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RESEARCH ARTICLE

Increased markers of cardiac vagal activity in leucine-rich repeat kinase 2-associated Parkinson's disease

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Abstract

Purpose Cardiac autonomic dysfunction manifests as reduced heart rate variability (HRV) in idiopathic Parkinson's disease (PD), but no significant reduction has been found in PD patients who carry the *LRRK2* mutation. Novel HRV features have not been investigated in these individuals. We aimed to assess cardiac autonomic modulation through standard and novel approaches to HRV analysis in individuals who carry the *LRRK2* G2019S mutation.

Methods Short-term electrocardiograms were recorded in 14 LRRK2-associated PD patients, 25 LRRK2-non-manifesting carriers, 32 related non-carriers, 20 idiopathic PD patients, and 27 healthy controls. HRV measures were compared using regression modeling, controlling for age, sex, mean heart rate, and disease duration. Discriminant analysis highlighted the feature combination that best distinguished LRRK2-associated PD from controls.

Results Beat-to-beat and global HRV measures were significantly increased in LRRK2-associated PD patients compared with controls (e.g., deceleration capacity of heart rate: $p = 0.006$) and idiopathic PD patients (e.g., 8th standardized moment of the interbeat interval distribution: $p = 0.0003$), respectively. LRRK2-associated PD patients also showed significantly increased irregularity of heart rate dynamics, as quantified by Rényi entropy, when compared with controls ($p = 0.002$) and idiopathic PD patients ($p = 0.0004$). Ordinal pattern statistics permitted the identification of LRRK2-associated PD individuals with 93% sensitivity and 93% specificity. Consistent results were found in a subgroup of LRRK2-non-manifesting carriers when compared with controls.

Conclusions Increased beat-to-beat HRV in *LRRK2* G2019S mutation carriers compared with controls and idiopathic PD patients may indicate augmented cardiac autonomic cholinergic activity, suggesting early impairment of central vagal feedback loops in LRRK2-associated PD.

Keywords Autonomic dysfunction · Heart rate variability · Parkinson's disease · LRRK2 · Deceleration capacity of heart rate · Rényi entropy

Introduction

Parkinson's disease (PD) is a progressive multisystem degenerative process involving motor and non-motor dysfunction associated with multiple neuroanatomical areas, neurotransmitters, and protein aggregates [1]. Symptoms and signs of autonomic dysfunction are common in idiopathic PD (iPD), and cardiac dysautonomia has been demonstrated by several measures derived from autonomic reflex tests and from heart rate variability (HRV) analysis, all of which have consistently revealed a decreased HRV in iPD [2–5]. However, the effect of *LRRK2* mutations, the most common monogenic cause of PD [6], on autonomic function is still debated.

The most prevalent mutation in the gene encoding leucine-rich repeat kinase 2 (LRRK2) results in a G2019S amino acid substitution, which increases the kinase activity of the protein [7]. Symptoms of dysautonomia are frequent in LRRK2-associated PD (LRRK2-PD), although differences in non-motor symptoms have been found between

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LRRK2-PD and iPD patients [8]. Some of us previously found no significant alterations in cardiac autonomic modulation in *LRRK2* G2019S (NM_198578.3 (*LRRK2*): c.6055G > A, p.Gly2019Ser) mutation carriers, as assessed by standard time and frequency domain HRV analysis [9], although others have indicated significant modifications in some frequency domain measures [10]. Thus, the involvement and timing of cardiac autonomic alterations over the course of LRRK2-PD remain unclear, and the extent of dysautonomia is not fully understood.

