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Trunk accelerometry reveals postural instability in untreated Parkinson's disease☆

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ABSTRACT

While several studies have shown that subjects with advanced Parkinson's disease (PD) exhibit abnormalities in sway parameters during quiet standing, abnormalities of postural sway associated with untreated PD have not been reported. Although not clinically apparent, we hypothesized that spontaneous sway in quiet stance is abnormal in people with untreated PD.

We examined 13 subjects, recently diagnosed with PD, who were not yet taking any anti-parkinsonian medications and 12 healthy, age-matched control subjects. Postural sway was measured with a linear accelerometer on the posterior trunk (L5 level) and compared with traditional force plate measures of sway. Subjects stood for 2 min under two conditions: eyes open (EO) and eyes closed (EC).

One of the most discriminative measures of postural changes in subjects with untreated PD was the increased 'JERK' of lower trunk in the EO condition, measured with the accelerometer. Root mean square and the frequency dispersion of postural sway in the EO condition also discriminated sway in untreated PD subjects compared to control subjects.

We conclude that accelerometer-based sway metrics could be used as objective measures of postural instability in untreated PD. Accelerometer-based analysis of spontaneous sway may provide a powerful tool for early clinical trials and for monitoring the effects of treatment of balance disorders in subjects with PD.

1. Introduction

Postural instability is an inevitable feature of Parkinson's disease (PD), clinically apparent in the advanced stages of the disease. Postural instability in PD is associated with: i) reduced magnitude of postural responses [1], ii) reduced anticipatory postural adjustments [2], and iii) reduced limits of stability [3]. Due to an inability to adequately balance the body's center of mass over its base of support, subjects with Parkinson's disease are at a high risk for falling, especially as the disease progresses.

To the best of our knowledge, the control of postural stability in quiet stance before any treatment has started, has never been investigated in PD, except for a study by Frenklach et al. [4], which found normal postural sway in 18 untreated subjects. However, that study only measured the peak-to-peak amplitude of postural sway in the antero–posterior direction using a Neurocom platform. Other studies have shown that subjects with PD exhibit abnormalities in spontaneous body sway during quiet stance using force plate measures of sway area and velocity [5–7]. However, in all of these studies, the PD subjects had already started dopaminergic treatment, which has been shown to increase postural sway [8,9].

Sway area has been related to the effectiveness of, or the stability achieved by, the postural control system, whereas mean velocity has been related to the amount of regulatory activity associated with this level of stability [10,11]. Thus, patients with untreated PD, who do not show clinical signs of balance or gait problems, may achieve the same level of stability as age-matched healthy control subjects, as reflected by normal sway area, but with more frequent corrections of postural sway, as reflected by abnormal higher derivatives of sway. In order to quantify the amount of these active postural corrections, we introduced a measure of smoothness of postural sway. JERK, the time derivative of acceleration, has been used as an

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empirical measure of the quality of smoothness, especially in cyclic movements [12].

Since patients with untreated PD do not show clinical signs of balance problems, quantitative detection of abnormal control of postural sway could provide an early sign of PD postural instability. Furthermore, since a recent study [13] suggested that dopamine denervation from PET scans is correlated with postural sway, a tool that could assess this subclinical change in postural control could provide a valid and useful instrument for monitoring clinical progression of PD.

Postural sway is usually described indirectly by the fluctuations of the center of pressure (COP) measured with a force plate under the feet [14]. The COP reflects control by the central nervous system of torques exerted on the ground to maintain equilibrium using integrated sensory information derived from visual, vestibular and somatosensory systems. Force plates are typically embedded in the ground and used in a laboratory setting. This type of postural measurement system places minimum constraints on subjects, although its current setup and costs do not currently make this a viable solution for most routine clinical or home-based assessments. Recent technological developments have led to the production of inexpensive, portable systems, based on miniaturized, inertial sensors (accelerometers, gyroscopes), that can reliably measure postural sway during quiet stance more directly [15,16].

