Journal of Neural Transmission (2022) 129:879–887
https://doi.org/10.1007/s00702-022-02501-9

NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - ORIGINAL ARTICLE

Distinct gait dimensions are modulated by physical activity in Parkinson's disease patients

Paulo Bastos[1] · Bruna Meira[2] · Marcelo Mendonça[3,4] · Raquel Barbosa[2,4]

Received: 28 February 2022 / Accepted: 6 April 2022 / Published online: 15 April 2022

Abstract

Parkinson's disease (PD) is the fastest growing neurodegenerative disease, but disease-modifying or preventive treatments are lacking. Physical activity is a modifiable factor that decreases the PD risk and improves motor symptoms in PD. Understanding which dimensions of gait performance correlate with physical activity in PD can have important pathophysiological and therapeutic implications. Clinical/demographic data together with physical activity levels were collected from thirty-nine PD patients. Gait analysis was performed wearing seven inertial measurement units on the lower body, reconstructing the subjects' lower body motion using 3D kinematic biomechanical models. Higher physical activity scores were significantly correlated with MDS-UPDRS part III scores ($r = -0.58$, p value $= 9.2 \times 10^{-5}$), age ($r = -0.39$, p value $= 1.5 \times 10^{-2}$) and quality-of-life ($r = -0.47$, p value $= 5.9 \times 10^{-3}$). Physical activity was negatively associated with MDS-UPDRS part III scores after adjusting for age and disease duration ($\beta = -0.08530$, p value $= 0.0010$). The effect of physical activity on quality-of-life was mediated by the MDS-UPDRS part III (62.10%, 95% CI = 0.0758–1.78, p value = 0.022). The level of physical activity was correlated primarily with spatiotemporal performance. While spatiotemporal performance displays the strongest association with physical activity, other quality-of-movement dimensions of clinical relevance (e.g., smoothness, rhythmicity) fail to do so. Interventions targeting these ought to be leveraged for performance enhancement in PD through neuroprotective and brain network connectivity strengthening. It remains to be ascertained to which extent these are amenable to modulation.

Keywords Parkinson's disease · Gait · Kinematic analysis · Physical activity · Biomechanical assessment

Introduction

Parkinson's disease (PD) is the fastest growing neurodegenerative disease and its prevalence and socioeconomic burden are expected to double by 2040 (GBD 2016 Parkinson's Disease Collaborators et al. 2018). While multiple symptomatic treatments are available, disease-modifying or preventive treatments are still lacking. Physical activity is a modifiable factor well known for its pleiotropic effects across a wide range of bodily functions and age-related phenomena, being a core part of the managing guidelines for conditions such as diabetes and cardiovascular diseases (Adamopoulos et al. 2019; Colberg et al. 2016). In the setting of PD models, preclinical studies have shown that physical training has both significant preventive and therapeutic effects against the development of parkinsonism via mechanisms not limited to changes in dopaminergic neurotransmission (Smith and Zigmond 2003; Petzinger et al. 2007). Moreover, exercise engagement has been shown to decrease the risk of PD in humans subjects when experienced in moderate to vigorous levels (e.g., tennis, biking, swimming, or heavy housework practice ~ 7 h per week) (Chen et al. 2005; Xu et al. 2010). In turn, in patients with an already established PD diagnosis, physical activity improves not only motor function but also non-motor symptoms and overall quality-of-life, providing a neuroprotective role that translates into attenuated disease progression (Amara et al. 2019; Mantri et al. 2018; Corcos

✉ Raquel Barbosa
ana.r.barbosa@hotmail.com

1 CEDOC, Chronic Diseases Research Centre, NOVA Medical School, Lisbon, Portugal

2 Neurology Department, Hospital de Egas Moniz, Centro Hospitalar de Lisboa Ocidental, Lisbon, Portugal

3 Champalimaud Research, Champalimaud Centre for the Unknown, Lisbon, Portugal

4 NOVA Medical School, Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisbon, Portugal

et al. 2013). Mechanistically, it has been recently demonstrated that a 6-month-long trial of aerobic exercise (stationary home-trainer) increases functional connectivity between the anterior putamen and the sensorimotor cortex and within the frontoparietal network in proportion to the improvements in one's physical capacity in an interventional study with 130 PD patients (Johansson et al. 2021). With PD being a neurodegenerative disease of older adulthood and with the worldwide population projected to significantly age in the upcoming years, physical activity-based interventions seem to be extremely well placed as inexpensive, first line disease-modifying approaches. Results from other studies have provided encouraging results supporting the protective effects of physical exercise not only in the context of PD but also well into the realms of old age, whereby physical activity has been shown to counteract the positive association between age-related neuropathology and motor function deterioration (Elbaz et al. 2013; Fleischman et al. 2015).

Leveraged by inertial sensor-based 3D kinematics, in the present study we aimed to quantify the strength of association between physical activity engagement, motor symptoms and quality-of-life in PD, and to identify which dimensions of gait significantly correlate with physical activity engagement.