Traditional statistical and spectral measures of HRV have been applied to the assessment of cardiac autonomic modulation in *LRRK2* mutation carriers. However, novel features that are more suitable for quantifying the complex, nonlinear, and nonstationary dynamics underlying cardiac autonomic control have not been explored in LRRK2-PD. Novel methods for analyzing HRV are complementary to the standard measures, and thus can provide further independent and clinically relevant information regarding cardiac autonomic modulation in LRRK2-PD that cannot be captured by traditional methods. Therefore, the aim of this study was to assess cardiac autonomic modulation through standard and novel approaches to HRV analysis in individuals who carry the *LRRK2* G2019S mutation. The novel HRV methods included in this work were the features derived from the phase-rectified signal averaging technique [11] and multiscale complexity measures from the information domain. The latter comprised permutation entropy [12] and Rényi entropy [13]. These new approaches have provided better results compared with conventional measures for assessing cardiac vagal modulation or quantifying the complexity of heart rate dynamics in different clinical settings [14–16].

Early recognition of autonomic impairment in individuals who carry the *LRRK2* mutation would potentially allow timely therapeutic intervention and could positively influence the disease course, thereby improving patient quality of life and reducing the social cost of PD. Furthermore, early biomarkers of prodromal PD, including pathophysiological, genetic, and epigenetic features, are needed in preparation of the eventual application of disease-modifying therapies for LRRK2-PD.

Methods

Subjects

We studied 14 LRRK2-PD patients, 25 LRRK2-non-manifesting carriers (LRRK2-NMC), 32 related non-carriers (RNC) (non-manifesting family members without the *LRRK2* mutation), 20 iPD patients, and 27 unrelated healthy controls. Probands with *LRRK2* p.G2019S mutations, iPD patients, and healthy individuals (without neurological disease or family history of PD) were recruited at the Toronto Western Hospital (ON, Canada) and the Parkinson's Institute (CA, USA). Family members of participants with the *LRRK2* mutation and iPD were also invited to participate. The presence or absence of p.G2019S was evaluated in all participants as previously described [17]. Subjects with iPD were defined as individuals with PD, according to clinical diagnosis by a movement disorder specialist, in the absence of a family history of the disease in first- or second-degree relatives.

Clinical evaluation

Clinical evaluation included a neurological examination, standardized videotaping of the neurological examination, the Unified Parkinson's Disease Rating Scale part 3 (UPDRSIII), and the Scales for Outcomes in PD-Autonomic (SCOPA-AUT). Individuals taking anticholinergic agents, sympathetic agonists, or sympathetic antagonists, or with evidence of thyroid dysregulation or diabetes were excluded from the study. Assessments were performed by experienced movement disorder clinicians blinded to the genetic status of participants, as described previously [18]. All participants with PD met UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria [19].

Electrocardiographic recording and cardiac interbeat intervals

Following 5 min of inactivity in a supine position, 7-min resting 4-lead electrocardiograms (EKGs) (aV_R, aV_L, N, aV_F) were collected during daylight hours from participants in a non-fasting state and digitized at 500 Hz using a laptop-based CardioCard EKG system (Nasiff Associates, Inc., Central Square, NY). Normal-to-normal (NN) cardiac interbeat intervals were extracted from the EKG recording using PhysioNet WAVE v6.11 software (www.physionet.org) in a Unix environment. The EKGs were manually checked for ectopic beats and regions of noise that were manually removed following the application of an automated algorithm for obtaining NN interval data [20].

HRV analysis

Sequences of 300 consecutive NN intervals were automatically selected, starting from the 81st sample of the original recording, and analyzed using traditional and novel HRV methods (Supplementary Fig. 1). The stationarity of the sequences was evaluated by comparing the NN interval distribution with the normal distribution and by visually inspecting the serial correlogram. Stationarity was confirmed for 84% of all sequences (see Electronic

Supplementary Material for further details on the methods for HRV analysis).

Time domain methods

These measures included the standard deviation of the NN intervals (SDNN), the width of NN interval distribution (W, difference between the longest and shortest NN intervals), the coefficient of variation of the NN intervals (CV), the square root of the mean of the sum of the squares of differences between adjacent NN intervals (rMSSD), the first-order autocorrelation coefficient (r_1), the autonomic stress index (ASI) (see Electronic Supplementary Material), and the standardized central moments of order $k = 3$–9 of NN interval distribution.

