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Time-dependent changes in postural control in early Parkinson's disease: what are we missing?

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¹ ABCs, Activities-specific Balance Confidence scale; ANCOVA, analysis of covariance; AP, anteroposterior; BMI, Body Mass Index; CL, Controls; f95%, CoP, centre of pressure; frequency below which is 95% of power of the acceleration power spectrum; GDS, Geriatric Depression Scale; Hz, Hertz; LEDD, Levodopa Equivalent Daily Dose; MDS-UPDRS, Movement Disorder Society version of the Unified Parkinson's Disease Rating Scale; *m*, slope; mins, minutes; ML, mediolateral; MMSE, Mini Mental State Exam; MoCA, Montreal Cognitive Assessment; n, number; ppm, parts per million; PC, Postural Control; PD, Parkinson's disease; PIGD, Postural Instability and Gait Disorder; RMS, Root Mean Square; s, seconds; SD, standard deviation.

Abstract

Impaired postural control (PC) is an important feature of Parkinson's disease (PD) but optimal testing protocols are yet to be established. Accelerometer-based monitors provide objective measures of PC. We characterised time-dependent changes in PC in people with PD and controls during standing, and identified outcomes most sensitive to pathology. Thirty-one controls and 26 PD patients were recruited: PC was measured with an accelerometer on the lower back for 2 minutes (mins). Preliminary analysis (autocorrelation) showed 2 seconds (s) was the shortest duration sensitive to changes in the signal; time series analysis of a range of PC outcomes was undertaken using consecutive 2s windows over the test. Piecewise linear regression was used to fit the time series data during the first 30s and the subsequent 90s of the trial.

PC outcomes changed over the 2mins, with the greatest change observed during the first 30s after which PC stabilised. Changes in PC were reduced in PD compared to controls, and Jerk was found to be discriminative of pathology.

Previous studies focusing on average performance over the duration of a test may miss timedependent differences. Evaluation of time-dependent change may provide useful insights into PC in PD and effectiveness of intervention.

Keywords: Postural control; time series; accelerometer; Jerk; Parkinson's.

1.0 Introduction

Postural control (PC) during quiet standing is an important component of clinical evaluation in Parkinson's disease (PD), and a cardinal sign of disease staging [9]. Recognising and evaluating balance dysfunction is of fundamental importance for managing PD because of the profound impact PC has on gait, mobility and falls [36]. The mechanisms underlying balance instability in PD are complex, and involve peripheral and central neural structures [36]. Previous research suggests that participants with PD even in the early stages exhibit abnormalities in PC measures during quiet standing (increased Jerk and root mean square values, decreased frequency) [16,17], and that the positive effect of dopaminergic replacement therapy on gait (particularly step hypokinesia and gait speed) may not be paralleled for PC where Levodopa has been shown to worsen some outcomes [11,31]. Understanding the features of PC especially in the early stage of the disease is therefore relevant to the management of PD.

However, interpretation and clinical inference of PC findings is challenging because testing protocols are not standardised. For example, PC during quiet standing has been routinely used for many years [25,20,33,34,36], with variations including: standing with bare feet [25]; with shoes on [8,4,29]; with eyes open or closed [25,24]; and with legs spaced a fixed distance and arms crossed on chest [17]. PC during quiet stance has also been evaluated over different trial durations ranging from 30 - 120 seconds [33].

More recently body worn accelerometer-based monitors have been used and recommended to accurately quantify PC in older adults and people with PD [16,17,19,27,30]. The outcomes determined with accelerometers have been shown to be reliable and consistent with those quantified from centre of pressure (CoP) data using traditional methods (i.e. force plates) [41], and have the additional advantage of yielding rate of change of acceleration (Jerk) which would otherwise require multiple derivations of CoP displacement. These monitors also have advantages over traditional clinical tests because data are collected continuously over the duration of the test allowing time-dependent changes in PC to be evaluated. To date PC outcomes are typically summarised over the test duration and change over time has not been considered. This is a methodological issue that needs to

be addressed because time-dependent fluctuation may provide a more subtle reflection of PC adaptations in addition to averaged values.

The aim of this study was to characterise time-dependent changes in a broad range of PC outcomes derived from an accelerometer over 2 minutes of quiet standing using a novel method of analysis. We compared the time dependence difference in early PD and older adults and aimed to identify the outcomes of PC most sensitive to pathology. We hypothesised that: 1) PC would change over the duration of a 2 minute test; 2) the greatest change would be observed in the early stage of the test in order to stabilise PC; and finally 3) stabilisation of PC (determined by time-dependent change) would be less efficient in PD compared to age matched controls.

2.0 Experimental procedures

PD participants and healthy age-matched controls (CL) were recruited from the larger Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation – Parkinson's Disease Gait study (ICICLE-PD GAIT) [13], which aimed to recruit all new cases of parkinsonism from secondary care services in Newcastle upon Tyne and Gateshead from June 1, 2009, to December 31, 2011.