Methods

Participants, clinical and demographic data

A total of 39 PD patients diagnosed according to the Movement Disorders Society (MDS) Clinical Diagnostic Criteria for PD with a Hoehn and Yahr stage ≤ 3 were recruited from our Movement Disorders outpatient clinic (*Centro Hospitalar de Lisboa Ocidental*, Lisbon, Portugal) between January and August 2021 (summary descriptive statistics may be found in Table 1). This study was approved by the local ethics committee and carried out according to the local institutional guidelines (Centro Hospitalar de Lisboa Ocidental, Lisbon, Portugal) and in agreement with the Helsinki Declaration. Verbal and written informed consents were obtained. The recruitment was carried out throughout the COVID-19 pandemic, having significantly impacted the outpatient clinical practice due to the imposed lockdowns, social distancing guidelines and with the patients often missing consultation. Patients with known orthopedic conditions that significantly caused gait deficits as per investigator judgement, major gait impairments due to conditions other than PD or dementia (MMSE < 24 with impairment on activities of the daily living) were excluded from the study. Clinical and demographic data collected included age at baseline, age at disease onset, disease duration, educational attainment, medications, levodopa equivalent daily doses (LEDD), MDS-UPDRS part III score, weight and height. Quality-of-life impairment was assessed using the Parkinson's Disease Questionaire-8 (PDQ-8) scale, where higher values correspond to higher compromises (i.e., lower quality-of-life). Physical activity was assessed using the Physical Activity Scale for the Elderly (PASE) scale, a self-reported questionnaire to assess the frequency, intensity, and duration of leisure, household-related or work/volunteering-related overall physical activity, where higher scores correspond to higher physical activity. None of the study participants was engaged in leisure/recreational activities, with the PASE scale. As such, any differences in physical activity scores are a direct reflection of employment status and house chores engagement and the study population is thus rather homogeneous in rather to the physical activity "source". In addition, the MDS-UPDRS-III scores were deconstructed into its sub-scores for rigidity (item 3.3), bradykinesia (sum of items 3.4–3.8 and 3.14), tremor (sum of items 3.15–3.17) and axial signs (sum of items 3.1 and 3.10–3.12) (Fabbri et al. 2016, 2019).

Table 1 Clinical and demographic data of the study participants

	Mean	SD	SEM	Median
Age (y)	68.77	12.08	1.934	47
UPDRS III	38.21	12.1	1.937	52
PASE	89.41	72.22	11.56	286.8
Educational attainment (y)	8,.706	4.869	0.8343	16
Age at onset (y)	61.33	12.31	1.971	49
Disease duration (y)	7.436	3.339	0.5346	13
LEDD	695.1	442.8	70.91	1973
BMI	26.05	5.109	0.8636	21.60
PDQ-8	26.24	18.04	3.141	63

Kinematics data collection

Gait analysis was performed with the patient in the ON medication state wearing a set of 7 inertial measurement units (IMUs) (Xsens, Technologies B.V. Enschede, Netherlands) on the lower body while walking three times at a self-selected speed along a ten-meter-long corridor (sampling rate: 120 Hz), as previously described (Alberto et al. 2021). The sensors were fixed onto the pelvis, thighs, calves and feet with Velcro elastic bands and the axes orientation was as follows: X pointing downwards, Y pointing to the right and Z pointing backwards. Data were collected and Kinetikos CE-marked cloud-based platform (Kinetikos, Coimbra, Portugal) was used to reconstruct participant lower body motion using 3D kinematic computer model of the skeletal system, as previously described(Alberto et al. 2021). The reconstructed models consisted of the representation of the subject's lower extremities and respective joints and comprised a total of 13 degrees-of-freedom (DOF). The hip was a ball

and socket joint (3 DOF). Both knees and ankles had a single DOF each that consisted of a revolute joint (1 DOF + 1 DOF). Each joint's coordinate system matches the International Society of Biomechanics (ISB) recommendations.

Data analysis

Data analysis was performed in R (version 4.0.4) and GraphPad (8.4.3) and a more in-depth description is available at (https://github.com/Le-bruit-de-nos-pas/PASE_3D_Kinematics_Gait_Biomechanics). A total of 44 kinematic features (11 spatiotemporal, 9 non-linear, 10 angular and velocity-related, 8 variability and 6 asymmetry features) were calculated based on the 3D biomechanical reconstruction of patient gait. For parameters with a bilateral nature (i.e., left and right knee flexion velocity), only the clinically defined worst side was considered. These features are in Supplementary Figs. S1, S2, S3, S4 and S5 individually depicted and a summary table describing these variables can be found in Supplementary Table S1.

Correlations were assessed using Spearman correlation. Whenever relevant, multiple linear regression was employed for statistically adjusting for covariates. Mediation analysis was performed by combining linear regression models and feeding them into Causal Mediation Analysis with Nonparametric Bootstrap (1000-fold) using the R "*mediation*" package. Unstandardized indirect effects were computed for each of the 1000 bootstrapped samples and the 95% confidence interval (CI) was computed by determining the indirect effects at the 2.5th and 97.5th percentiles.

To characterize patient gait across multiple movement dimensions at a subclinical level in a more objective and comprehensive way over a continuous range of values, kinematic feature reduction, unsupervised Principal Component Analysis (PCA) and accompanying analyses were performed using the "*caret*", "*factoextra*", "*MASS*" and "*ROCR*" packages in R. PCA was performed, the corresponding scree plot was generated and a total of 10 principal components were retained according to the Kaiser's criterion (eigenvalues > 1), explaining a cumulative variance of 87% (Supplementary Fig. S6). Dimensionality reduction was thus applied to the original kinematic dataset and the respective loadings of each variable on each principal component were computed (Supplementary Fig. S7). Subsequently, to maximize the variance of the identified gait dimensions and thus improve data interpretability, Varimax rotation was performed by orthogonally rotating the loadings matrix with Kaiser normalization (i.e., re-scaling to unit length prior to rotation and scaling back afterwards) using the "*varimax*" function of the R "*stats*" package. Individual patient scores of these lower-dimensional space variables/factors were correlated back with each patient's own PASE score as to identify which "quality-of-movement" dimensions significantly correlate with physical activity engagement.