The main aims of the present study were to: i) show if subjects with untreated PD demonstrate abnormalities of postural sway, and which sway measures can best differentiate between untreated PD and control subjects ii) demonstrate if a body-worn accelerometer can measure sway abnormalities in a manner comparable to laboratory measures, and iii) determine whether sway measures are related to severity of clinical signs in subjects with early PD.

2. Methods

2.1. Participants

Thirteen subjects with idiopathic PD (7 male and 6 female, 60.4 ± 8.5 years) and 12 age-, height- and weight-matched healthy control subjects (5 male and 7 female, 60.2 ± 8.2 years) were tested. A diagnosis of idiopathic PD was made by a movement disorders neurologist (JGN). Only subjects who were early-to-middle stage in the disease course, had never been treated with dopaminergic or other anti-parkinsonian medication, and were able to walk independently for long distances without assistive devices were invited to participate. Some of the included subjects were untreated because their disease was mild, while others were untreated due to personal choice, despite clinicians concerns; and half of these subjects started dopaminergic medication shortly after this study. Subjects were excluded if they presented any neurological disorders other than PD or if they had any other condition that could affect their balance. Severity of PD was rated by the same trained clinical examiner on the Motor Section (III) of the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr Scale immediately before the experimental sessions (Table 1). All participants provided informed consent according to the Oregon Health & Science University, Institutional Review Board.

2.2. Procedure

All participants were instructed to maintain an upright standing position on a force plate (AMTI OR6-6, Watertown, MA), with arms crossed and heel-to-heel distance fixed at 10 cm. Feet were allowed to be externally rotated at a comfortable amount for each subject [17]. Initial stance position was consistent from trial to trial by tracing foot outlines on the force plate.

Subjects wore an MTX Xsens sensor (49A33G15, XSens, Enschede, NL) with 3-D accelerometers (±1.7 g range), and 3-D gyroscopes (±300°/s range) mounted on the posterior low back at the level of L5, near the body center of mass. The sensing axes were oriented along the anatomical antero-posterior (AP), medio-lateral (ML), and vertical directions.

Nine, 2-min trials were performed consisting of three randomized, blocked repetitions for three different conditions: i) eyes open (EO) with gaze straight ahead at an art poster 6 m ahead, ii) eyes closed (EC), and iii) eyes closed with a concurrent cognitive task. In the present study, we present results for the EO and EC conditions only.

The COP displacement was calculated from the ground reaction forces recorded by the force plate at a 100-Hz sampling frequency and after applying a 10-Hz cut-off, zero-phase, low-pass Butterworth filter. Acceleration signals from the trunk AP and ML directions were collected with a 50-Hz sampling frequency, transformed to a horizontal–vertical coordinate system [16] and filtered with a 3.5 Hz cut-off, zero-phase, low-pass Butterworth filter. This filter was applied also to the COP in order to eliminate possible contributions of tremor at rest which may be present in the range from 4-to-7 Hz [18].

Table 1
Subject characteristics (individual means and group means ± S.E.M).

Subject	Disease duration since diagnosis (months)	UPDRS Motor Score	H&Y	Tremor	Rigidity	PIGD
P1	26	46	3	0	12	5
P2	8	21	1.5	4	2	0
P3	10	35	2	5	5	1
P4	6	18	1	2	5	0
P5	11	32	2	5	9	1
P6	26	33	2	2	9	0
P7	13	45	2.5	6	10	2
P8	8	21	2	2	7	1
P9	15	35	2.5	2	7	4
P10	5	7	1	2	3	0
P11	13	27	2	2	5	0
P12	22	17	1	2	1	0
P13	13	29	2	2	1	0
Mean	14.3	28.15	1.8	2.8	5.8	1.1
Std	6.9	11.2	0.6	1.7	3.5	1.6

Abbreviations: H&Y = Hoehn and Yahr Scale, PIGD = Postural Instability and Gait Disorder subscore, the sum of Items 13–16 (posture, gait, sit to stand, and pull test) in the UPDRS III.