2.1 Participants

Participants were assessed during their visit to the Clinical Ageing Research Unit, Newcastle University. Participants were excluded if they had any neurological (other than PD), orthopaedic or cardiothoracic conditions that may have markedly affected their walking or safety during the testing sessions. In addition, PD participants had to be diagnosed with idiopathic PD according to the UK Parkinson's Disease Brain Bank criteria and were excluded if they presented with significant memory impairment (Mini Mental State Exam (MMSE) < 24 [6]), dementia with Lewy bodies, drug induced parkinsonism, 'vascular' parkinsonism, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration or poor command of English.

This study was conducted according to the declaration of Helsinki and had ethical approval from the Newcastle and North Tyneside research ethics committee. All participants signed an informed consent form prior to testing.

2.2. Demographic and clinical measures

Age, sex and body mass index (BMI) were recorded for each participant. Cognition was assessed with the MMSE and the Montreal Cognitive Assessment (MoCA) [26]. Depression was evaluated with the Geriatric Depression Scale (GDS) [37]; physical fatigue was assessed using the Multidimensional Fatigue Inventory (MFI) [38]; and balance self-efficacy was measured using the self-rated Activities-specific Balance Confidence scale (ABCs) [28]. The severity of PD motor symptoms in the PD participants was measured using the Hoehn and Yahr scale [9], which ranges from 0 (no symptoms) to 5 (wheelchair bound or bedridden if unaided) and section III of the modified Movement Disorder Society version of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS [7]), which ranges from 0 (no motor symptoms) to 132 (severe motor symptoms). The Postural Instability and Gait Disorder (PIGD) and Tremor phenotype subscales were also calculated from the MDS-UPDRS [39]. Levodopa equivalent daily dose (LEDD) scores were calculated according to established methods [40].

2.3. Standing balance test

Participants were instructed to start from a standing position, with their feet positioned within the boundaries of a predefined area (400 mm wide \times 600 mm long), to place the hands by their sides [29], and to maintain an upright standing position for 2 minutes while looking straight ahead. Similar to previous studies, participants wore their shoes during the test with no restriction with regard to foot placement [24]. The recording of data started 3 seconds after participant acknowledged they understood what was required of them. Each subject performed one test, in line with previous recommendations [41], and to avoid familiarisation to the assessment and fatigue [22,3]. PD participants who were on medication were tested approximately 1 hour after medication intake.

2.4 Equipment

PC was measured with a single tri-axial accelerometer-based monitor² (resolution 0.976mg, clock accuracy: ± 20 parts per million (ppm)) located on the lower back (5th lumbar vertebra, L5, Figure 1). The device is small ($6.0 \times 21.5 \times 31.5$ mm) and lightweight (9.0g) with no external wiring which has been validated for its suitability in capturing high-resolution data akin to human movement [14]. Data were sampled at a rate of 50 Hertz (Hz) in order to have consistency with previous literature [17] and downloaded to a computer once recording was complete. The accelerometer was attached directly to the skin with the aid of a hydrogel adhesive³ and covered with a Hypafix⁴ bandage for extra support.

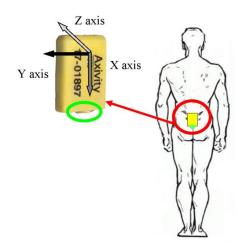


Figure 1.

Experimental set up: the site of attachment and orientation of the tri-axial accelerometer device on the lower back (L5). In dark grey x (vertical) axis, in black y (mediolateral) axis, and in light grey z (anteroposterior) axis.

2.5 Data processing and analysis

Once data were downloaded to a computer they were analysed by a bespoke MATLAB[®] (R2012a) program. Of particular interest were the accelerations in the mediolateral and anteroposterior planes as quiet standing balance is reflected in these directions [17]. Data were filtered using a 4th order zero phase, low pass Butterworth filter with a cut-off frequency of 3.5Hz [17]. In accordance with previous work [17], data were transformed to a horizontal-vertical coordinate system [21] before extracting the following outcomes for the mediolateral (ML), anteroposterior (AP) and combined directions, which have been shown to be valid, reliable, and sensitive to early PD [17,16,19]:

² Axivity AX3, York, UK

³ PAL Technologies, Glasgow, UK

⁴ BSN Medical Limited, Hull, UK

- 1. Jerk: the rate of change of acceleration, a measure of the smoothness of PC [17];
- 2. Root mean square (RMS): magnitude of the acceleration traces [23,17];
- 3. Frequency: the frequency below which is 95% of power of the acceleration power spectrum (f95%) [17] was evaluated using both the *fft* and the *cumsum* MATLAB functions (Figure 2);
- 4. Ellipsis: the area including the 95% of the ML and AP acceleration trajectories [27] was evaluated using the *eig* and *prod* MATLAB functions (Figure 2).

