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Longitudinal changes over thirty-six months in postural control dynamics and cognitive function in people with Parkinson's disease

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Abstract

Background: Postural instability is a common motor feature in people with Parkinson's disease (PD) together with non-motor features such as cognitive dysfunction. Management of postural instability is challenging as it is often resistant to dopaminergic therapy. Greater knowledge of postural control is essential to understand postural instability in PD.

Research Question: This study aimed to answer how postural control differs in people with PD compared to healthy older adults (HOA). Additionally, postural control changes over a 36 month period and its relationship to cognitive impairment and motor scores were investigated.

Methods: The study group consisted of 50 people diagnosed with PD and 59 HOAs, recruited as part of an incident cohort study (ICICLE-GAIT). Participants stood still for 2 minutes, eyes open and arms by their side. A single tri-axial accelerometer (Axivity AX3, York, UK) on the lower back recorded acceleration. Measurements were taken at 18, 36 and 54 months after recruitment. Sample entropy (SampEn), which measures signal predictability, was determined for the accelerometry data. Cognitive tests included the Montreal Cognitive Assessment and the Unified Parkinson's Disease Rating Scale (UPDRS III) quantified motor function. Linear mixed models, regression analysis and correlation analysis were applied to the data.

Results: Results indicated that SampEn was greater for the PD group at all three time-points and along all three axes. However, there was no increase of SampEn with disease progression. Higher SampEn values were associated with greater cognitive impairment and lower UPDRS III, although correlations were weak. There was a difference between axial directions and cognitive and motor scores.

Significance: People with PD exhibit decreased regularity of trunk dynamics when standing compared to HOAs. Nonlinear accelerometer metrics along all three axes are therefore a

potential biomarker of PD. The relationship between trunk dynamics and cognitive function indicates common neural pathways.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease with a worldwide prevalence greater than 1% in adults over 70 [1]. Early motor symptoms include rigidity, bradykinesia, tremor and gait impairment with postural instability emerging as the disease progresses [2]. Postural instability is a known predictor of falls with consequential impact on wellbeing [3]. Over 20% of people with PD have also been reported to have mild cognitive impairment (MCI) at initial diagnosis [4]. Changes in cognitive function are associated with postural instability [5, 6] and with an increased risk of falls [7, 8]. A neuroimaging study supports the link between cognitive function and falling in PD with reduced grey matter reported in the posterior caudate (associated with cognitive function) in fallers compared to fallers [8]. Management of postural instability is challenging as it is often resistant to dopaminergic therapy [9]. Nonpharmaceutical interventions include different treadmill training protocols which show limited improvements in gait and balance [10, 11].

Clinically, assessment of postural instability is the Pull test, included in the Unified Parkinson's Disease Rating Scale (UPDRS III), which is insensitive to small changes in postural stability [12]. Objectively, postural stability has been assessed through centre of pressure (COP) parameters recorded from a force platform [13] and more recently, from body-worn monitors such as accelerometers [14-16]. The derived postural parameters are generally linear, providing information about signal characteristics averaged across time. However, as postural stability is a function of postural control, parameters that reflect underlying neural control mechanisms may yield additional information. For example, people with PD have reduced automatic control and greater conscious control of posture [17, 18]. This altered regulatory mechanism may present as a change in regularity or predictability of postural parameters.

The purpose of this study was to investigate predictability of postural trunk dynamics through nonlinear analysis of tri-axial accelerometer signals. We included vertical accelerometry data as postural control operates in three dimensions and changes in perception of the postural vertical in older adults have been postulated [19]. We compared postural trunk predictability in people with recently diagnosed PD to postural trunk predictability in healthy older adults (HOA). Additionally, we investigated changes in this parameter over a 36 month period and its relationship to cognitive dysfunction. We hypothesised that (1) Postural trunk predictability is different in people with PD due to the loss of automatic control; (2) Postural trunk predictability changes over time in people with PD, as a result of increasing loss of automatic motor behaviour; (3) Postural trunk predictability is correlated with clinical measures of cognitive dysfunction, reflecting common dysfunctional neural pathways. This analysis may offer information about the underlying postural control mechanisms, its application as an early biomarker and as an indicator of disease progression.

METHODS

Study design

This study was approved by the Newcastle and North Tyneside Research Ethics Committee (project registration number 09/H0906/82). The study group consisted of 50 people (17 female) recently diagnosed with PD and 59 HOA (26 female), recruited as part of the Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation-GAIT (ICICLE-GAIT) study conducted between June 2009 and December 2011. Postural and cognitive assessments were undertaken at approximately 18 months, 36 months and 54 months after the baseline assessment. All participants were monitored for at least two of the three sessions and all had an assessment at 54 months to eliminate bias that may arise from the more severely impaired participants leaving the study early (Table 1).

Participants

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. Diagnosis of idiopathic PD was made according to the UK Parkinson's Disease Brain Bank criteria. Exclusion criteria included significant memory impairment (Mini Mental State Exam (MMSE) < 24 [6]), dementia with Lewy bodies or poor command of English. This study was conducted according to the declaration of Helsinki and all participants signed an informed consent form prior to testing.