2.3. Data analysis

For each trial, four variables were computed from the resultant planar (2D) displacement of the COP to characterize postural steadiness: 1) root mean square distance (RMS), which quantifies the magnitude of COP displacements; 2) mean velocity (MV); 3) the frequency below which is 95% of the power of the COP displacement power spectra (F95%); and 4) the frequency dispersion (FD), a unitless measure of variability of the frequency content of the power spectral density (0 for a pure sinusoid, it increases with spectral bandwidth to 1). This set of parameters was chosen to adequately characterize different aspect of postural sway, according to Rocchi et al. [19].

The same four parameters were calculated from the resultant 2D acceleration (Acc) measured at L5 level: 1) root mean square acceleration (RMS), which quantifies the magnitude of Acc traces; 2) mean velocity (MV), computed by the integration of the AP and ML components of acceleration; 3) the frequency below which is 95% of power of the Acc traces power spectra (F95%); and 4) the frequency dispersion (FD). In addition, the resultant JERK, an indicator of the smoothness of postural sway, was computed as follows, according to [20]:

$$\mathrm{JERK} = \frac{1}{2}\int_0^t \left(\frac{dAccAP}{dt}\right)^2 + \left(\frac{dAccML}{dt}\right)^2$$

where AccAP and AccML are the acceleration components measured in AP and ML direction, respectively. As a function of the time derivative of the acceleration, JERK can be seen as a measure of the ability to control and/or to decelerate motion and, as such, as a measure of dynamic stability.

For each subject, the mean over the three trials of each parameters was used for statistical analysis.

2.4. Statistical analyses

Each subjects' mean of three trials was used for statistical analysis. A linear mixed model was used to account for the repeated measurements of the same participants in the two conditions (EO and EC), as well as to investigate the effect of groups and interaction between group and condition (treating both group and condition as a fixed effect). A Bonferroni pair-wise correction was applied to account for multiple comparisons ($p < 0.025$ accounting for 2 pair-wise comparison).

A paired Receiver Operating Characteristics (ROC) analysis, in which both individuals with and without disease received the same tests, was carried out to analyze the discriminative ability of COP and Acc parameters. The discriminative ability is defined as the ability to correctly classify subjects into different categories when the true group belonging is known [21]. The ROC curves graph the false-positive rate (1-specificity, control subjects classified as having PD) on the horizontal axis and the true-positive rate (sensitivity, PD subject correctly classified as having PD) on the vertical axis with each point representing a different cut-off value.

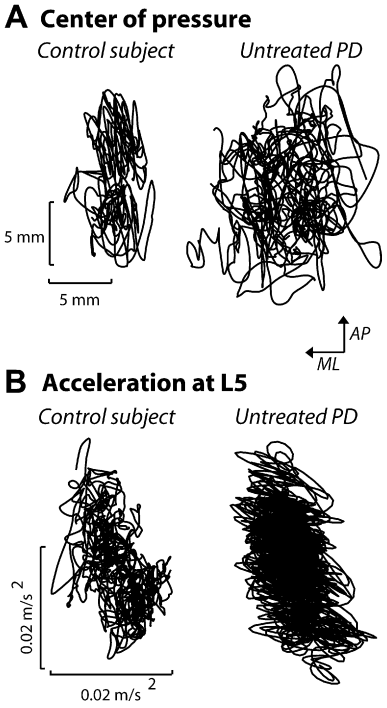

Fig. 1. (A) Center of pressure and (B) corresponding lower trunk acceleration trajectories in the horizontal plane for two representative subjects in the eyes open condition. Left: control subject. Right: untreated PD (P2 in Table 1).

A precise way of characterizing the trace is to look at the area under the ROC curve (AUC) [21]. The AUC values usually range from 0.5 (no separation between groups) to 1 (perfect separation). The AUC, its associated standard error, and confidence intervals for each of the variables were reported.

Obviously, a useful diagnostic test should have a cut-off value at which the true-positive rate is high and the false-positive rate is low (ideally 1 and 0, respectively). The proportion of subjects correctly classified into either of two groups will depend on the selected cut-off value. In addition to the AUC values, we determined the optimal cut-off values for each parameters, cut-off values which maximize sensitivity and specificity. In conjunction with the selected cut-off values, we also reported sensitivity, specificity, and the associated likelihood ratio (LR). The positive LR is calculated as the sensitivity divided by the false-positive rate, the further the LR is from 1, the more useful is the parameter in discriminating the two groups. With an LR > 10, the test gives strong evidence that the subject belong to the PD group. The sensitivity, specificity, and LR of each parameter were reported.