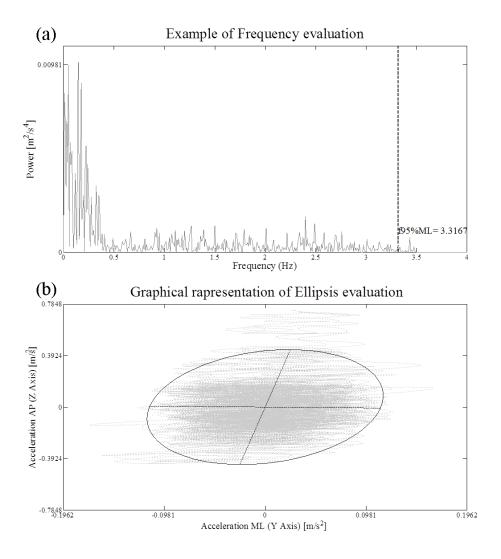


Figure 2.

(a): example frequency evaluation along mediolateral direction (f95%ML), in grey the power spectrum, in black dotted line the obtained result.

(b): example of ellipsis evaluation: in grey accelerometer signal on the y - z (mediolateral (ML)-anteroposterior (AP)) axis plane, in black the ellipsis graphical representation corresponding to the area including the 95% of the acceleration trajectories along ML and AP directions.

2.6 Data considerations

To examine time-dependent changes in PC, it was first important to identify the shortest duration of time within the 2 minutes test that was sensitive to changes in acceleration signal. To do this we used autocorrelations of squared values of the acceleration traces and squared first-derivative of the acceleration traces (the precursors of RMS and Jerk values, respectively). Averaged autocorrelation values showed that a 2 second bout was optimal with correlation values dropping to zero after no more than a lag of 100 samples (2 seconds), this choice took also into account the frequency components of the signal [2]. Therefore outcomes for PC strategies were calculated during consecutive non-overlapping 2 second windows (i.e. 0-2 seconds, 2-4 seconds, ..., 118-120 seconds). Figure 3 ((a)-(d)) describes the process used to extract data showing accelerometer raw data, autocorrelation and examples of clinical outcomes. All variables except for the f95% were normalised by duration of the bout length (2 seconds).

2.7 Statistical analysis

The process of data analysis corresponded with our hypotheses, as outlined below:

Hypothesis 1: Between group differences for each PC outcome were evaluated over the 60 consecutive 2 second bouts using repeat-measures analysis of covariance (ANCOVA). Group (CL vs. PD) was entered as a between-person factor and time (consecutive 2 second windows) as a within-person factor. Age and sex were included as covariates. ANCOVA revealed no significant group differences; however significant main effects of time for RMS indicated PC outcomes were non-stationary and justified examining how PC changed over time.

Hypothesis 2: Inspection of data and preliminary analysis based on consecutive bouts of 30 seconds (0-30s, 30s-60s, 60s-90s, 90-120s) revealed that time-dependent changes in PC occurred mostly in the first 30 seconds for both CL and PD, and no significant changes were found between PD and CL data for the last 3 bouts (30-60s, 60-90s, 90-120s). To formally test whether most change would occur during the first 30 seconds of the standing test, piecewise linear regression was fitted to data from the first 30 seconds (0-30 seconds) and subsequent 90 seconds (30-120 seconds) of the standing test.

Hypothesis 3: Differences in the slopes (*m*) of the regression lines between the 0-30 second and the 30-120 second sections were then tested using ANCOVA with group (PD, CL) as between-person factor, time section (0-30 seconds, 30-120 seconds) as a within-person factor, and age and sex as covariates. Data analysis was carried out using SPSS v19 (IBM).

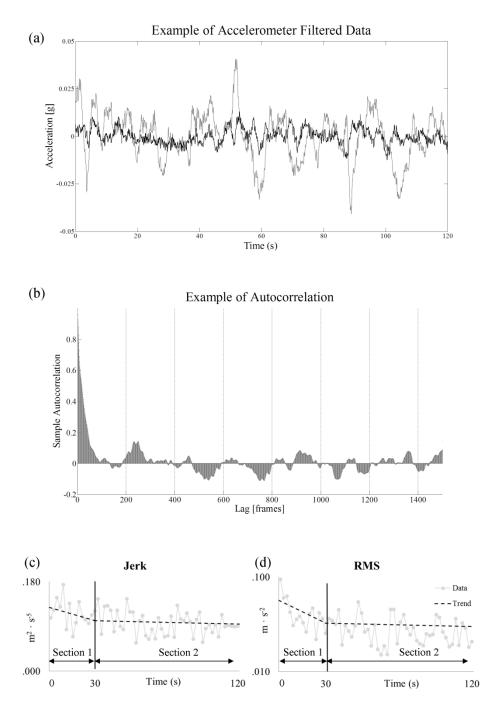


Figure 3.