Demographic and clinical measures

Age, sex and body mass index (BMI) were recorded for each participant. Cognitive tests included the MMSE [20] and also the Montreal Cognitive Assessment (MoCA), which discriminates more effectively MCI and dementia in PD [21] . The UPDRS III was used to assess the level of motor dysfunction with values raging from 0 (no motor symptoms) to 132 (severe motor symptoms) [22].

Standing balance test

Participants were instructed to stand still, with shoes on, hands by their sides, within a rectangular area (400 mm wide × 600 mm long), while looking straight ahead for 2 minutes. Stance width was not controlled for. The PD participants were tested approximately 1 hour after medication intake.

Equipment

A single tri-axial accelerometer (Axivity AX3, York, UK) on the lower back recorded acceleration at a sampling rate of 100 Hz [14].

Data processing

The tri-axial accelerometry data were exported to the MATLAB® (R2015a, Mathworks, Natick, MA) environment, downsampled to 10 Hz and rotated using the Moe-Nilssen transformation into anteroposterior, mediolateral and vertical accelerations [14, 23]. No filtering was applied. A nonlinear method that quantifies predictability is sample entropy (SampEn), defined as the logarithmic probability that two sequences, similar for *m* points extracted from a time-series, will remain similar at a sequence length of $m + 1$ [24]. Higher values of SampEn indicate low predictability whereas lower values indicate high predictability. SampEn was calculated for accelerations along the three axes, using the method described by Richman and Moorman (2000) [24]. A vector length of 2 and tolerance of 0.2 were selected, based on analysis of combinations of different vector lengths (1,2,3,4) and tolerances (0.1, 0.15, 0.2, 0.25) [25, 26] (see Supplementary Material Appendix 1). Signal nonlinearity was assessed by applying the rank sum test to SampEn values for nineteen surrogate signals generated using the Iterated Amplitude Adjusted Fourier Transform (IAAFT) which preserves the power spectrum and linear correlations [27].

Data analysis

Only nonlinear signals, those with SampEn less than the surrogate signals' SampEn, were included in the analysis as application of nonlinear methods requires the timeseries to contain nonlinear structures. All statistical analyses were performed in SPSS (v21, IBM, Chicago, Il., USA), $p < 0.05$. Differences in SampEn between groups (i.e., people with PD vs HOA) and time-point (i.e., 18 months, 36 months and 54 months) were analysed using linear mixed models, which models missing data, and regression analysis. Sidak corrections for multiple comparisons were applied to the *post hoc* analyses. Pearson's and Spearman's correlation were used to explore associations between SampEn and MoCA, MMSE and UPDRS III.

RESULTS

Demographic and cognitive data

The age range of participants across the three time-periods was 44.9–92.0 years for the PD group and 53.7–90.8 years for the HOA. The PD group were significantly younger ($F_{1, 280}$=10.3, p=0.001). There was a smaller proportion of females in the PD group compared to the HOA group (34% versus 44%), and they had a lower MoCA score ($F_{1, 280}$=7.3, p=0.007) (Table 1).

Sample entropy

a) Signal nonlinear characterization

Figure 1 illustrates representative 20 second tri-axial accelerometer data for a person with Parkinson's and a healthy older adult. The SampEn values of accelerometry signals along the mediolateral and vertical axes were less than SampEn for the surrogate signals for over 80% of the signals, indicating nonlinear properties. The percentage of nonlinear signals for anteroposterior signals was lower, particularly at 18 months (HOA 63.3% nonlinear, PD group 54.8% nonlinear) due to greater noise on the anteroposterior axis associated with the physical construction of the accelerometer. A small percentage of signals had a SampEn greater than the surrogate SampEn (see Supplementary Material Appendix 2) reflecting the statistical nature of the rank-sum test and limited surrogate signals generated.

b) Group, time and interaction effects on sample entropy

i) *Group*

SampEn was greater for the PD group compared to the HOA along all three axes and all three time-points (anteroposterior: $F_{1, 101}$=15.2, p<0.001; mediolateral: $F_{1, 99}$=18.3, p<0.001;

vertical, $F_{1, 103}$=16.0, p<0.001) (Figure 2). The SampEn in the anteroposterior direction was significantly less ($F_{2, 477}$=62.0, p<0.001) than in the mediolateral and vertical directions.

ii) *Time-period*

Time was significant for SampEn ($F_{2, 139}$=3.08, p=0.049) in the anteroposterior direction. Pairwise comparisons were tending to significance (p=0.055) between 18 months and 54 months across groups with SampEn decreasing between these time-points (Figure 2). Regression analysis showed a significant decrease with time (p=0.009) for SampEn in the anteroposterior direction only with no difference in decline between groups.

iii) *Interaction between group and time-point.*

No significant interaction effects were found for group and time-point along any axes, indicating no difference in pattern of temporal change in SampEn between the groups.