Frequency domain methods

The power spectral density was calculated over NN interval sequences of 215 s for the low-frequency band (LF) (0.04–0.15 Hz), the high-frequency band (HF) (0.15–0.4 Hz), and the total spectral power band (TP) (see Electronic Supplementary Material). LF and HF power in normalized units (LFnu and HFnu, respectively), as well as the LF/HF ratio, were also determined.

Information domain methods

The irregularity of NN intervals was determined by Shannon entropy (ShE), Rényi entropy (RE), and permutation entropy (PE), each of which distinguishes random from regular HR changes [12, 13]. ShE considers the probability of any NN value appearing in the data sequence. RE generalizes ShE to include measures at different scales (order α) based on the probability of NN sequences of different length (λ) to appear in the HR signal. PE considers the probability of ordinal patterns π (p_π) of different length (λ) occurring over different timescales (τ) of the HR signal. The different p_π were also analyzed as features for characterizing HRV.

Phase-rectified signal averaging (PRSA)

The PRSA algorithm is based on averaging NN data segments around NN intervals previously defined as anchors (events that trigger particular HR changes), to quantify the average deceleration and acceleration capacity of the HR (DC and AC, respectively) [11].

Poincaré plot features

Additionally, we examined the standard deviation along the identity line (SD2) of an ellipse fitted to the scatterplot of each NN interval vs. the next NN interval, the standard deviation perpendicular to the ellipse identity line (SD1), and the SD2/SD1 ratio.

The presence of erratic sinus rhythm in the short-term HR data sequences was assessed considering previous suggestions [21].

Statistical analysis

Statistical analyses were performed using STATISTICA software (StatSoft, Inc., Tulsa, OK). Continuous variables were assessed for normality by a Kolmogorov–Smirnov test, and were natural log-transformed (Ln) to adjust for skewness, except for the coefficient r_1, which was transformed as: $0.5 \times \mathrm{Ln}\ [(1 + r_1)/(1 - r_1)]$. Group differences in HRV measures were assessed using multiple linear regression analysis, adjusted for age, sex, and mean HR. The LRRK2-PD vs. iPD contrasts were also adjusted for disease duration. PE contrasts between age- and sex-matched groups were assessed using a Mann–Whitney *U* test, whereas a *t* test was applied for contrasting the remaining continuous variables. Sex differences between groups were assessed using the Chi-square test. Differences in the distribution of variables were assessed through a Kolmogorov–Smirnov test. Pearson *r* or Spearman *R* correlation coefficients were also determined, depending on the data characteristics.

Linear discriminant analysis was performed to explore the classification accuracy of a set of HRV measures and select the feature combination with the best discriminative power between LRRK2-PD patients and controls, following a forward stepwise variable selection procedure. The candidate set of features was extracted from a randomly selected training sample (80% of total cases), where the discriminant model was also estimated. Five HRV measures with the greatest differences between LRRK2-PD and controls, which covered all the families of features that were statistically significant, were selected. The predictive accuracy of the classification functions was assessed in the remaining test sample, with no overlap of cases. Participants in both training and test subsamples were age- and sex-matched.

HRV values were standardized (*Z* scores) considering the mean value adjusted for age, sex, and HR through multiple regression analysis, for those features affected by these confounders. The mean and standard deviation (SD) of the standardized distribution were 5 and 1, respectively. Statistical significance was set at p value < 0.05 and adjusted for multiple comparisons by controlling for the false discovery rate at q value < 0.1, using the Benjamini–Hochberg correction. Twenty single-scale HRV measures comparing LRRK2-PD vs. control, LRRK2-PD vs. iPD, and LRRK2-NMC vs. RNC accounted for a total number of tests $m = 60$. Multi-scale Rényi and permutation entropy analyses were corrected for multiple comparisons as an independent family of tests, to determine any differences between LRRK2-PD

vs. control and LRRK2-PD vs. iPD, accounting for $m = 12$ and $m = 40$ tests, respectively. Analyses performed in the training sample were also independently corrected.