Results

Physical activity is negatively associated with motor symptoms severity and self-reported quality-of-life

Thirty-nine patients consisting of 24 males and 15 females with an average of 68.8 years old and mean disease duration of 7.4 years were evaluated (clinical and demographic details may be found in Table 1). The levels of physical activity (i.e., PASE scores) were significantly associated with the MDS-UPDRS part III scores ($r = -0.58$, p value $= 9.2 \times 10^{-5}$), younger age ($r = -0.39$, p value $= 1.5 \times 10^{-2}$) and quality-of-life impairment ($r = -0.47$, p value $= 5.9 \times 10^{-3}$), but not with disease duration (Fig. 1A and Supplementary Fig. S8). When querying which motor features assessed by the MDS-UPDRS part III were significantly correlated with the physical activity level, an overall trend towards diminished scores with higher levels of physical activity across all motor sub-scores was observed, but it only reached statistical significance in the case of axial symptoms ($r = -0.42$, p value $= 0.0137$, Fig. 1B). Of note, the study population was balanced when it comes to PD phenotype, with 15 patients being tremor-dominant (TD) and 15 postural instability/gait difficulty (PIGD) (9 undetermined). The association between PASE and MDS-UPDRS part III scores remained significant after adjusting for age and disease duration ($\beta = -0.08530$, p value $= 0.0010$).

The effect of physical activity on quality-of-life is mediated via the MDS-UPDRS part III

MDS-UPDRS part III scores were positively correlated with quality-of-life impairment ($r = 0.52$, p value $= 2.1 \times 10^{-3}$, Fig. 1A). In order to fully dissect the effect of physical activity onto quality-of-life, a structural equation model mediation was employed. Causal Mediation Analysis has revealed that the effect of physical activity on quality-of-life was mediated via the MDS-UPDRS part III scores. Accordingly, the average causal mediation effect (i.e., the effect mediated by the MDS-UPDRS part III scores) was statistically significant, revealing that the causal effect of physical activity on quality-of-life goes through the MDS-UPDRS part III mediator (Estimate $= -0.0642$, 95% CI $= -0.1368$ to -0.01, p value $= 0.022$). The average total effect of physical activity onto quality-of-life was -0.1034 (95% CI $= -0.1792$ to -0.05, p value $= 2 \times 10^{-16}$), with 62.10% of it being mediated by the MDS-UPDRS part III mediator (95% CI $= -0.0758$ to 1.78, p value $= 0.022$, Fig. 2A).

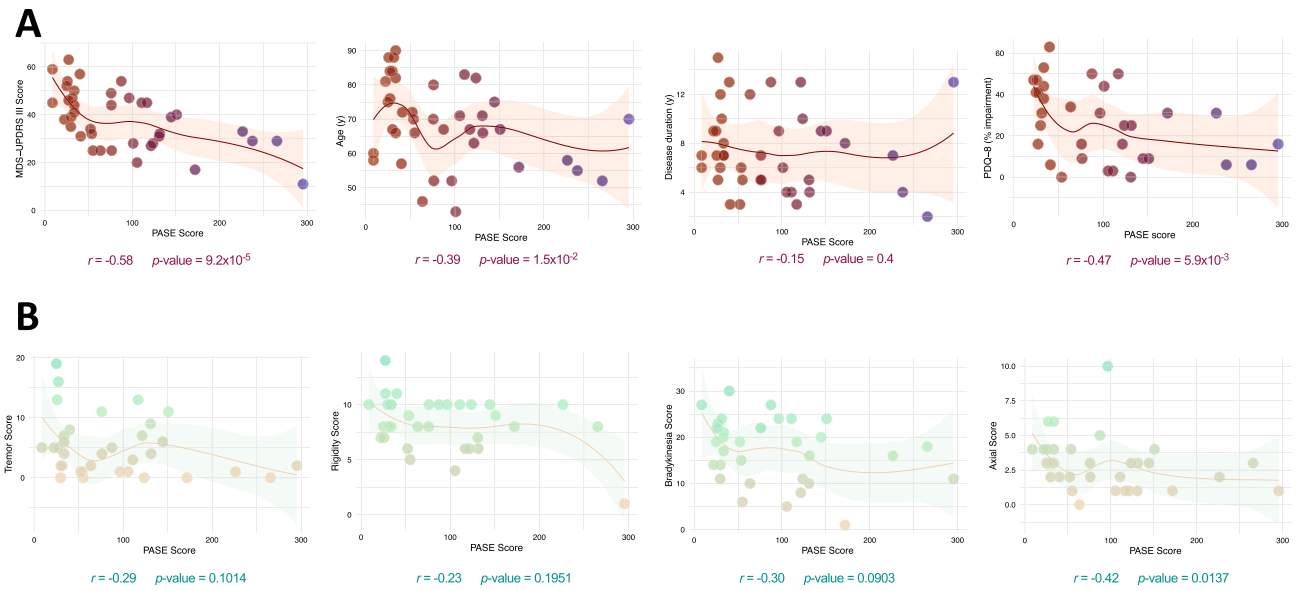

Fig. 1 Scatter plots for selected raw clinical and demographic values with Spearman's coefficients and respective *p* values (**A**). Sub-plot (**B**) represents the MDS-UPDRS part III breakdown into its motor subs-cores and respective correlation with the *Physical Activity Scale for the Elderly* (PASE) scores. Shaded areas correspond to a local polynomial regression fitting (loess). For the entire correlation matrixes, please refer back to Supplementary Fig. S8