(a): an example of corrected and filtered data extracted from a subject with Parkinson's disease during a two minutes quiet standing test. In black y axis (mediolateral) data, and in grey z axis (anteroposterior) data. (b): example of autocorrelation signal. (c): example of Jerk time series extracted from the accelerometer signal using a 2 second window. (d): example of RMS time series extracted from the accelerometer signal using a 2 second window.

3.0 Results

Participant demographic, clinical and cognitive descriptors are shown in Table 1. Compared to CL, participants with PD were aged matched; included proportionally less women (CL: 45%, PD: 23%); presented with lower balance confidence; poorer cognition; and increased fatigue and depression (although the depression scores remained within the normal range). Participants with PD were in the early stages of the disease with mild motor symptoms. PC was shown to vary over time (time and time \times group effects were found, see Table 3) with changes occurring in the first 30 seconds of the test in CL, but not PD. A summary of the piecewise linear regressions are shown in Figures 2-4 and data relating to the slopes for the first 30 seconds and the subsequent 90 seconds are shown in Table

Table 1.

2.

Clinical and demographic characteristics for control participants (CL), and people with Parkinson's disease (PD).

Characteristic	CL (n = 31) Mean (SD)	· /	р
Male/female (n)	17/14	20/6	.080
Age (years)	67.6 (7.5)	67.2 (11.1)	.859
MMSE (0 – 30)	29.3 (1.0)	28.5 (1.0)	.024
MoCA (0 – 30)	27.7 (1.8)	24.5 (3.1)	<.001
GDS (0 – 15)	1.2 (1.7)	2.4 (1.8)	.016
MFI Physical fatigue $(0 - 20)$	8.5 (3.8)	10.3 (3.0)	.055
ABCs (0 – 100%)	91.7 (12.1)	83.5 (17.7)	.052
Hoehn & Yahr stage: HYI, HYII (n)	-	9, 17	-
MDS-UPDRS III (0 – 132)	-	26.1 (10.3)	-
Motor Phenotype (n)	-	PIGD 9 ID 2 TD 15	-
Levodopa Equivalent Daily Dose (mg/day)	-	169.42 (141.9)	-

Group means have been adjusted for age and sex differences between groups; MMSE: Mini Mental State Exam; MoCA: Montreal Cognitive Assessment; GDS: Geriatric Depression Scale; MFI – Multidimensional Fatigue Inventory; ABCs: Activities specific balance confidence scale; UPDRS: Unified Parkinson's Disease Rating Scale; PIGD: Postural instability and gait disorder phenotype; ID: indeterminate phenotype; TD: Tremor dominant phenotype. *p* difference between CL and people with PD. In bold significant *p*-values (p < 0.05).

3.1 Differences in PC in PD and controls averaged over 2 minutes.

Between group differences (PD vs. CL) for each of the four PC measures evaluated using the average value of the time series from 2 second bout windows showed no difference between PD and CL for Jerk values (combined, ML or AP) (Figure 4 (a)-(c)). For PD participants, combined RMS was significantly greater than controls (p = 0.049), while RMS AP was marginally higher (p = 0.057), and RMS ML comparable (p = 0.444) (Figure 4 (d)-(f)). Ellipsis and f95% AP and ML values were comparable for PD and CL participants (Figure 4 (g)-(i)).

3.2 Time-dependent changes in PC in PD and CL.

The values of the slopes of the regression lines used to fit the data during the first 30 seconds (0-30 seconds) and the subsequent 90 seconds (30-120 seconds) of the standing test are shown in Figure 3 (panel (c) and (d)). ANCOVA analysis revealed a significant main effect of time for all outcomes apart from Jerk ML and f95% AP. There was also a time \times group interaction for both Jerk and Jerk ML (Table 3) whereby CL decreased their total Jerk and Jerk ML more than PD participants during the first 30 seconds. In contrast Jerk remained stable in both groups over the last 90 seconds (Figure 4 (a)-(c)).

Table 2.

Values of the slopes (*m*) for each accelerometers outcome. Values are shown as Mean (SD). Significant (p < 0.05) Time Effect (between sections, \ddagger) and Time × Group Effect (\ast) of the ANCOVA analysis for the linear regression slopes results (*m*) are shown for each variable.