Results

Participant clinical and demographic characteristics

LRRK2-PD and iPD patients were of similar ages, while LRRK2-NMC individuals were significantly younger (Table 1). Disease duration was significantly longer in the LRRK2-PD than in the iPD group; however, no significant differences in the severity of motor signs (UPDRSIII) were found. Symptoms of autonomic dysfunction (SCOPA-AUT) were significantly more frequent in LRRK2-PD patients compared with the control and iPD individuals, although no significant differences were found in the cardiovascular subscale. Information regarding orthostatic hypotension and L-dopa equivalent daily dose was not available for all patients and therefore not included in the current analysis.

Associations between HRV measures and clinical characteristics

HRV was not significantly associated with disease duration or severity of motor signs (UPDRSIII) in any of the PD groups. Among the LRRK2-PD patients, DC, AC, and

Table 1 Demographic, clinical, and standard heart rate variability characteristics of participants

Feature	Control	LRRK2-PD	LRRK2-PD vs. control	iPD	LRRK2-PD vs. iPD	NMC	NMC vs. LRRK2-PD	RNC	NMC vs. RNC
Demographic									
N	27	14	–	20	–	25	–	32	–
Fem/Male	15/12	3/11	0.037	10/10	ns	8/17	ns	16/16	ns
Age (years)	58.7 ± 13.9	63.3 ± 10.8	ns	64.1 ± 10.8	ns	50.3 ± 13.6	0.004	45.2 ± 14.8	ns
Clinical									
HR (bpm)	69 ± 11	67 ± 10	ns	69 ± 7	ns	63 ± 9	ns	63 ± 10	ns
DD (years)	na	10.8 ± 5.1	–	6.3 ± 6.0	0.015	na	–	na	–
UPDRSIII	1.00 ± 3.00	16.70 ± 15.60	< 0.0001	23.00 ± 12.00*	ns	2.00 ± 4.85	< 0.0001	0.00 ± 2.50	0.026
SCOPA-AUT	8.53 ± 6.72	23.00 ± 12.66	0.0003	12.82 ± 6.23**	0.025	10.07 ± 5.13	0.001	8.23 ± 5.94	ns
HRV measures									
SDNN	34.70 ± 15.54	35.14 ± 11.67	–	27.45 ± 14.77	–	42.24 ± 19.46	–	45.25 ± 17.97	–
rMSSD	21.33 ± 12.37	35.14 ± 11.67	–	18.96 ± 10.29	–	33.51 ± 23.34	–	38.65 ± 22.18	–
LF	10.91 ± 1.04	11.08 ± 1.00	–	10.20 ± 1.22	–	11.35 ± 0.99	–	11.53 ± 1.11	–
LF (%)	55.72 ± 11.10	56.23 ± 14.20	–	49.24 ± 14.90	–	52.40 ± 12.96	–	51.33 ± 13.00	–
HF	9.93 ± 1.19	10.21 ± 0.85	–	9.53 ± 1.18	–	10.77 ± 1.05	–	11.00 ± 1.33	–
HF (%)	29.89 ± 16.28	31.07 ± 15.82	–	36.12 ± 21.65	–	37.21 ± 16.23	–	38.35 ± 15.82	–
LF/HF	1.11 ± 0.09	1.09 ± 0.07		1.08 ± 0.11		1.06 ± 0.07		1.05 ± 0.08	
TP	11.51 ± 0.98	11.69 ± 0.86	–	10.96 ± 1.10	–	12.03 ± 0.90	–	12.23 ± 1.05	–