The relation between postural parameters and UPDRS Motor Scores were investigated by Pearson's correlation analysis. All the statistical analyses were performed with NCSS Software, Kaysville, Utah.

3. Results

The COP trajectories and the corresponding accelerations of the lower trunk of a representative control subject and an untreated PD subject during quiet stance EO are illustrated in Fig. 1A and B. The magnitude of both COP and acceleration signals is increased in the subject with untreated PD. In addition, both sway-related signals (COP and acceleration) showed faster components (reflected in more jerky signals) in the untreated PD subject (P11, JERK = 0.41 m^2/s^5) compared to the control subject (JERK = 0.18 m^2/s^5) (Fig. 1). Consistent with these observations, several sway variables, measured with the force plate as well as with the linear accelerometers on the body, showed differences between the untreated PD and control groups.

3.1. COP analysis

The linear mixed model analysis revealed group effects for RMS (F-value = 17.6), F95% (F-value = 31.6), and FD (F-value = 29.55); in addition a condition effect was shown for FD (F-value = 10.2); no interaction effects were present. Compared to the control group, the untreated PD group showed (Table 2, upper panel): i) a larger RMS ($p = 0.01$), a smaller F95% ($p = 0.005$), and a larger FD ($p = 0.008$) in the EO condition; and ii) a smaller F95% ($p = 0.003$) in the EC condition. The untreated PD, but not the control group's sway, had a significantly smaller FD ($p = 0.01$) in the EC condition compared to the EO condition.

Fig. 2A illustrates the ROC analysis for the COP parameters. The most discriminative COP parameters to differentiate untreated PD from control subjects were F95% and FD in the EO condition, which showed an area under the curve (AUC) of 0.90 (95% CI 0.69–0.99) and 0.87 (95% CI 0.68–0.96), respectively (Fig. 2A).

Table 2
Mean (±S.E.M) of COP and L5 acceleration parameters in eyes open (EO) and eyes closed (EC) conditions. Statistical differences between groups and conditions are shown, after Bonferroni correction. (*$p < 0.025$, **$p < 0.001$).

COP parameters

	RMS [mm]		MV [mm/s]		F95% [Hz]		FD	
	EO	EC	EO	EC	EO	EC	EO	EC
Control subjects	4.9 (0.4)	5.4 (0.5)	7.7 (0.7)	10.2 (1.2)	1.50 (0.07)	1.64 (0.06)	0.77 (0.01)	0.75 (0.01)
Untreated PD	7.3 (0.5)	7.2 (0.4)	6.8 (0.5)	9.1 (0.8)	0.98 (0.06)	1.16 (0.06)	0.83 (0.08)	0.78 (0.01)
	*				**	**	*	*

ACC L5 parameters

	RMS [m/s²]		MV [m/s]		F95% [Hz]		FD	
	EO	EC	EO	EC	EO	EC	EO	EC
Control subjects	0.068 (0.003)	0.078 (0.004)	1.12 (0.11)	1.29 (0.12)	1.83 (0.12)	1.81 (0.08)	0.78 (0.01)	0.78 (0.01)
Untreated PD	0.106 (0.011)	0.094 (0.007)	1.79 (0.24)	1.69 (0.20)	1.52 (0.13)	1.60 (0.14)	0.83 (0.01)	0.81(0.01)
	**		*					