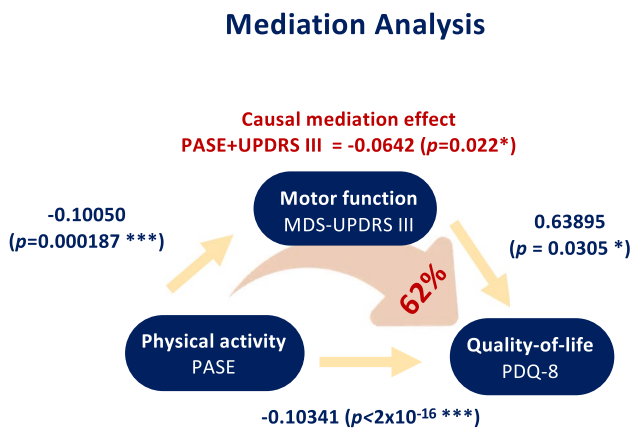

Fig. 2 Mediation analysis results revealing how the impact of physical activity on quality-of-life "goes through" its effect over motor function as assessed by the MDS-UPDRS part III scale

Not all dimensions of self-paced gait are associated with physical activity

Scale-based assessment of motor symptoms in PD does not fully capture features of motor performance at subclinical levels, as these may be too subtle and/or complex for physician-based detection and quantification. As such, we have complemented clinical assessment with 3D kinematics gait analysis. In doing so, strong correlations with physical activity were found at individual feature level, with a relatively small group (14/44, 31.8%) of movement sub-components significantly modulated by the physical activity level (Supplementary Fig. S9). Accordingly, step width, stride time variability, center-of-mass in the vertical axis, anterior–posterior entropy, step time variability, double support time and double support time asymmetry are significantly decreased in patients with higher levels of physical activity, while hip flexion mean velocity, hip flexion range of motion, speed, knee angle mean velocity, step width variability, stride length and ankle angle mean velocity are significantly increased among patients with higher physical activity scores (Supplementary Fig. S10). Overall, physical activity seemed to be most strongly correlated with spatiotemporal gait parameters as evaluated by displacement-related dimensions (e.g., speed, stride length) and joint range-of-movement, while failing to do so at the level of overall walking smoothness, rhythmicity or dynamic stability, as observed by the relatively small influence over harmonic ratios and most asymmetry scores. However, many of these individual kinematic features may be colinear and redundant, have significantly overlapping contributions and the dissection of exact individual gait feature/quality contributions, thus called for gait analysis on a lower dimensionality space.

To uncover which dimensions of motor performance are most strongly associated with physical activity, PCA was performed to deal with the high correlation / co-linearity between different kinematic features (Supplementary Figs. S6 and S7). In doing so, the original kinematic variables were projected into a reduced set of new variables that

result from a combination of the original variables but in an orthogonal fashion as to reduce the amount of redundant information. In other words, we have reconstructed the data according to a new set of variables that explains the maximal amount of variance in the data. The individual patient scores on each of these newly extracted/identified orthogonal gait dimensions were correlated back with each patient's own physical activity score. In doing so, it was observed that only PC1 significantly correlated with physical activity scores (followed by PC2, PC7 and PC8, Fig. 3A). When querying which domains of movement "quality" most heavily contributed to each of these new orthogonal variables (i.e., principal components), it was observed that these dimensions consisted primarily of spatiotemporal features (Fig. 4). However, several other domains of movement "quality" (predictability, variabilities or asymmetries) failed to display a significant association with general physical activity as assessed by the PASE scale (Fig. 4).

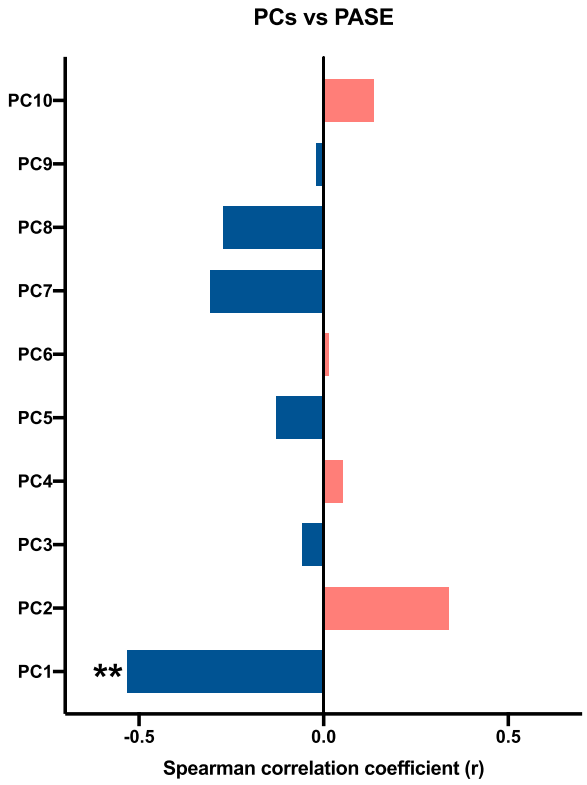

Fig. 3 Effect size plot for the correlation between physical activity as assessed by the *Physical Activity Scale for the Elderly* (PASE) scores and each principal component (P1 to P10) score (**A**). Statistical significance is indicated as < 0.05 *, < 0.01 ** or < 0.001 ***