Table shows demographic and clinical features and absolute values of standard heart rate variability (HRV) measures for the control, LRRK2-associated Parkinson's disease (LRRK2-PD), idiopathic Parkinson's disease (iPD), *LRRK2* non-manifesting carrier (NMC), and related non-carrier (RNC) groups. Values are expressed as mean ± standard deviation or number of cases (*N*). UPDRSIII score is expressed as median ± interquartile range. Sex differences were assessed using a Chi-square test; mean heart rate (HR) using a multiple regression analysis adjusted for age, sex, and the effect of age and sex interaction; age, natural log-transformed disease duration (DD), and SCOPA-AUT score using a *t* test; and UPDRSIII using a Mann–Whitney *U* test

DD disease duration, *Fem* female, *HF* power spectral density of the high-frequency band (0.15–0.4 Hz), *HR* mean heart rate, *LF* power spectral density of the low-frequency band (0.04–0.15 Hz), *N* number of cases, *na* not applicable, *ns* $p \geq 0.05$, not statistically significant, *rMSSD* square root of the mean of the sum of the squares of differences between adjacent normal-to-normal intervals, *SCOPA-AUT* scales for outcomes in Parkinson's Disease-autonomic, *SDNN* standard deviation of normal-to-normal intervals, *UPDRSIII* Unified Parkinson's Disease Rating Scale part 3

*$N = 9$ iPD patients

**$N = 11$ iPD patients

HF power were inversely associated with the SCOPA-AUT total score ($r=-0.71$, $p=0.010$; $r=-0.66$, $p=0.020$; and $r=-0.62$, $p=0.033$, respectively). RE and PE features provided additional information on cardiac rhythm characteristics, as they were weakly or not at all correlated with other HRV measures. PE features and the ordinal pattern statistics that best distinguished LRRK2-PD from controls showed no dependence on HR.

HRV in LRRK2-PD vs. controls

Generally, HRV values were greater in LRRK2-PD patients than in controls, although only the beat-to-beat measures of HRV, i.e., rMSSD, HF power, DC, and AC, reached statistical significance (Table 2, Supplementary Fig. 2). Consistent with this, a significant increase in the irregularity of HR dynamics was verified in LRRK2-PD patients, as assessed by RE features (Table 2). DC and RE revealed that 7% and 28% of LRRK2-PD patients, respectively, had standardized

Table 2 Heart rate variability in Parkinson's disease patients and healthy controls

Description	Feature	Control	LRRK2-PD	LRRK2-PD vs. control	iPD	LRRK2-PD vs. iPD
Overall HRV	LnSDNN	3.45 ± 0.46	3.51 ± 0.34	ns	3.19 ± 0.51	**0.005**
	LnCV	1.27 ± 0.42	1.31 ± 0.33	ns	1.03 ± 0.45	**0.005**
	LnASI	3.42 ± 0.91	3.30 ± 0.65	ns	3.89 ± 0.96	**0.010**
	LnTP	2.44 ± 0.09	2.46 ± 0.07	ns	2.39 ± 0.10	0.047
	H	5.69 ± 0.59	5.81 ± 0.43	ns	5.36 ± 0.65	**0.001**
	LnMom3	−1.23 ± 1.27	−1.91 ± 1.39	ns	−1.05 ± 1.13	**0.01**
	LnMom4	1.25 ± 0.26	1.17 ± 0.33	ns	1.38 ± 0.38	**0.0006**
	LnMom5	1.18 ± 1.15	0.06 ± 1.68	ns	1.48 ± 1.12	**0.003**
	LnMom6	3.09 ± 0.68	2.77 ± 0.75	ns	3.32 ± 0.88	**0.0004**
	LnMom7	3.55 ± 1.33	2.19 ± 1.52	ns	3.87 ± 1.49	**0.0008**
	LnMom8	5.19 ± 1.13	4.57 ± 1.19	ns	5.52 ± 1.38	**0.0003**
	LnMom9	5.90 ± 1.67	4.41 ± 2.01	ns	6.25 ± 1.96	**0.0007**
Beat-to-beat HRV	LnrMSSD	2.92 ± 0.55	3.13 ± 0.40	**0.015**	2.80 ± 0.56	ns
	LnHF	2.29 ± 0.12	2.32 ± 0.09	**0.012**	2.25 ± 0.12	ns
	LnDC	1.98 ± 0.59	2.13 ± 0.47	**0.006**	1.68 ± 0.64	**0.026**
	Ln|AC|	1.97 ± 0.58	2.11 ± 0.42	**0.012**	1.71 ± 0.66	**0.032**
Intermediate-term HRV	LnLF	2.38 ± 0.10	2.40 ± 0.09	ns	2.32 ± 0.12	**0.032**
HR Irregularity	H_R (−α, 4)	1.29 ± 0.04	1.23 ± 0.06/1.05 ± 0.02	**0.002**	1.06 ± 0.02	**0.009**
	H_R (+α, 4)	0.94 ± 0.02	0.95 ± 0.02	**0.004**	0.94 ± 0.02	ns
	H_R (−α, 8)	1.24 ± 0.05	1.18 ± 0.07/1.05 ± 0.04	**0.002**	1.07 ± 0.04	**0.001**
	H_R (+α, 8)	0.94 ± 0.02	0.96 ± 0.02	**0.003**	0.94 ± 0.03	ns
	H_R (−α, 16)	1.12 ± 0.06	1.07 ± 0.05/1.04 ± 0.03	**0.003**	1.06 ± 0.04	**0.0004**
	H_R (+α, 16)	0.93 ± 0.02	0.95 ± 0.02/0.98 ± 0.01	**0.003**	0.97 ± 0.01	**0.0008**