c) ***Association between sample entropy and clinical measures***

All Pearson's correlation coefficients and Spearman's rho had a magnitude below 0.3, The MoCA, MMSE and UPDRS III are semi-quantitative in nature [28] and have a ceiling effect which may account for the weak correlations in addition to the heterogenous nature of the PD group. We therefore report on weak correlations, r>0.2.

i) Cognitive clinical scores

There was a weak negative correlation between SampEn and both MoCA and MMSE scores along the anteroposterior and vertical axes at 54 months (Table 2, Figure 3), with better cognitive function associated with lower SampEn. Additionally, SampEn in the vertical direction was negatively correlated at 36 months with cognitive scores (Table 2, Figure 3). There was no correlation greater than 0.2 between SampEn in the mediolateral direction and cognitive measures for any time-point (Table 2).

ii) Motor Clinical Score (UPDRS III)

SampEn along all 3 axes showed positive correlations with UPDRS III, although at differing time-points (Table 2, Figure 3). Mediolateral and vertical SampEn had the strongest association with UPDRS III, with positive correlations at 18 months (mediolateral: $r = 0.218$, vertical: $r = 0.200$) and 36 months (mediolateral: $r = 0.281$, vertical: $r = 0.281$), indicating better motor function is related to lower SampEn.

DISCUSSION

This study investigated three dimensional postural dynamics in people with PD and HOA over a 36 month period, through SampEn analysis of trunk accelerometry signals. Trunk acceleration is less predictable in people with PD when standing, suggesting less constrained regulation of posture is associated with reduced automatic control, confirming our first hypothesis. We did not observe any progression of postural movement unpredictability with time in the people with PD, contrary to our second hypothesis. Instead, we observed that both people with PD and HOA develop more predictable patterns of postural movement over a thirty-six month period along the anteroposterior axis. We found weak positive correlations between postural movement predictability and clinical motor function and weak negative correlation between postural movement predictability and cognitive scores, partially supporting our third hypothesis.

Lower predictability of postural movements in people with PD. SampEn was greater along all three axes in people with PD compared to older adults, indicating greater unpredictability of postural movement. No previous study, to the best of the authors' knowledge, has examined nonlinear analysis of accelerometry signals during standing in people with PD. Results from nonlinear analysis of postural COP signals in people with PD are inconsistent. Pelykh et al. (2015) reported no difference in the temporal structure of the resultant COP signal between people with PD (non-freezers) and a control group [29]. Although trunk

accelerometer and COP measures are correlated, it is not known if the same holds for nonlinear measures and therefore how valid comparisons are [30].

Nonlinear analysis of postural accelerometer signals has been undertaken in non-PD populations. Lamoth et al. (2012) reported that SampEn for postural accelerometer signals was higher for older adult ice-skaters than non-skating older adults and similar to young adults [31]. They concluded that the greater postural unpredictability in older adult skaters represents greater signal complexity and improved ability to respond to perturbations. In our study, we have observed that SampEn is greater in people with PD indicating less predictability. However, SampEn does not provide a measure of complexity as random signals have higher SampEn [32] .

The increased SampEn in the people with PD indicates altered postural motor control which may be explained by impairment of neural pathways associated with sensorimotor integration and cortical regions involved with habitual control of movement [33]. This neural dysfunction will impact the closed-loop system of postural motor control with diminished fine adjustments in response to internal and external sensory changes resulting in greater irregularity in postural movements. This explanation is supported by a study investigating finger pressures in people with PD when compressing a spring. Nonlinear attractor reconstruction was applied to the pressures and weaker attractors and more chaotic phase portraits were found in people with PD compared to older adults suggesting impairment of closed-loop motor control [34].

Temporal changes in sample entropy. The time-period was significant only for SampEn in the anteroposterior direction across both groups, with a decrease tending to significance between 18 months and 54 months. These findings are similar to a study investigating accelerometry linear metrics over a 12 month period in HOA and people with PD [15]. This

suggests that adaptive postural control mechanisms are already well integrated in PD at 18 months and further change over time follows the normal ageing process, with increased predictability of trunk dynamics. The challenge is to find at what stage the temporal structure of the postural signal in PD starts to diverge from that of the HOA.

Cognition and sample entropy. We observed weak negative correlations between SampEn and cognitive measures, supporting our third hypothesis. Although the MMSE is less sensitive for mild cognitive impairment than MoCA as [35], both showed negative correlations at 36 months and 54 months. No correlation was observed at 18 months, probably due to high cognitive function and the ceiling effect of the tests (Table 1). The correlation between SampEn and cognition was only present for the anteroposterior and vertical components. The relationship may be interpreted either as independent parallel declines in postural or cognitive function or deterioration in neural pathways common to both motor and cognitive function. Further neuroimaging studies are needed to clarify the association.

