FisioTec Brazil; 8 channels 2000 samples/s) from the tibialis anterior (TA) and gastrocnemius medialis (GM). TA and GM were chosen because upright standing is correlated highly with ankle joint rotation specially performed by ankle agonist and antagonist muscles (Loram et al. 2005). Circular passive electrodes (Ag/AgCl) were placed on the skin over the muscle belly of the TA and GM according to the European recommendations for surface electromyography (Merletti et al. 2001). The signal was filtered using a 4th order band-pass (20–500 Hz) Butterworth filter determined by residual analysis rectified and amplified (1000-fold gain). The following EMG parameters were calculated for each muscle of the limb positioned to the back (least affected limb): RMS of the average power of the raw EMG signal representing muscle activity and the co-contraction index between the TA and GM muscle (Equation (1)). The co-contraction index represents the antagonistic muscle activity (the lower EMG amplitude between TA and GM that generate opposite joint torques) divided by the sum between the agonistic and antagonistic muscle activations (Falconer and Winter 1985).

$$co-contraction\,index = \left(\frac{2*iEMG\,of\,the\,antagonist}{iEMG\,of\,the\,agonist + iEMG\,of\,the\,antagonist}\right)*100 \quad (1)$$

where iEMG is the amplitude of EMG signals of the TA and GM.

An electroencephalogram (EEG) with 64 active electrodes recorded cortical activity (eego™sports ANT Neuro Netherlands; 1024 samples/s). The cap and electrode position followed the 10–10 International system electrode placement (Oostenveld and Praamstra 2001) and manufacturers recommendations (ANT Neuro Netherlands). The impedance remained below 10 Ω. Signal data obtained from all 64 electrodes were imported to EEGlab (Delorme et al. 2011) and the electrode position was determined according to manufacturer's guidelines (see Fig. S1 in the Supplementary material). The data were filtered with a band-pass filter (cut-off frequency 0.5–50 Hz) and visually inspected to identify large artefact periods (Whittier et al. 2020). Channels with a standard deviation (SD) higher than 400 μV and > 5SD from the mean were removed (https://sccn.ucsd.edu/wiki/EEGLAB_Wiki) (Gwin et al. 2010). Also the TrimOutlier (version 0.16) plugin was used for channel rejection (Gray et al. 2017). Across participants, an average of 2–4 channels were rejected. Outliers were automatically identified and removed using the z-score principle (i.e. $3.29 > z > +3.29$) (Tabachnick and Fidell 2019). Data were down-sampled to 512 Hz and the data were referenced to the signal average (Whittier et al. 2020). Independent Component Analysis (ICA-Runica) was used to remove artefacts such as eye movements, blinks, facial muscle activity and other potential artefacts (such as heart beats) (Radüntz et al. 2015). Delta (δ): 0.5–3 Hz, theta (θ): 4–7 Hz, alpha (α): 8–12 Hz and beta (β): 13–30 Hz were determined by power spectral density (Yuvaraj et al. 2014). Four regions of interest (ROI) were determined for the cortical analysis: (1) frontal (F3 F4 and Fz); (2) motor (C3 C4 and Cz); (3) parietal (P3 P4 and PZ) and (4) occipital (O1 O2 and OZ) (Presacco et al. 2012). These ROI were chosen because they reflect muscle contraction and sensory information transfer and processing (Jacobs et al. 2015; Sipp et al. 2013). To exclude the possibility of divergence when processing the EEG signals, one researcher performed all procedures.

4.5. Statistical analysis

All analyses were performed using SPSS 22.0 (SPSS Inc) with significance set at $p < 0.05$.

4.5.1. Visit 1

Wilcoxon signed-rank tests were used to compare H&Y scores UPDRS-III and BBS between OFF-state and ON-60 (full evaluation). Non-

parametric Mann-Whitney test compared delta values of UPDRS-III (motor portion) and BBS items every 30 minutes.

4.5.2. Visit 2

Data collected during the standing task were averaged across the two trials. Data were normally distributed and assumptions associated with sphericity (Wilk and Mauchly) and equality of variance (Levene's test) were not violated. To evaluate the temporal dynamics of cortical activity, body sway parameters and muscle activity in response to levodopa, ten repeated MANOVAs were performed (five for AP and ML CoP parameters, one for TA and GM muscle activity, and four for frontal, motor, parietal and occipital cortical areas – factor: medication status (OFF-state × ON-30 × ON-60 × ON-90 × ON-120 × ON-150 × ON-180)). A one-way ANOVA with repeated measures for medication status was employed to compare co-contraction index between time intervals. Tukey-Kramer adjustments were used to perform pairwise comparisons (p-adjusted < 0.002). Partial eta-squared (η^2) was reported to measure effect size and interpreted as small (>0.01), moderate (>0.06) or large (>0.14) effects (Cohen 2013). In addition, for post hoc comparisons Cohen's d (d) was calculated to measure effect size and interpreted as small (0.2–0.5) moderate (0.6–0.8) and large (>0.8) effect sizes (Cohen 2013).

CRediT authorship contribution statement. **Fabiana Araújo-Silva:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft. **Felipe B. Santinelli:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Visualization, Writing – original draft, Writing – review & editing. **Luis Felipe I. Imaizumi:** Investigation, Data curation, Formal analysis, Writing – original draft. **Aline P.B. Silveira:** Investigation, Data curation, Formal analysis, Writing – original draft. **Luiz H.P. Vieira:** Investigation, Data curation, Formal analysis, Writing – original draft. **Lisa Alcock:** Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Fabio A. Barbieri:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brainres.2021.147727.

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