Table shows heart rate variability (HRV) values for the control ($N=27$), LRRK2-associated Parkinson's disease (LRRK2-PD) ($N=14$), and idiopathic Parkinson's disease (iPD) ($N=20$) groups. Values are expressed as mean ± standard deviation. Beat-to-beat HRV features reflect the vagal modulation of heart rate (HR), whereas the remaining features may reflect the contribution of both vagal and sympathetic modulation. Group contrasts show p values for mean HRV differences as assessed through multiple regression analysis adjusted for age, sex, and mean HR. The LRRK2-PD vs. iPD contrasts were also adjusted for disease duration. Only significant values at $p<0.05$ are shown. p values remaining significant after correcting for multiple comparisons appear in bold text. The best results of Rényi entropy H_R calculated over sequences of length $\lambda=4$, 8, and 16 cardiac interbeat intervals, for positive and negative order α are shown. As distinct α values may be used, the values of the H_R revealing the greatest differences for the contrasts LRRK2-PD vs. control and LRRK2-PD vs. iPD are shown in that order. Increased irregularity of HR variations is manifested as an increase in H_R with positive order $+\alpha$ or as a decrease in H_R with negative order $-\alpha$.

α order of Rényi entropy, $\alpha=\{-5,-4,-3,-2,-1,+1,+2,+3,+4,+5\}$

AC acceleration capacity of heart rate, *ASI* autonomic stress index, *CV* coefficient of variation of normal-to-normal intervals, *DC* deceleration capacity of heart rate, *H* Shannon entropy, H_R Rényi entropy, *HF* power spectral density of the high-frequency band (0.15–0.4 Hz), *LF* power spectral density of the low-frequency band (0.04–0.15 Hz), *Ln* natural log-transformed value; Mom3–Mom9: standardized central moments of interbeat interval distribution of 3rd to 9th order, *ns* $p\geq0.05$, not statistically significant, *rMSSD* square root of the mean of the sum of the squares of differences between adjacent normal-to-normal intervals, *SDNN* standard deviation of normal-to-normal intervals, *TP* power spectral density of the total power band (0.04–0.4 Hz)

values outside the normal range (3–7, mean ± 2SD). PE analysis also revealed increased irregularity in the ordinal structure of HR dynamics over longer timescales ($\tau = 10$, 13, and 16 NN intervals) in the LRRK2-PD patients, with statistically significant results before correcting for multiple comparisons (e.g., $p = 0.031$). Additionally, the combination of two uncorrelated ordinal pattern statistic features, which showed the greatest differences between LRRK2-PD and controls ($p = 0.002$ and $p = 0.003$), facilitated the identification of significant cardiac rhythm alterations at an individual level ($p < 0.0001$) (Fig. 1). The best classification functions performed with overall accuracy, sensitivity, and specificity of 93% each (Supplementary Table 1).