	Section 1: 0-30 seconds		Section 2: 30-120 seconds	
Variable	CL n = 31	PD n = 26	CL n = 31	PD n = 26
Jerk <i>m</i> (deg $\cdot 10^{-2}$) ‡*	-0.3193 (0.600)	-0.0176 (0.003)	-0.0005 (.100)	-0.0246 (0.100)
Jerk AP $m (\deg \cdot 10^{-2}) \ddagger$	-0.1575 (0.200)	-0.0565 (0.002)	-0.0006 (0.030)	-0.0131 (0.030)
Jerk ML $m (\deg \cdot 10^{-2})^*$	-0.1618 (0.500)	0.0390 (0.003)	0.0005 (0.040)	-0.0115 (0.100)
RMS $m (\deg \cdot 10^{-2}) \ddagger$	-0.2736 (0.400)	-0.0997 (0.003)	0.0158 (0.100)	0.01985 (0.100)
RMS AP $m (\deg \cdot 10^{-2}) \ddagger$	-0.2552 (0.400)	-0.0724 (0.003)	0.0132 (0.100)	0.0201 (0.100)
RMS ML $m (\deg \cdot 10^{-2}) \ddagger$	-0.0684 (0.100)	-0.0403 (0.001)	0.0007 (0.020)	0.0002 (0.020)
f95% AP m (deg $\cdot 10^{-2}$)	2.5346 (8.100)	-0.8517 (8.989)	-0.4956 (2.100)	-0.7702 (1.800)
f95% ML $m (\deg \cdot 10^{-2}) \ddagger$	2.8111 (8.300)	3.4203 (7.725)	-0.5034 (1.200)	-0.5181 (2.600)
Ellipsis $m (\deg \cdot 10^{-2}) \ddagger$	-0.0484 (0.100)	-0.000153 (0.001)	0.0004 (0.010)	-0.0003 (0.001)

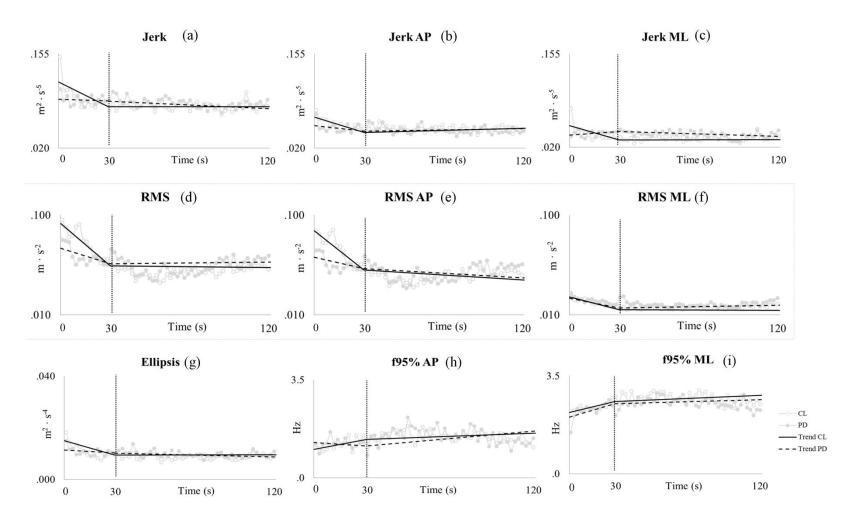
Table 3.

Results of the ANCOVA analysis for the linear regression slopes (*m*) results using a 30 seconds cut-off: *p* values of Time Effect (between sections, \ddagger) and Time × Group Effect (CL vs. PD,^{*}) are reported for each variable, in bold are shown the significant *p* values (*p* <0.05).

Variable	+ Time Effect	*Time × Group Effect
Jerk m * *	0.021	0.013
Jerk AP m ŧ	0.006	0.560
Jerk ML m *	0.108	0.020
RMS m ŧ	0.001	0.092
RMS AP m ŧ	0.008	0.103
RMS ML m ŧ	0.001	0.238
f95% AP m	0.132	0.137
f95%ML m ŧ	0.004	0.982
Ellipsis m ŧ	0.015	0.074

Figure 4.

Mean time series data using a 2 second (s) window for Jerk (a), Jerk along anteroposterior direction (AP) (b), Jerk along mediolateral direction (ML) (c), RMS (d), RMS along anteroposterior direction (AP) (e), RMS along mediolateral direction (ML) (f), Ellipsis (g), f95% along anteroposterior direction (AP) (h), and f95% along mediolateral direction (ML) (i), considering effect of pathology (Control participants (CL) vs. people with Parkinson's disease (PD)). Results from linear regression using a 30 second cut-off are overlapped.



4.0 Discussion

The specific aim of this study was to characterise time-dependent change in PC in participants with early PD compared to age-matched CL and identify the outcomes most sensitive to pathology. To date this is the largest study examining PC in PD and healthy older controls (n = 57) with an instrumented balance test (previous studies ranged on average from n = 19 to n = 40 [2,16-19,27]). The novel findings of this study were that PC changes during the first 30 seconds of a test in healthy controls after which it is maintained, in contrast to PD who did not show early time-dependent change in PC. These findings were in contrast to values averaged over the duration of the test. The findings support our hypotheses and suggest that time-dependent changes in PC may identify subtle changes in PC missed when reporting average performance and should also be considered.