Discussion

We have herein demonstrated that the level of physical activity is significantly associated with motor symptom severity and quality-of-life in PD, being most strongly associated with axial features at a clinical level and correlated primarily with spatiotemporal gait performance at a kinematic level. The stronger correlation between axial features and physical activity is in line with previous cross-sectional and longitudinal studies (Bryant et al. 2016; Amara et al. 2019). As the axial symptom burden is a particularly robust indicator of disease progression and milestone event occurrence, these data underscore the putative impact physical activity may have on PD. However, compared to previous cohorts, physical activity in the present cohort was considerably lower (Mantri et al. 2018, 2019), which may partially reflect the impact of current public health restrictions, with several patients representing recent retirees or otherwise experiencing significantly impaired engagement in activities outside their residential place. Accordingly, the impact of the COVID-19 pandemic and associated lockdowns in PD has been recently quantified in the country, whereby the COVID-19 confinement translated into significantly decreased mobility (walking minutes/day) among PD patients (Vila-Viçosa et al. 2021). Likewise, the COVID-19 lockdown has also been recently shown to lead to a dramatic reduction in physical activity as assessed by PASE scores among older adults (Huber et al. 2021).

As a complement to scale-based rating, inertial sensor-based 3D kinematics was herein employed to ascertain a more unbiased and complete view of motor function (in addition to motor symptoms) with a higher resolution. While gait assessment in a non-ecological environment may not perfectly capture gait performance otherwise experienced during activities of the daily living in ambulatory settings (Galperin et al. 2019; Mazzà et al. 2021), the approach herein employed has nonetheless been proven insightful even when performed in clinical/laboratorial settings (Di Lazzaro et al. 2020; O'Day et al. 2022; Lukšys and Griškevičius 2022). In doing so, spatiotemporal features were shown to correlate the most with physical activity levels. In turn, many other gait dimensions of clinical relevance seem not to be significantly associated with self-reported physical activity scores (e.g., step length or swing time asymmetries, anterior–posterior or medio-lateral harmonic ratios, speed or double support time variabilities). These last gait parameters reflecting gait smoothness, variability or predictability have important diagnostic and prognostic value. For instance, compared to that of age-matched controls, the gait of PD patients has been reported significantly less smooth, more variable and less