HRV in LRRK2-PD vs. iPD

Most of the global HRV measures, LF power, and the beat-to-beat HRV markers DC and AC were significantly greater in LRRK2-PD than in iPD, although the greatest group differences were seen in central moments and RE features (Table 2). Additionally, we confirmed distinct forms of HRV alterations between the two PD groups, as significantly lower values were found in older iPD patients than in control individuals for SDNN, LF power, and TP ($p = 0.002$, $p = 0.004$, and $p = 0.011$, respectively), whereas no significant differences were found for rMSSD or HF power. Bradycardia (HR < 60 bpm) associated with elevated deceleration capacity of HR (DC > 5.5) was found in 21% of LRRK2-PD patients, compared with 4% of controls and 5% of iPD patients ($p > 0.05$ in both cases). A pattern of periodic HR accelerations between periods of respiratory sinus arrhythmia (Fig. 2) was also found in 21% of LRRK2-PD patients, compared with 4% of controls and 5% of iPD patients ($p > 0.05$ in both cases). Erratic sinus rhythm was not observed in any patient.

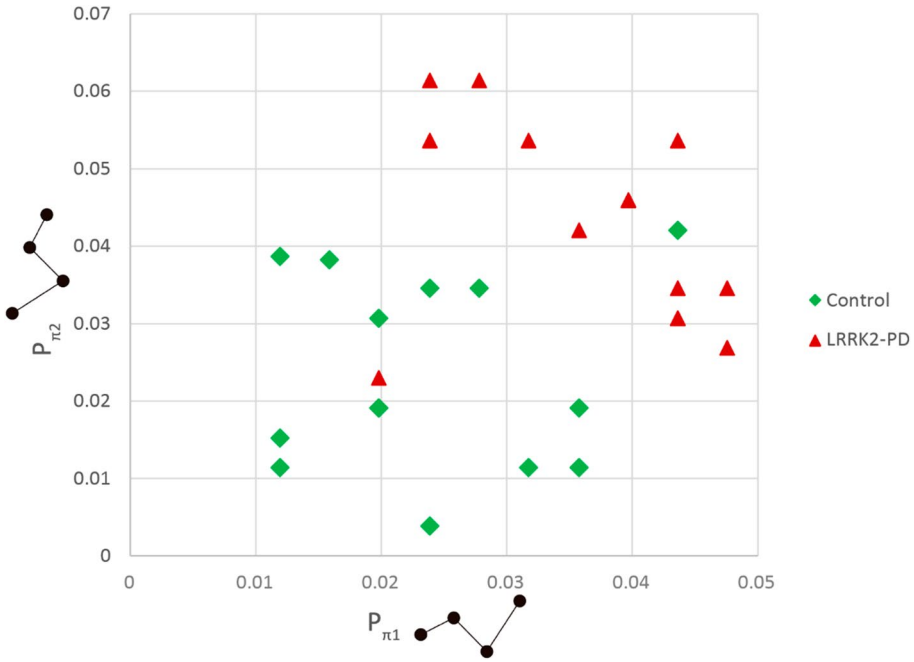

Fig. 1 Discrimination of LRRK2-associated Parkinson's disease (LRRK2-PD) patients and healthy controls based on ordinal pattern statistics of heart rate dynamics. The discrimination of patients and controls based on the probabilities of ordinal pattern $p_{\pi 1}$ and $p_{\pi 2}$ achieved the best classification accuracy (discriminant model $p < 0.0001$). $p_{\pi 1}$ and $p_{\pi 2}$ were calculated for patterns expanding four interbeat intervals over the timescales 13 and 16, respectively