Lower postural predictability is associated with greater movement impairment. SampEn correlated positively although weakly, with the UPDRS III, indicating lower postural predictability is associated with greater movement impairment. This finding is surprising as the UPDRS III contains only one test, the Pull test, that relates directly to postural instability [12]. The positive association suggests that temporal structure of postural movement is an indicator of more general motor control function. A previous study reported no correlation between linear acceleration parameters (e.g. jerk) and UPDRS III [16]. However, none of the patients in Mancini et al.'s study were on dopaminergic or other antiparkinsonian treatment, whereas in our study all patients were on medication. Levodopa has been reported to increase postural sway [36]. Correlation analysis between levodopa equivalent dose (LEDD) and SampEn revealed negative correlation at the 18 months time-point (anteroposterior SampEn,

r = -0.364; mediolateral SampEn, r = -0.244; vertical SampEn, r = -0.244). Variations in patients' medication in addition to the different parameters assessed may explain the conflicting results. Changes in dosage and responsiveness to dopaminergic medication may account for the increase followed by decrease in SampEn over 36 months (Figure 2).

Direction of postural control is differentially associated with cognitive and motor function. Vertical acceleration SampEn had the most correlations with both cognitive function and motor function. Postural control when standing places less constraint on vertical movement compared to anteroposterior and mediolateral movement as balance is less affected by vertical movement. Control of vertical acceleration may be related more to goal directed postural control involving the prefrontal cortex rather than habitual control, with consequential greater links to cognitive function. The association of vertical SampEn with the clinical motor score can be explained by the more complex neural control strategy employed in vertical acceleration of the trunk, with a greater number of muscles activated and joints involved. The association between mediolateral SampEn and motor function is supported by another study which reported that mediolateral sway measures are more sensitive at detecting differences in sway than anteroposterior measures [15]. Sensorimotor integration is differentially affected leading to diverse ankle and hip/trunk strategies with hip/trunk strategy more associated with lateral sway [37]. An additional explanation is that people with PD have a smaller stance width which is likely to result in greater ML movement [38, 39]. A negative weak correlation was found between SampEn in the anteroposterior direction and cognitive function. Riley et al. reported a similar link between postural nonlinear measures in the anteroposterior direction and cognitive tasks but not the mediolateral direction [40].

Limitations.

This study has several limitations. We investigated a small number of people with PD presenting with diverse phenotypes who received different types and dosages of medication. They also varied in extent of postural impairment and level of cognitive function. Many of the older and PD participants had additional co-morbidities, such as low back pain or lower limb joint degeneration that may account for some of the differences in trunk acceleration. Stance width was not controlled for, which might have affected acceleration. Another limitation is that not all participants were present for all three sessions. However, we applied the linear mixed model which models the missing data. A further limitation is that several signals we included as deterministic, may have been identified as nondeterministic if we had increased the number of surrogates. The MoCA, MMSE and UPDRS III scores are semi-quantitative and have a ceiling effect which may account for the weak correlations we found.

CONCLUSION

Sample entropy of postural acceleration provides a sensitive measure to distinguish people with PD from HOA. However, it does not monitor progression of PD. A novel finding is the association of postural control in the anteroposterior and vertical directions with cognitive function and mediolateral direction with motor function. Further studies will determine how these nonlinear parameters relate to underlying neural correlates and clinical function.

REFERENCES

[1] T. Pringsheim, N. Jette, A. Frolkis, T.D. Steeves, The prevalence of Parkinson's disease: a systematic review and meta-analysis, Mov. Disord. 29 (2014) 1583-1590.

[2] A. Schrag, Y. Ben-Shlomo, N. Quinn, How common are complications of Parkinson's disease?, J. Neurol. 249 (2002) 419-423.

[3] D.R. Williams, H.C. Watt, A.J. Lees, Predictors of falls and fractures in bradykinetic rigid syndromes: a retrospective study, J. Neurol. Neurosurg. Psychiatry 77 (2006) 468-473.

[4] R.A. Lawson, A.J. Yarnall, G.W. Duncan, D.P. Breen, T.K. Khoo, C.H. Williams-Gray, et al., Cognitive decline and quality of life in incident Parkinson's disease: The role of attention, Parkinsonism Relat. Disord. 27 (2016) 47-53.

[5] T. Kido, Y. Tabara, M. Igase, N. Ochi, E. Uetani, T. Nagai, et al., Postural instability is associated with brain atrophy and cognitive impairment in the elderly: the J-SHIPP study, Dement. Geriatr. Cogn. Disord. 29 (2010) 379-387.

[6] D. Xu, M.H. Cole, K. Mengersen, P.A. Silburn, F. Qiu, C. Graepel, et al., Executive function and postural instability in people with Parkinson's disease, Parkinsons Dis. 2014 (2014) 684758

[7] O. Segev-Jacubovski, T. Herman, G. Yogev-Seligmann, A. Mirelman, N. Giladi, J.M. Hausdorff, The interplay between gait, falls and cognition: can cognitive therapy reduce fall risk?, Expert Rev. Neurother. 11 (2011) 1057-1075.

[8] K. Rosenberg-Katz, T. Herman, Y. Jacob, A. Mirelman, N. Giladi, T. Hendler, et al., Fall risk is associated with amplified functional connectivity of the central executive network in patients with Parkinson’s disease, J. Neurol. 262 (2015) 2448-2456.