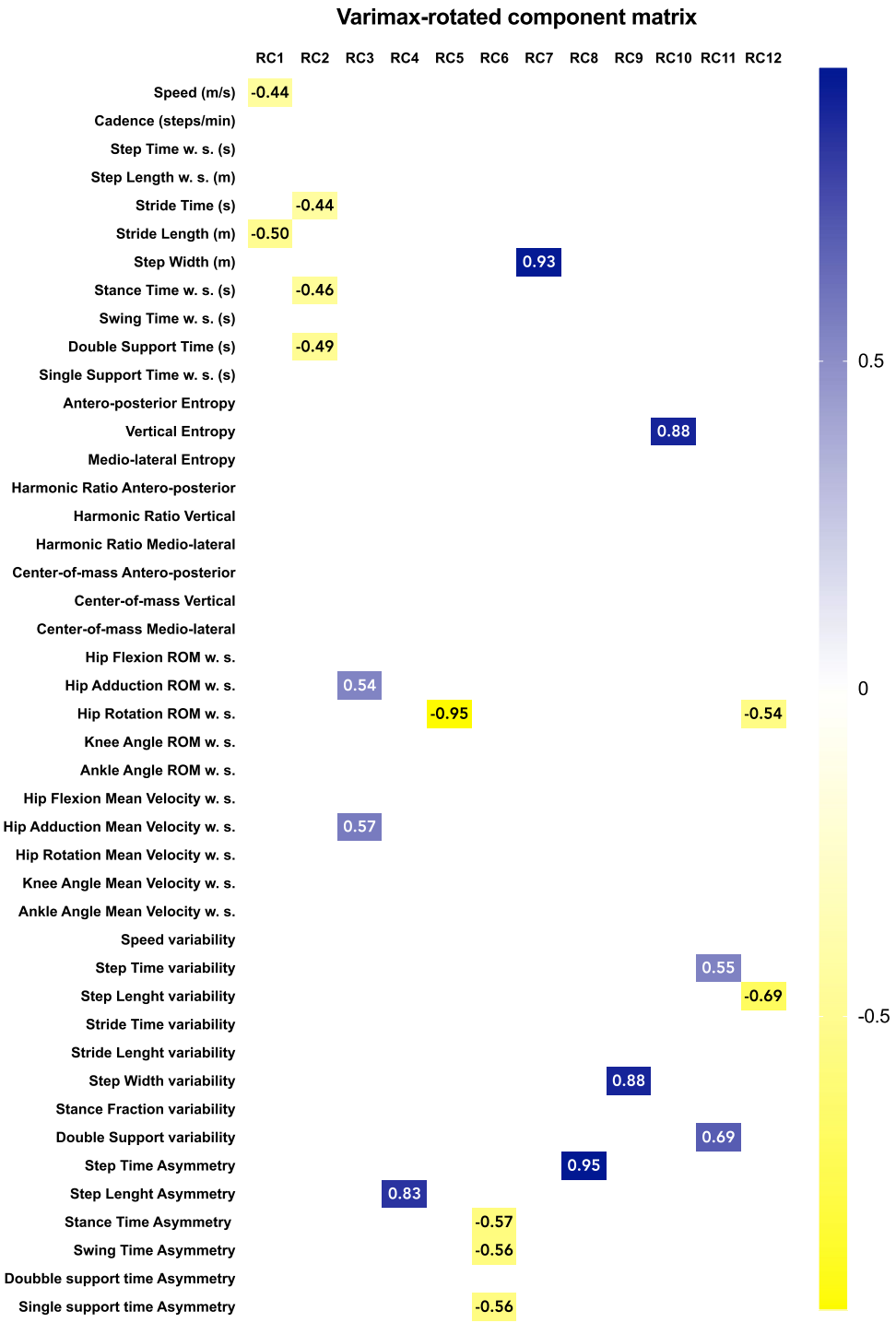

Fig. 4 Factor loadings of each kinematic variable after varimax rotation. Only values ≥ 0.4 are shown. *RC* rotated component

predictable (Coates et al. 2020; Fling et al. 2018; Orcioli-Silva et al. 2020). In PD patients, gait smoothness deserves further scrutiny because its deterioration is associated with an increased risk of falls (Latt et al. 2009) and freezing events (Hausdorff et al. 2003). In the non-PD elderly population, a higher risk of falls and a higher incidence of depression have also been documented with higher gait variability (Stergiou et al. 2020; Hausdorff et al. 2001; Herman et al. 2005). All in all, one is tempted to assume that striving for higher smoothness, rhythmicity and predictability of gait could be of particular relevance. In the setting of stroke, it has been shown that the improvements in gait symmetry brought about by physical rehabilitation are mediated by increases in connectivity between brain regions and between the brain and musculoskeletal system (Chen et al. 2019). At the same time, we know that

changes in functional connectivity after exercise in PD patients are intensity-dependent (Shah et al. 2016), and that fostering such connectivity translates into decreased disease severity (Chung et al. 2020).

Self-reported activity as herein evaluated does not correlate well with moderate to vigorous physical activity in patients with PD (Mantri et al. 2019). Alternative, more complex and intense interventions (e.g., cue-guided balance training (Lowry et al. 2010)) would probably be necessary to modulate specific gait dimensions such as variability, predictability and smoothness that. On the one hand, these do capture a significant amount of the total variability across subjects (Fig. 4 and Supplementary Fig. S6). On the other hand, these may have important prognostic value.

Lastly, we should acknowledge that the direction of causality between the association of physical activity level, motor symptoms and quality-of-movement cannot be inferred from the data presented. It remains to be inquired whether alterations in the physical activity truly translate into improvements in motor symptoms and quality-of-life, or if the reverse is true (i.e., if patients with milder disease phenotypes experience higher exercise engagement). Nonetheless, as recently reiterated, it is possible to maintain moderate-to-vigorous levels of physical activity even in more advanced stages of disease progression and it is the decline in physical activity that accounts for decreased motor performance (von Rosen et al. 2021). In all likelihood, these two phenomena feed into each other in a positive feedback loop. Regardless, the strong correlations herein reported between physical activity, motor symptoms and gait performance may be taken advantage for the management of PD motor symptoms and general motor performance. Overall, because physical activity has been shown to modulate brain circuity connectivity, to attenuate disease progression and to account for motor performance, physical activity-based interventions may be very well placed as disease-modifying approaches.

Conclusion

Spatiotemporal performance correlates the most with self-reported physical activity in PD. Higher physical activity levels are significantly associated with milder symptoms and improved quality-of-life. Many other quality-of-movement dimensions of clinical relevance (e.g., smoothness, rhythmicity) do not display a strong association with non-specific physical activity, so that specific interventions targeting these ought to be leveraged for motor improvement in PD.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00702-022-02501-9.

Author contributions PB: Research Project: Conception, Organization, Execution; Statistical Analysis: Design, Execution, Review and Critique; Manuscript Preparation: Writing of the First Draft, Review and Critique. BM: Research Project: Execution, Statistical Analysis: Review and Critique, Manuscript Preparation: Review and Critique. MM: Research Project: Conception, Organization, Statistical Analysis: Design, Review and Critique, Manuscript Preparation: Review and Critique. RB: Research Project: Conception, Organization, Execution, Statistical Analysis: Review and Critique, Manuscript Preparation: Review and Critique.

Funding No funding was received for this study.

Declarations

Conflict of interest The authors declare the absence of any conflict of interest.

Ethical approval This study was approved by the local ethics committee and carried out according to the local institutional guidelines (Centro Hospitalar de Lisboa Ocidental, Lisbon, Portugal) and in agreement with the Helsinki Declaration. Verbal and written informed consents were obtained.