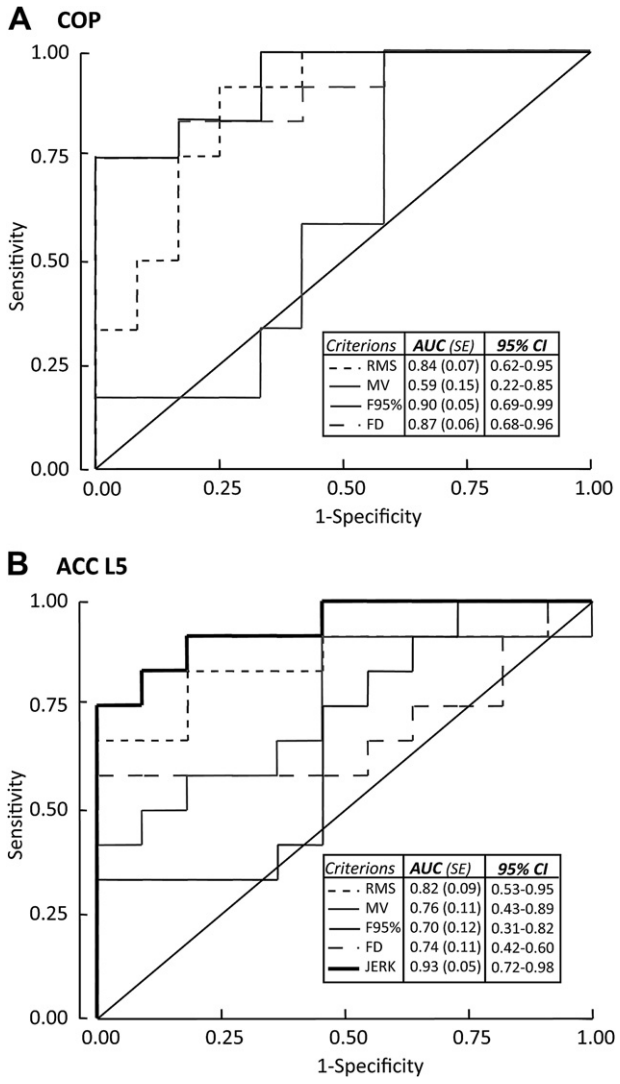

Fig. 2. ROC curves in the eyes open condition for: A) COP parameters, B) lower trunk acceleration parameters. AUC = area under the curve for each parameter. CI = confidence interval.

3.2. Acceleration analysis

The linear mixed model analysis revealed group effects for JERK (F-value = 30.4), RMS (F-value = 29.4), and MV (F-value = 4.7); no condition or interaction effects were present. In detail, for the EO condition, untreated PD subjects compared to the control group showed (Table 2, lower panels) larger RMS ($p = 0.002$) and larger MV ($p = 0.02$) as computed from the lower back acceleration. Surprisingly, differences in sway variables measured with accelerometers were not significant between groups in the EC condition.

PD subjects also showed larger JERK than control subjects in the EO condition ($p = 0.001$) (Fig. 3), but not in the EC condition. The ROC analysis revealed an AUC of 0.93 (95% CI 0.72 to 0.98) for JERK of the lower back acceleration in the EO condition, which was the highest discriminative value (both the low and high CI are larger) of all COP and acceleration parameters (Fig. 2B).

In addition, optimal cut-off values with relative sensitivity and specificity for COP and ACC L5 parameters are showed in Table 3. JERK showed the largest LR (9) of all the parameters based on its sensitivity and specificity.

No significant correlation was found between COP or acceleration parameters and UPDRS III Motor Summary Score or Sub-scores.

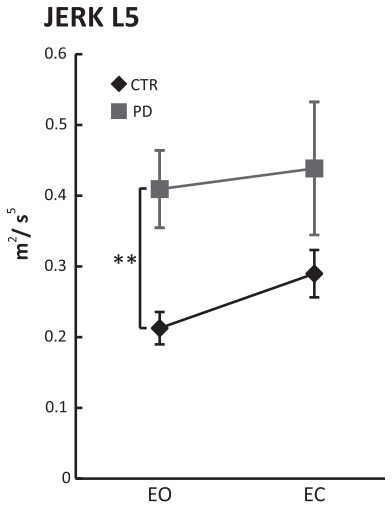

Fig. 3. Comparison of group mean JERK in PD and control subjects. The mean values (±S.E.M) of JERK of the lower trunk are presented. Significant differences, after Bonferroni correction, are showed with $^{**}p < 0.01$.