[9] M.L. Muller, R.L. Albin, V. Kotagal, R.A. Koeppe, P.J. Scott, K.A. Frey, et al., Thalamic cholinergic innervation and postural sensory integration function in Parkinson's disease, Brain 136 (2013) 3282-3289.

[10] M.S. Bryant, C.D. Workman, J.G. Hou, H.K. Henson, M.K. York, Acute and Long-Term Effects of Multidirectional Treadmill Training on Gait and Balance in Parkinson Disease, P.M. R. 8 (2016) 1151-1158.

[11] S. Klamroth, S. Steib, H. Gassner, J. Gossler, J. Winkler, B. Eskofier, et al., Immediate effects of perturbation treadmill training on gait and postural control in patients with Parkinson's disease, Gait Posture 50 (2016) 102-108.

[12] B.R. Bloem, D.J. Beckley, B.J. van Hilten, R.A.C. Roos, Clinimetrics of postural instability in Parkinson's disease, J. Neurol. 245 (1998) 669-673.

[13] D. Winter, Human balance and posture control during standing and walking, Gait Posture 3 (1995) 193-214.

[14] S. Del Din, A. Godfrey, S. Coleman, B. Galna, S. Lord, L. Rochester, Time-dependent changes in postural control in early Parkinson's disease: what are we missing?, Med. Biol. Eng. Comput. 54 (2016) 401-410.

[15] M. Mancini, P. Carlson-Kuhta, C. Zampieri, J.G. Nutt, L. Chiari, F.B. Horak, Postural sway as a marker of progression in Parkinson's disease: a pilot longitudinal study, Gait Posture 36 (2012) 471-476.

[16] M. Mancini, F.B. Horak, C. Zampieri, P. Carlson-Kuhta, J.G. Nutt, L. Chiari, Trunk accelerometry reveals postural instability in untreated Parkinson's disease, Parkinsonism Relat. Disord. 17 (2011) 557-562.

[17] J.R. Mahoney, R. Holtzer, M. Izzetoglu, V. Zemon, J. Verghese, G. Allali, The role of prefrontal cortex during postural control in Parkinsonian syndromes a functional near-infrared spectroscopy study, Brain Res. 1633 (2016) 126-138.

[18] P. Redgrave, M. Rodriguez, Y. Smith, M.C. Rodriguez-Oroz, S. Lehericy, H. Bergman, et al., Goal-directed and habitual control in the basal ganglia: implications for Parkinson's disease, Nat. Rev. Neurosci. 11 (2010) 760-772.

[19] G. Barbieri, A.S. Gissot, D. Perennou, Ageing of the postural vertical, Age (Dordr) 32 (2010) 51-60.

[20] M.F. Folstein, S.E. Folstein, P.R. McHugh, "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician, J. Psychiatr. Res. 12 (1975) 189-198.

[21] J.C. Dalrymple-Alford, M.R. MacAskill, C.T. Nakas, L. Livingston, C. Graham, G.P. Crucian, et al., The MoCA: well-suited screen for cognitive impairment in Parkinson disease, Neurology 75 (2010) 1717-1725.

[22] C.G. Goetz, B.C. Tilley, S.R. Shaftman, G.T. Stebbins, S. Fahn, P. Martinez-Martin, et al., Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results, Mov. Disord. 23 (2008) 2129-2170.

[23] R. Moe-Nilssen, A new method for evaluating motor control in gait under real-life environmental conditions. Part 1: The instrument, Clin. Biomech. (Bristol, Avon) 13 (1998) 320-327.

[24] J.S. Richman, J.R. Moorman, Physiological time-series analysis using approximate entropy and sample entropy, Am. J. Physiol. Heart Circ. Physiol. 278 (2000) H2039-2049.

[25] J.M. Yentes, W. Denton, J. McCamley, P.C. Raffalt, K.K. Schmid, Effect of parameter selection on entropy calculation for long walking trials, Gait Posture 60 (2018) 128-134.

[26] L.N. Zhao, S.S. Wei, C.Q. Zhang, Y.T. Zhang, X.G. Jiang, F. Liu, et al., Determination of Sample Entropy and Fuzzy Measure Entropy Parameters for Distinguishing Congestive Heart Failure from Normal Sinus Rhythm Subjects, Entropy 17 (2015) 6270-6288.

[27] T. Schreiber, A. Schmitz, Improved surrogate data for nonlinearity tests, Phys. Rev. Lett. 77 (1996) 635-638.

[28] D.A. Heldman, A.J. Espay, P.A. LeWitt, J.P. Giuffrida, Clinician versus machine: Reliability and responsiveness of motor endpoints in Parkinson's disease, Parkinsonism Relat. Disord. 20 (2014) 590-595.

[29] O. Pelykh, A.M. Klein, K. Botzel, Z. Kosutzka, J. Ilmberger, Dynamics of postural control in Parkinson patients with and without symptoms of freezing of gait, Gait Posture 42 (2015) 246-250.