References

Adamopoulos S, Corrà U, Laoutaris ID, Pistono M, Agostoni PG, Coats AJS, Crespo Leiro MG et al (2019) Exercise training in patients with ventricular assist devices: a review of the evidence and practical advice. A position paper from the committee on exercise physiology and training and the committee of advanced heart failure of the heart failure associat. Eur J Heart Fail 21(1):3–13. https://doi.org/10.1002/ejhf.1352

Alberto S, Cabral S, Proença J, Pona-Ferreira F, Leitão M, Bouça-Machado R, Kauppila LA et al (2021) Validation of quantitative gait analysis systems for Parkinson's disease for use in supervised and unsupervised environments. BMC Neurol 21(1):331. https://doi.org/10.1186/s12883-021-02354-x

Amara AW, Chahine L, Seedorff N, Caspell-Garcia CJ, Coffey C, Simuni T, Parkinson's Progression Markers Initiative (2019) Self-reported physical activity levels and clinical progression in early Parkinson's disease. Parkinsonism Relat Disord 61:118–125. https://doi.org/10.1016/j.parkreldis.2018.11.006

Bryant MS, Hou JG, Collins RL, Protas EJ (2016) Contribution of axial motor impairment to physical inactivity in Parkinson disease. Am J Phys Med Rehabil 95(5):348–354. https://doi.org/10.1097/PHM.0000000000000384

Chen H, Zhang SM, Schwarzschild MA, Hernán MA, Ascherio A (2005) Physical activity and the risk of Parkinson disease. Neurology 64(4):664–669. https://doi.org/10.1212/01.WNL.0000151960.28687.93

Chen I-H, Yang Y-R, Lu C-F, Wang R-Y (2019) Novel gait training alters functional brain connectivity during walking in chronic stroke patients: a randomized controlled pilot trial. J NeuroEng Rehabil 16(1):33. https://doi.org/10.1186/s12984-019-0503-2

Chung SJ, Kim H-R, Jung JH, Lee PH, Jeong Y, Sohn YH (2020) Identifying the functional brain network of motor reserve in early Parkinson's disease. Mov Disord 35(4):577–586. https://doi.org/10.1002/mds.28012

Coates L, Jian S, Lynn R, Silvia DD, Annette P (2020) Entropy of real-world gait in Parkinson's disease determined from wearable sensors as a digital marker of altered ambulatory behavior. Sensors (basel, Switzerland). https://doi.org/10.3390/s20092631

Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, Horton ES, Castorino K, Tate DF (2016) Physical activity/exercise and diabetes: a position statement of the american diabetes association. Diabetes Care 39(11):2065–2079. https://doi.org/10.2337/dc16-1728

Corcos DM, Robichaud JA, David FJ, Leurgans SE, Vaillancourt DE, Poon C, Rafferty MR, Kohrt WM, Comella CL (2013) A two-year randomized controlled trial of progressive resistance exercise for Parkinson's disease. Movement Disord 28(9):1230–1240. https://doi.org/10.1002/mds.25380

Di Lazzaro G, Ricci M, Al-Wardat M, Schirinzi T, Scalise S, Giannini F, Mercuri NB, Saggio G, Pisani A (2020) Technology-based objective measures detect subclinical axial signs in untreated, de novo Parkinson's disease. J Parkinson's Dis 10(1):113–122. https://doi.org/10.3233/JPD-191758

Elbaz A, Vicente-Vytopilova P, Tavernier B, Sabia S, Dumurgier J, Mazoyer B, Singh-Manoux A, Tzourio C (2013) Motor function in the elderly: evidence for the reserve hypothesis. Neurology 81(5):417–426. https://doi.org/10.1212/WNL.0b013e31829d8761

Fabbri M, Coelho M, Abreu D, Guedes LC, Rosa MM, Costa N, Antonini A, Ferreira JJ (2016) Do patients with late-stage Parkinson's disease still respond to levodopa? Parkinsonism Relat Disord 26(May):10–16. https://doi.org/10.1016/J.PARKRELDIS.2016.02.021

Fabbri M, Coelho M, Abreu D, Guedes LC, Rosa MM, Godinho C, Cardoso R et al (2019) Dysphagia predicts poor outcome in late-stage Parkinson's disease. Parkinsonism Relat Disord 64(July):73–81. https://doi.org/10.1016/J.PARKRELDIS.2019.02.043

Fleischman DA, Yang J, Arfanakis K, Arvanitakis Z, Leurgans SE, Turner AD, Barnes LL, Bennett DA, Buchman AS (2015) Physical activity, motor function, and white matter hyperintensity burden in healthy older adults. Neurology 84(13):1294–1300. https://doi.org/10.1212/WNL.0000000000001417

Fling BW, Curtze C, Horak FB (2018) Gait asymmetry in people with Parkinson's disease is linked to reduced integrity of callosal sensorimotor regions. Front Neurol 9(April):215. https://doi.org/10.3389/fneur.2018.00215

Galperin I, Hillel I, Del Din S, Bekkers EMJ, Nieuwboer A, Abbruzzese G, Avanzino L et al (2019) Associations between daily-living physical activity and laboratory-based assessments of motor severity in patients with falls and Parkinson's disease. Parkinsonism Relat Disord 62(May):85–90. https://doi.org/10.1016/J.PARKRELDIS.2019.01.022

GBD 2016 Parkinson's Disease Collaborators, Ray E, Elbaz A, Nichols E, Abd-Allah F, Abdelalim A, Adsuar JC, Ansha MG et al (2018) Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the global burden of disease study 2016. The Lancet Neurol 17(11):939–953. https://doi.org/10.1016/S1474-4422(18)30295-3

Hausdorff JM, Schaafsma JD, Balash Y, Bartels AL, Gurevich T, Giladi N (2003) Impaired regulation of stride variability in Parkinson's disease subjects with freezing of gait. Exp Brain Res 149(2):187–194. https://doi.org/10.1007/S00221-002-1354-8