4.1 Time-dependent changes in PC and effect of pathology.

We hypothesised that PC would show time-dependent change over the duration of a 2 minute test and would be greatest in the early stage of the test as PC is stabilised. Furthermore, time-dependent change would be reduced in PD compared to age-matched controls. Our results confirm these hypotheses. PC changed over the course of 2 minutes quiet standing with the greatest change observed in the first 30 seconds and was different in PD and CL. Controls showed a reduction in PC outcomes during the first 30 seconds of the PC test in contrast to PD participants who did not demonstrate change over time (as evident by Jerk, RMS and ellipsis), which suggests less adaptive PC strategies overall.

When average values were compared over the 2 minute test, although participants with PD showed higher values with respect to CL, no significant difference was found between the groups except for RMS. These findings are in contrast to previous studies [17,16] however this may be explained by differences in the characteristics of the PD participants and subtle differences in methodology (constrained versus non-constrained stance).

When time dependant changes were examined (slopes of the linear regression of the first 30 seconds vs. those of the last 90 seconds) PD and CL participants showed differences in PC outcomes during a static PC test [16,17], which is not surprising given the effect of PD pathology on motor control

[36,12]. Differences were more evident in the ML than AP direction, which concurs with findings from two previous studies [31,27].

Our results therefore show the need to inspect time-dependent change over the first 30 seconds in order to depict between-group difference rather than examine values for each discrete 2 second bout windows as the analysis from the 2 minutes standing test revealed that pooled data were not sensitive to pathology (RMS only was found to differentiate between CL and participants with PD).

4.2 Sensitivity of outcome measures of PC.

With respect to the measurement of PC, we found that Jerk was the most sensitive outcome which for combined directions discriminates between CL and participants with PD. In contrast with Mancini et al. 2011[17] we did not find differences in relation to RMS, f95%, ellipsis and Jerk in the AP direction. This again may be due to differences in methodology adopted and clinical characteristics of the participants (who were untreated in contrast to our study). We also found that PC characteristics in the ML direction were more sensitive than in the AP direction. This may reflect a decrease in postural tone at the trunk and hip levels, which would decouple the trunk from lower limb sway [31], whereas a reduced sway in AP direction might reflect the increase stooped position mainly consisting in flexion of the hips and knees which is often observed in more advanced PD [31,36]. These results concur with the view that adaptation takes place over time through motor learning but this is less effective for people with PD.

4.3 Substrates of PC underlying time-dependent change.

Time-dependent changes in PC for all groups in our study occurred in the first 30 seconds of the test, suggesting early stabilisation before reaching a plateau. This is supported by literature which suggests motor learning underpins fast and effective adjustment of postural responses to change in position, which is then followed by a period of stabilisation [12,35]. Differences in PC strategies in PD may be due to both abnormal spatiotemporal coordination of muscles' postural responses which are often hypometric (small) in people with PD and a decreased ability to generate and sustain PC as a result of biomechanical [12] and impaired sensory-motor integration as shown by previous studies [1,15,5].

Moreover and in agreement with published literature [36], the difficulty to choose and maintain a postural strategy may reflect an important role of the voluntary motor control mediated by the basal ganglia which is impaired in PD. This concurs with the view that adaptation takes place over time through motor learning but this is less effective for participants with PD and further inhibited by medication even in the early stage of the disease [31,27].

4.4 Implications for clinical testing.

The time-dependent changes in PC observed in this study has implications for test protocols. The early stage of the test appears to be critical to examine postural adaptation and a 30 second trial is likely to be sufficient to capture this. Data collected after this time period reflects a stable state of PC. Most protocols use average values masking these early changes which could provide additional important information with respect to the influence of disease severity and intervention [16,19,17,31]. Furthermore, the ability to stabilise PC rather than maintain a static state most likely reflects requirement for real world postural stability.

The consequence of impaired PC includes restricted functional mobility, reduction in levels of daily physical activity, and the onset of falls [10]. Tentative implications for the management of early PD therefore arise from this study. If PC is refractory to dopaminergic replacement therapy even in the early stages of disease onset when response to medication is optimal [11,18], early efforts need to be directed towards ameliorating PC deficit. Furthermore, rehabilitation strategies that focus on improved directional control (mediolateral) and aim to enhance more rapid stabilisation may be important to improve stabilisation and enhance PC in early PD. Early intervention is also warranted before secondary, compensatory change becomes more evident [32]. Therefore we propose that our novel methodology has the potential to be adopted as a "tool" to understand the effect of pathology, efficacy of new pharmacological, surgical and physical interventions and provide insight into time dependant PC mechanisms which may have not been examined so far.

4.5 Limitations.

These results are preliminary and further examination in a larger cohort is needed to determine whether these results can be confirmed, in addition examination of other pathologies will allow us to determine whether these time-dependant changes are specific to PD. Future work will examine PC strategies, effect of test protocol (shoes/no shoes, eyes open/closed), and effect of disease severity due to follow up time points in the larger incident PD cohort compared to age matched controls (ICICLE-PD GAIT).