[30] M. Mancini, A. Salarian, P. Carlson-Kuhta, C. Zampieri, L. King, L. Chiari, et al., ISway: a sensitive, valid and reliable measure of postural control, J. Neuroeng. Rehabil. 9 (2012) https://doi.org/10.1186/1743-0003-9-59.

[31] C.J. Lamoth, M.J. van Heuvelen, Sports activities are reflected in the local stability and regularity of body sway: older ice-skaters have better postural control than inactive elderly, Gait Posture 35 (2012) 489-493.

[32] M.U. Ahmed, D.P. Mandic, Multivariate multiscale entropy: A tool for complexity analysis of multichannel data, Phys. Rev. E 84 (2011).

[33] G.N. Lewis, W.D. Byblow, Altered sensorimotor integration in Parkinson's disease, Brain 125 (2002) 2089-2099.

[34] L. Peppoloni, E.L. Lawrence, E. Ruffaldi, F.J. Valero-Cuevas, Characterization of the disruption of neural control strategies for dynamic fingertip forces from attractor reconstruction, PLoS One 12 (2017) e0172025.

[35] R.J. Spencer, C.R. Wendell, P.P. Giggey, L.I. Katzel, D.M. Lefkowitz, E.L. Siegel, et al., Psychometric Limitations of the Mini-Mental State Examination Among Nondemented Older Adults: An Evaluation of Neurocognitive and Magnetic Resonance Imaging Correlates, Exp. Aging Res. 39 (2013) 382-397.

[36] L. Rocchi, L. Chiari, F.B. Horak, Effects of deep brain stimulation and levodopa on postural sway in Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 73 (2002) 267-274.

[37] A.D. Kuo, R.A. Speers, R.J. Peterka, F.B. Horak, Effect of altered sensory conditions on multivariate descriptors of human postural sway, Exp. Brain Res. 122 (1998) 185-195.

[38] F.B. Horak, D. Dimitrova, J.G. Nutt, Direction-specific postural instability in subjects with Parkinson's disease, Exp. Neurol. 193 (2005) 504-521.

[39] S.M. Henry, J. Fung, F.B. Horak, Effect of stance width on multidirectional postural responses, J. Neurophysiol. 85 (2001) 559-570.

[40] M.A. Riley, A.A. Baker, J.M. Schmit, E. Weaver, Effects of visual and auditory short-term memory tasks on the spatiotemporal dynamics and variability of postural sway, J. Mot. Behav. 37 (2005) 311-324.