Note that even subjects with low Motor UPDRS scores (P2, P4, P8, and P12) can show high levels of JERK in their postural sway (Fig. 4).

Finally, a power analysis using the program Gpower [22] was carried out using a *t*-test between means with alpha at 0.05. This analysis reveals an achieved power (1-β) over 0.9 in all parameters except three (0.11 for COP MV, 0.4 for ACC MV, 0.6 for ACC F95%).

4. Discussion

The key findings of this study are: 1) postural control is affected in subjects with untreated PD; 2) acceleration-based parameters are able to distinguish between the two groups as well as COP parameters.

Our results showed, for the first time, that postural control is impaired in subjects with untreated PD, even when it is not clinically apparent (12 out of 13 subjects had normal stepping responses to the pull test). Previous studies examining postural sway during quiet stance in subjects with PD presented inconsistent results. Some studies [4,8] agree that postural sway is abnormal in PD, whereas others [4,23] did not find differences between PD and control subjects. The majority of studies focused on the advanced stages of the disease, when levodopa medication and dyskinesia increase postural sway [8,24]. Partially consistent with our results, recent studies [5–7] focusing on earlier stages of the disease, also showed subclinical signs of postural instability, using force plates. However, all of the previous studies included subjects who had already started dopaminergic treatment, and were tested in the ON state [6,7] or, in one study [5], tested OFF and ON medication. Sway in subjects with PD who are in the ON state has been shown to be larger and faster than when in the OFF state, perhaps because levodopa reduces rigidity without improving control of posture, or because subclinical dyskinesia increases body motion [8].

Unlike a previous study by Frenklach A. et al. [4], we found larger postural sway area in untreated PD compared to age-matched control subjects. The differences in results are likely due to how postural sway area was measured. Frenklach et al. [4], used only peak-to-peak, anterior–posterior, postural sway amplitude, whereas we used 2D RMS, that is, sway variability in both the AP and ML directions. In fact, ML sway area may be more affected than AP sway in PD [25]. Increased postural sway in untreated PD might reflect noisy somatosensory feedback from foot pressure, muscle proprioceptors and joint receptors in the postural control loop,

Table 3
Sensitivity, Specificity, and Likelihood ratio for COP and Acc parameters related to the ROC curves of Fig. 2. Further, Effect Size values are reported for COP and Acc parameters (a value of 0.20 represents a small change, 0.50 a moderate change, and 0.80 a large change).

Criterions	Cut-off value interval (c)	Sensitivity (95% CI)	Specificity (95% CI)	LR (95% CI)	Effect size
COP parameters					
RMS	$6.39 > c \geq 6.26$ [mm]	0.75 (0.43–0.94)	0.83 (0.52–0.98)	4.5 (3–6.8)	1.65
MV	$8.71 \geq c > 8.63$ [mm/s]	0.91 (0.61–0.99)	0.42 (0.61–0.99)	1.6 (0.8–3.1)	−0.33
F95%	$1.18 \geq c > 1.17$ [Hz]	0.91 (0.61–0.99)	0.83 (0.52–0.98)	5.5 (4.1–7.5)	−2.09
FD	$0.82 > c \geq 0.80$ [−]	0.91 (0.61–0.99)	0.82 (0.52–0.98)	5.5 (4.1–7.5)	2.4
Acc parameters					
RMS	$0.088 > c \geq 0.081$ [m/s^2]	0.82 (0.52–0.98)	0.82 (0.52–0.98)	4.5 (3–6.9)	1.93
MV	$1.82 > c \geq 1.68$ [m/s]	0.55 (0.28–0.85)	0.82 (0.52–0.98)	6.0 (3.5–11)	1.52
F95%	$1.76 \geq c > 1.70$ [Hz]	0.73 (0.42–0.94)	0.55 (0.27–0.84)	1.6 (1–3.2)	0.58
FD	$0.84 > c \geq 0.81$ [−]	0.63 (0.30–0.89)	1.00 (0.71–1.00)	7.0 (4.3–11)	−0.78
JERK	$0.46 > c \geq 0.40$ [m^2/s^5]	0.82 (0.52–0.98)	0.91 (0.62–1.00)	9.0 (6.2–13)	1.98

resulting in inaccurate information about body position in space and an abnormal internal map of stability limits [3,8]. Frequent corrections of postural sway direction in untreated PD may be responsible for higher JERK compared to control subjects and might reflect attempts to compensate for poor proprioceptive control of posture with longer-loop, visual postural feedback.