5.0 Conclusions

Time-dependent adjustments in PC occur in the first 30 seconds of quiet standing and are less efficient in PD suggesting poorer adaptive PC. Testing conditions for examining time-dependent changes in PC therefore require a minimum of 30 seconds to reflect postural adaptation. Time-dependent differences in stability also appear to be greater in the mediolateral direction with Jerk the most sensitive outcome to discriminate between groups. Rehabilitation strategies that focus on mediolateral control may be optimal for improving balance in people with PD and should be started early. In future our methodology could be applied to various pathologies which affect balance, providing insight into PC strategies with respect to pathology and response to intervention.

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7.0 Conflict of Interest

There are no conflicts of interest.

9.0 References

- Abbruzzese G, Berardelli A (2003) Sensorimotor integration in movement disorders. Movement Disorders 18 (3):231-240
- Baston C, Mancini M, Schoneburg B, Horak F, Rocchi L (2014) Postural strategies assessed with inertial sensors in healthy and parkinsonian subjects. Gait Posture 40 (1):70-75. doi:10.1016/j.gaitpost.2014.02.012
- 3. Benvenuti F, Mecacci R, Gineprari I, Bandinelli S, Benvenuti E, Ferrucci L, Baroni A, Rabuffetti M, Hallett M, Dambrosia JM (1999) Kinematic characteristics of standing disequilibrium: reliability and validity of a posturographic protocol. Archives of physical medicine and rehabilitation 80 (3):278-287
- Brenton-Rule A, Bassett S, Walsh A, Rome K (2011) The evaluation of walking footwear on postural stability in healthy older adults: An exploratory study. Clinical Biomechanics 26 (8):885-887
- 5. Brown LA, Cooper SA, Doan JB, Clark Dickin D, Whishaw IQ, Pellis SM, Suchowersky O (2006) Parkinsonian deficits in sensory integration for postural control: temporal response to changes in visual input. Parkinsonism & related disorders 12 (6):376-381
- Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of psychiatric research 12 (3):189-198
- 7. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stern MB, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, LeWitt PA, Nyenhuis D, Olanow CW, Rascol O, Schrag A, Teresi JA, van Hilten JJ, LaPelle N, Movement Disorder Society URTF (2008) Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 23 (15):2129-2170. doi:10.1002/mds.22340
- Hijmans JM, Geertzen JHB, Dijkstra PU, Postema K (2007) A systematic review of the effects of shoes and other ankle or foot appliances on balance in older people and people with peripheral nervous system disorders. Gait & posture 25 (2):316-323
- Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression and mortality. Neurology 17 (5):427-442
- 10. Horak FB (2006) Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? Age and ageing 35 (suppl 2):ii7-ii11

- 11. Horak FB, Frank J, Nutt J (1996) Effects of dopamine on postural control in parkinsonian subjects: scaling, set, and tone. Journal of Neurophysiology 75 (6):2380-2396
- Horak FB, Henry SM, Shumway-Cook A (1997) Postural perturbations: new insights for treatment of balance disorders. Physical Therapy 77 (5):517-533
- Khoo TK, Yarnall AJ, Duncan GW, Coleman S, O'Brien JT, Brooks DJ, Barker RA, Burn DJ (2013) The spectrum of nonmotor symptoms in early Parkinson disease. Neurology 80 (3):276-281
- Ladha C, Jackson, Dan, Ladha, Karim, Olivier, Patrick Shaker table validation of OpenMovement AX3 accelerometer. In: 3rd International Conference on Ambulatory Monitoring of Physical Activity and Movement, Ahmerst, 2013. pp 69-70
- Lewis GN, Byblow WD (2002) Altered sensorimotor integration in Parkinson's disease. Brain 125 (9):2089-2099
- 16. Mancini M, Carlson-Kuhta P, Zampieri C, Nutt JG, Chiari L, Horak FB (2012) Postural sway as a marker of progression in Parkinson's disease: a pilot longitudinal study. Gait Posture 36 (3):471-476. doi:10.1016/j.gaitpost.2012.04.010
- Mancini M, Horak FB, Zampieri C, Carlson-Kuhta P, Nutt JG, Chiari L (2011) Trunk accelerometry reveals postural instability in untreated Parkinson's disease. Parkinsonism & related disorders 17 (7):557-562
- Mancini M, Rocchi L, Horak FB, Chiari L (2008) Effects of Parkinson's disease and levodopa on functional limits of stability. Clinical Biomechanics 23 (4):450-458
- Mancini M, Salarian A, Carlson-Kuhta P, Zampieri C, King L, Chiari L, Horak FB, Muto T, Herzberger B, Hermsdoerfer J (2012) ISway: a sensitive, valid and reliable measure of postural control. Journal of NeuroEngineering and Rehabilitation 9 (1):59
- 20. Mansfield A, Mochizuki G, Inness EL, McIlroy WE (2012) Clinical Correlates of Between-Limb Synchronization of Standing Balance Control and Falls During Inpatient Stroke Rehabilitation. Neurorehabilitation and Neural Repair 26 (6):627-635
- Moe-Nilssen R (1998) A new method for evaluating motor control in gait under real-life environmental conditions. Part 1: The instrument. Clinical Biomechanics 13 (4):320-327
- 22. Moe-Nilssen R (1998) Test-retest reliability of trunk accelerometry during standing and walking. Arch Phys Med Rehabil 79 (11):1377-1385
- 23. Moe-Nilssen R, Helbostad JL (2002) Trunk accelerometry as a measure of balance control during quiet standing. Gait Posture 16 (1):60-68