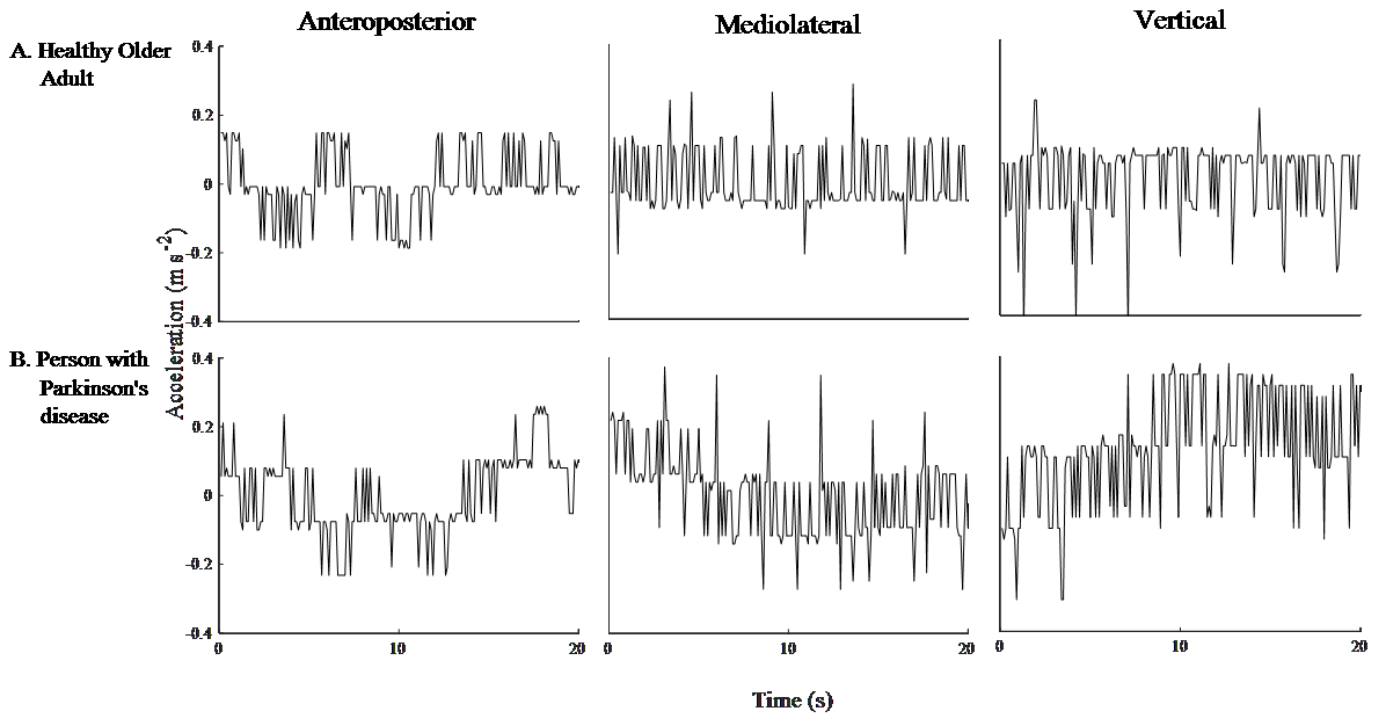

Figure 1. Unfiltered trunk accelerometer signals at 18 month timepoint along anteroposterior, mediolateral and vertical axes during 20 seconds of standing for: A) Healthy older adult; B) Person with Parkinson's disease.

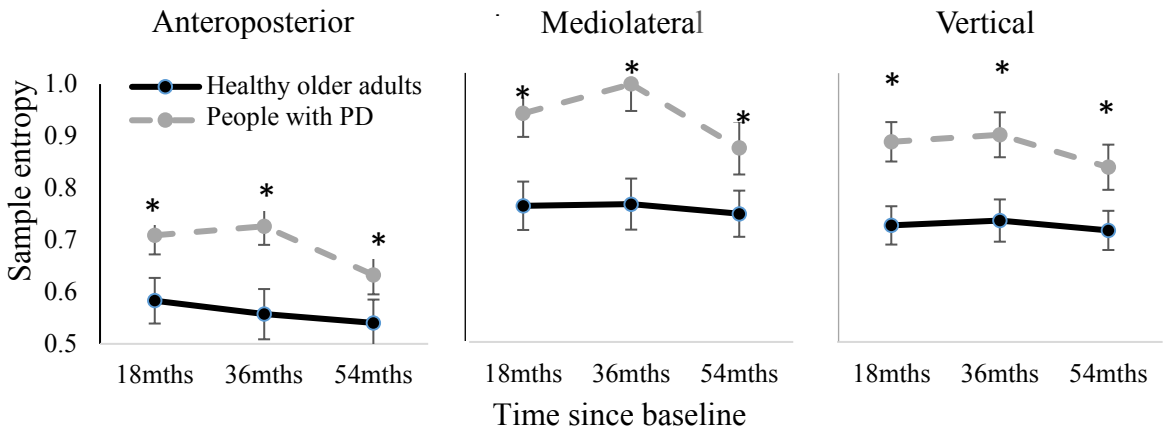

Figure 2. Changes in sample entropy at 18 months, 36 months and 54 months for acceleration signals in the anteroposterior, mediolateral and vertical axes. * $p < 0.05$