Surprisingly, the PD subjects did not show more dependence upon vision to control postural sway than control subjects. Studies show that subjects with PD are very dependent upon vision for accurate pointing or stepping tasks due to impaired use of proprioception [26,27]. In contrast, in our study, the EO condition was best for differentiating postural sway in untreated PD subjects from age-matched control subjects. The fact that PD subjects are not able to increase reliance on vision for postural control when their eyes are open as much as control subjects may reflect a problem with sensory re-weighting in patients with PD.

One of the parameter that best discriminated postural sway between untreated PD and control subjects was JERK of the lower trunk. JERK, the relative smoothness of postural sway can be interpreted as a measure of dynamic stability, reflecting the amount of active postural corrections. It is not likely due simply to changes in postural tone or movement speed clinically apparent in untreated PD because it did not correlate with the Motor UPDRS or its rigidity or bradykinesia subcomponents. It is possible, however, that increased JERK reflects increases in axial rigidity at the trunk that is not measured in the UPDRS but can shown to be increased in early-to-moderate PD using sensitive torque measures [28]. The JERK increase in our subjects was not due to resting tremor because we low-pass filtered the acceleration signals at 3.5 Hz to eliminate parkinsonian resting tremor that ranges from 4 to 7 Hz and JERK did not correlate with Motor UPDRS tremor. Studies of patients with Parkinson's disease [29] reported statistically significant abnormalities of JERK measures in handwriting likely related to a reduced capability to coordinate the finger and wrist and by reduced control of wrist flexion.

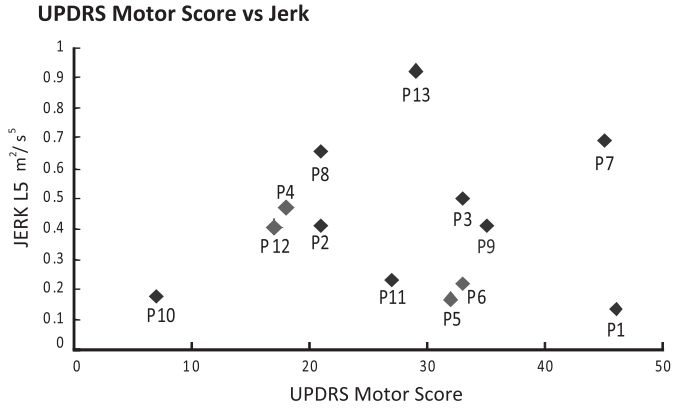

Fig. 4. UPDRS Motor score versus JERK in PD subjects.

None of the sway parameters were related to severity of disease as measured with the Motor UDPRS. The lack of relationship between both COP and accelerometer measures of postural sway and the UPDRS motor signs might suggest that postural sway during stance measures neural control processes that are independent of, and in addition to, the traditional, clinical signs of PD. These results are not surprising, since the UPDRS only dedicates one item to measure postural instability (the Pull test) and this item is not sensitive to mild impairments of postural control [30].

In summary, we demonstrated that postural control is compromised in untreated PD, and that accelerometers on the lower back can detect those impairments at least as well as a force plate. An accelerometer attached to a patient's belt is a practical, inexpensive alternative to force plate measures of postural sway because it is an unobtrusive and accurate measure of postural control that can be used in a clinic or community setting.

Future studies, in a larger population, are needed to: i) confirm these preliminary findings on the accuracy of Acc measures, and ii) determine the reliability and sensitivity of accelerometry-based measures of postural sway. Longitudinal studies of postural sway are also needed to determine if acceleration parameters might be a sensitive descriptor of disease progression and hence useful in clinical trials of neuroprotective interventions.

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