- 24. Moghadam M, Ashayeri H, Salavati M, Sarafzadeh J, Taghipoor KD, Saeedi A, Salehi R (2011) Reliability of center of pressure measures of postural stability in healthy older adults: Effects of postural task difficulty and cognitive load. Gait & Posture 33 (4):651-655
- 25. Murray HC, Elliott C, Barton SE, Murray A (2000) Do patients with ankylosing spondylitis have poorer balance than normal subjects? Rheumatology 39 (5):497-500
- 26. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 53 (4):695-699. doi:10.1111/j.1532-5415.2005.53221.x
- 27. Palmerini L, Rocchi L, Mellone S, Valzania F, Chiari L (2011) Feature selection for accelerometer-based posture analysis in Parkinson's disease. Information Technology in Biomedicine, IEEE Transactions on 15 (3):481-490
- 28. Powell LE, Myers AM (1995) The Activities-specific Balance Confidence (ABC) Scale. J Gerontol A Biol Sci Med Sci 50A (1):M28-34
- 29. Qiu F, Cole MH, Davids KW, Hennig EM, Silburn PA, Netscher H, Kerr GK (2013) Effects of textured insoles on balance in people with Parkinson's disease. PloS one 8 (12):e83309. doi:10.1371/journal.pone.0083309
- 30. Rine RM, Schubert MC, Whitney SL, Roberts D, Redfern MS, Musolino MC, Roche JL, Steed DP, Corbin B, Lin CC, Marchetti GF, Beaumont J, Carey JP, Shepard NP, Jacobson GP, Wrisley DM, Hoffman HJ, Furman G, Slotkin J (2013) Vestibular function assessment using the NIH Toolbox. Neurology 80 (11 Suppl 3):S25-31. doi:10.1212/WNL.0b013e3182872c6a
- 31. Rocchi L, Chiari L, Horak FB (2002) Effects of deep brain stimulation and levodopa on postural sway in Parkinson's disease. Journal of Neurology, Neurosurgery & Psychiatry 73 (3):267-274
- 32. Rochester L, Nieuwboer A, Lord S (2011) Physiotherapy for Parkinson's disease: defining evidence within a framework for intervention. NeurodegenDisManage 1 (1):57-65
- Ruhe A, Fejer R, Walker B (2010) The test–retest reliability of centre of pressure measures in bipedal static task conditions–A systematic review of the literature. Gait & Posture 32 (4):436-445

- 34. Ruhe A, Fejer R, Walker B (2013) Does postural sway change in association with manual therapeutic interventions? A review of the literature. Chiropractic & Manual Therapies 21 (1):9
- 35. Schmidt RA, Lee T (2011) Motor control and learning: A behavioral emphasis (5th ed.). . Champaign, IL: Human Kinetics Publishers.,
- 36. Schoneburg B, Mancini M, Horak F, Nutt JG (2013) Framework for understanding balance dysfunction in Parkinson's disease. Mov Disord
- 37. Schrag A, Barone P, Brown RG, Leentjens AF, McDonald WM, Starkstein S, Weintraub D, Poewe W, Rascol O, Sampaio C, Stebbins GT, Goetz CG (2007) Depression rating scales in Parkinson's disease: critique and recommendations. Mov Disord 22 (8):1077-1092. doi:10.1002/mds.21333
- 38. Smets EM, Garssen B, Bonke B, De Haes JC (1995) The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. Journal of psychosomatic research 39 (3):315-325
- 39. Stebbins GT, Goetz CG, Burn DJ, Jankovic J, Khoo TK, Tilley BC (2013) How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: comparison with the unified Parkinson's disease rating scale. Mov Disord 28 (5):668-670. doi:10.1002/mds.25383
- Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE (2010) Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 25 (15):2649-2653. doi:10.1002/mds.23429
- Whitney SL, Roche JL, Marchetti GF, Lin CC, Steed DP, Furman GR, Musolino MC, Redfern MS (2011) A comparison of accelerometry and center of pressure measures during computerized dynamic posturography: a measure of balance. Gait Posture 33 (4):594-599. doi:10.1016/j.gaitpost.2011.01.015