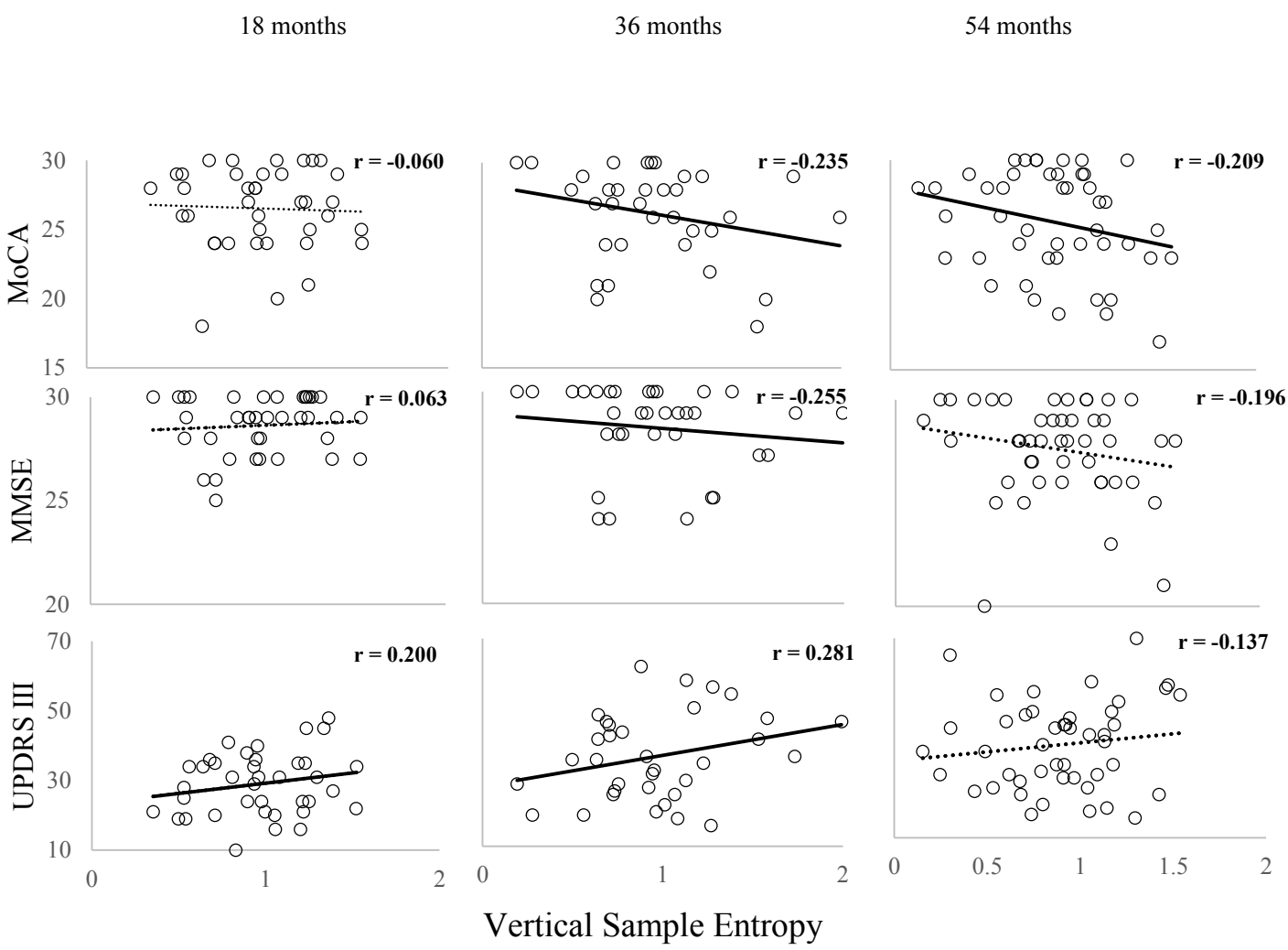

Figure 3. Scatter-plots illustrating the relationship of clinical cognitive scores and clinical motor scores (Y) against the vertical acceleration signals (X). Regression lines are included with solid lines showing $|r| > 0.20$, dashed lines $|r| < 0.20$.

MoCA - Montreal Cognitive Assessment, MMSE –Mini-Mental State Examination, UPDRS III – Unified Parkinson's Disease Rating Scale motor examination.

Table 1. Demographics, cognitive and motor scores of healthy older adults (HOA) and people with Parkinson's disease (PD).

Time-period (months)	Group	N	BMI	Age	Gender	MoCA	MMSE	UPDRS III
18	HOA	49	28.5 (3.8)	69.7 (7.5)	25(f)	27.7 (2.5)	28.5 (1.6)	n/a
	PD	42	27.2 (4.2)	66.8 (9.4)	14(f)	26.7 (2.9)	28.3 (1.7)	29.3 (8.5)
36	HOA	53	28.2 (3.8)	71.1 (7.1)	20(f)	27.7 (2.4)*	28.8 (2.2)	n/a
	PD	39	26.9 (4.7)	68.1 (8.6)	14(f)	26.4 (3.2)*	28.3 (1.9)	36.7 (12.6)
54	HOA	59	27.9 (3.7)	72.7 (7.6)*	26(f)	26.2 (3.6)	28.6 (1.9)*	n/a
	PD	50	26.8 (4.8)	69.0 (9.6)*	17(f)	25.6 (3.7)	27.6 (2.2)*	37.8 (13.0)

BMI – Body Mass Index, MoCA - Montreal Cognitive Assessment, MMSE – Mini-Mental State Examination, UPDRS – Unified Parkinson's Disease Rating Scale, n/a – not applicable.

* represents significant differences between PD and HOA ($p < 0.05$).

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Table 2. Correlations between sample entropy in anteroposterior, mediolateral and vertical directions and cognitive and motor scores

	MoCA	**MMSE**	**UPDRS III**
Anteroposterior Sample entropy	*Spearman's rho (p)*	*Spearman's rho (p)*	*Spearman's rho (p)*
18 months	-0.183 (0.202)	0.059 (0.395)	-0.092 (0.338)
36 months	-0.004 (0.491)	0.028 (0.441)	0.171 (0.184)
54 months	***-0.245 (0.075)***	***-0.249(0.072)***	***0.273 (0.053)***
Mediolateral Sample entropy	*Spearman's rho (p)*	*Spearman's rho (p)*	*Pearson coeff (p)*
18 months	-0.098 (0.281)	0.009(0.479)	***0.218 (0.098)***
36 months	-0.167 (0.177)	-0.180 (0.158)	***0.281 (0.057)***
54 months	-0.183 (0.114)	-0.191(0.104)	0.126 (0.205)
Vertical Sample entropy	*Spearman's rho (p)*	*Spearman's rho (p)*	*Pearson coeff (p)*
18 months	-0.060 (0.361)	0.063 (0.355)	***0.200 (0.115)***
36 months	***-0.235 (0.090)***	***-0.255 (0.073)***	***0.281 (0.053)***
54 months	***-0.209 (0.082)***	***-0.196 (0.096)***	0.137 (0.183)

MoCA - Montreal Cognitive Assessment; MMSE – Mini-Mental State Examination; UPDRS – Unified Parkinson's Disease Rating Scale. Bold values indicate significance level $p < 0.05$.