Hausdorff JM, Rios DA, Edelberg HK (2001) Gait variability and fall risk in community-living older adults: a 1-year prospective study. Arch Phys Med Rehabil 82(8):1050–1056. https://doi.org/10.1053/apmr.2001.24893

Herman T, Giladi N, Gurevich T, Hausdorff JM (2005) Gait instability and fractal dynamics of older adults with a "cautious" gait: why do certain older adults walk fearfully? Gait Posture 21(2):178–185. https://doi.org/10.1016/j.gaitpost.2004.01.014

Huber BC, Jenny S, Michael D, Julius S, Stefan B (2021) Change of the physical activity scale for the elderly (PASE) score after COVID-19 outbreak. J Sports Med Phys Fitness https://doi.org/10.23736/S0022-4707.21.12453-3

Johansson ME, Cameron IGM, van der Kolk NM, De Vries NM, Klimars E, Toni I, Bloem BR, Helmich RC (2021) Aerobic exercise alters brain function and structure in Parkinson's disease a randomized controlled trial. Ann Neurol. https://doi.org/10.1002/ana.26291

Latt MD, Hylton BM, Victor SF, Stephen RL (2009) Acceleration patterns of the head and pelvis during gait in older people with Parkinson's disease: a comparison of fallers and nonfallers. J Gerontol a, Biol Sci Med Sci 64(6):700–706. https://doi.org/10.1093/gerona/glp009

Lowry KA, Carrel AJ, McIlrath JM, Smiley-Oyen AL (2010) Use of harmonic ratios to examine the effect of cueing strategies on gait stability in persons with Parkinson's disease. Arch Phys Med Rehabil 91(4):632–638. https://doi.org/10.1016/j.apmr.2009.12.016

Lukšys D, Griškevičius J (2022) Application of nonlinear analysis for the assessment of gait in patients with Parkinson's disease. Technol Health Care 30(1):201–208. https://doi.org/10.3233/THC-219003

Mantri S, Fullard ME, Duda JE, Morley JF (2018) Physical activity in early Parkinson disease. J Parkinson's Dis 8(1):107–111. https://doi.org/10.3233/JPD-171218

Mantri S, Wood S, Duda JE, Morley JF (2019) Comparing self-reported and objective monitoring of physical activity in Parkinson disease. Parkinsonism Relat Disord 67(October):56–59. https://doi.org/10.1016/J.PARKRELDIS.2019.09.004

Mazzà C, Alcock L, Aminian K, Becker C, Bertuletti S, Bonci T, Brown P et al (2021) Technical validation of real-world monitoring of gait: a multicentric observational study. BMJ Open. https://doi.org/10.1136/BMJOPEN-2021-050785

O'Day J, Marissa L, Kirsten S, Shannon H, Ava J-S, Łukasz K, Scott D, Helen B-S (2022) Assessing inertial measurement unit locations for freezing of gait detection and patient preference. J Neuroeng Rehabil. https://doi.org/10.1186/S12984-022-00992-X

Orcioli-Silva D, Barbieri FA, Rocha PC, dos Santos V, Beretta S, Simieli L, Vitorio R, Lirani-Silva E, Gobbi LTB (2020) Double obstacles increase gait asymmetry during obstacle crossing in people with Parkinson's disease and healthy older adults: a pilot study. Sci Rep 10(1):2272. https://doi.org/10.1038/s41598-020-59266-y

Petzinger GM, Walsh JP, Akopian G, Hogg E, Abernathy A, Arevalo P, Turnquist P et al (2007) Effects of treadmill exercise on dopaminergic transmission in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse model of basal ganglia injury. J Neurosci 27(20):5291–5300. https://doi.org/10.1523/JNEUROSCI.1069-07.2007

Shah C, Beall EB, Frankemolle AMM, Penko A, Phillips MD, Lowe MJ, Alberts JL (2016) Exercise therapy for Parkinson's disease: pedaling rate is related to changes in motor connectivity. Brain Connectivity 6(1):25–36. https://doi.org/10.1089/brain.2014.0328

Smith AD, Zigmond MJ (2003) Can the brain be protected through exercise? Lessons from an animal model of Parkinsonism. Exp Neurol 184(1):31–39. https://doi.org/10.1016/j.expneurol.2003.08.017

Stergiou N, James TC (2020) Gait variability: a theoretical framework for gait analysis and biomechanics. Biomech Gait Analysis. https://doi.org/10.1016/B978-0-12-813372-9.00008-7

Vila-Viçosa D, Clemente A, Pona-Ferreira F, Leitão M, Bouça-Machado R, Kauppila LA, Costa RM, Matias R, Ferreira JJ

(2021) Unsupervised walking activity assessment reveals COVID-19 impact on Parkinson's disease patients. Movement Disord 36(3):531–532. https://doi.org/10.1002/mds.28514

von Rosen P, Hagströmer M, Franzén E, Leavy B (2021) Physical activity profiles in Parkinson's disease. BMC Neurol 21(1):71. https://doi.org/10.1186/s12883-021-02101-2

Xu Q, Park Y, Huang X, Hollenbeck A, Blair A, Schatzkin A, Chen H (2010) Physical activities and future risk of Parkinson disease. Neurology 75(4):341–348. https://doi.org/10.1212/WNL.0b013e3181ea1597