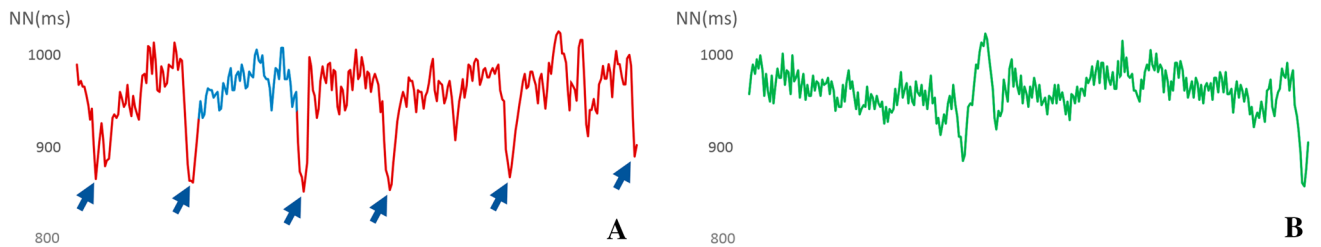

Fig. 2 Periodic heart rate accelerations in LRRK2-associated Parkinson's disease (LRRK2-PD). **a** Tachogram of a LRRK2-PD patient showing heart rate accelerations (indicated by blue arrows) separated by periods of respiratory sinus arrhythmia (one of these periods is illustrated by the blue tracing). **b** Tachogram of a control participant comparable in age, sex, and mean heart rate to the patient in panel A. *NN* intervals are plotted vs. the interval order (horizontal axis), *NN* normal-to-normal cardiac interbeat interval

HRV in LRRK2-NMC vs. RNC

Overall, HRV values in the LRRK2-NMC group were in an intermediate range between those in controls and LRRK2-PD patients, and no significant differences were found between LRRK2-NMC and RNC. However, there was an increase in the proportion of LRRK2-NMC individuals with values of beat-to-beat HRV measures above the mean standardized interval (4.5–5.5), as was found in the LRRK2-PD group (Fig. 3). Significant differences in the distribution of these features between LRRK2-NMC and controls were found only for HF power ($p < 0.05$). By analyzing the HRV *Z* scores above the normal range in LRRK2-NMC, it was possible to identify an individual who satisfied criteria for prodromal PD according to the International Parkinson and Movement Disorder Society (see Electronic Supplementary Material) (red bars in Fig. 3). However, not all of the LRRK2-NMC individuals showed high values, and a small percentage had values below the normal range for rMSSD and DC (purple bars in Fig. 3).

In addition, the RE feature H_R that best distinguished LRRK2-PD from controls, H_R (−α, 8) as seen in Table 2, showed a higher proportion of values on both sides of its distribution in LRRK2-NMC compared with controls, a pattern similar to that found for DC (Fig. 3). The subgroup of LRRK2-NMC that showed the highest DC and the lowest H_R (−α, 8) values (28%) also overlapped with the individuals in the LRRK2-PD group (Fig. 4).

Discussion

In this study, we assessed cardiac autonomic modulation in carriers of the *LRRK2* G2019S mutation manifesting and non-manifesting PD, through the HRV analysis of short-term interbeat interval sequences derived from EKGs recorded in a supine position at rest. Our findings indicated altered cardiac autonomic modulation that was independent of disease duration and occurred early in the course of LRRK2-PD, as suggested by consistent results obtained in both LRRK2-NMC and LRRK2-PD groups. These alterations could be identified in individual LRRK2-PD patients and were found to be different from the cardiac autonomic impairment described for iPD.

We found a significant increase in rMSSD and HF power in LRRK2-PD patients compared with controls, which might

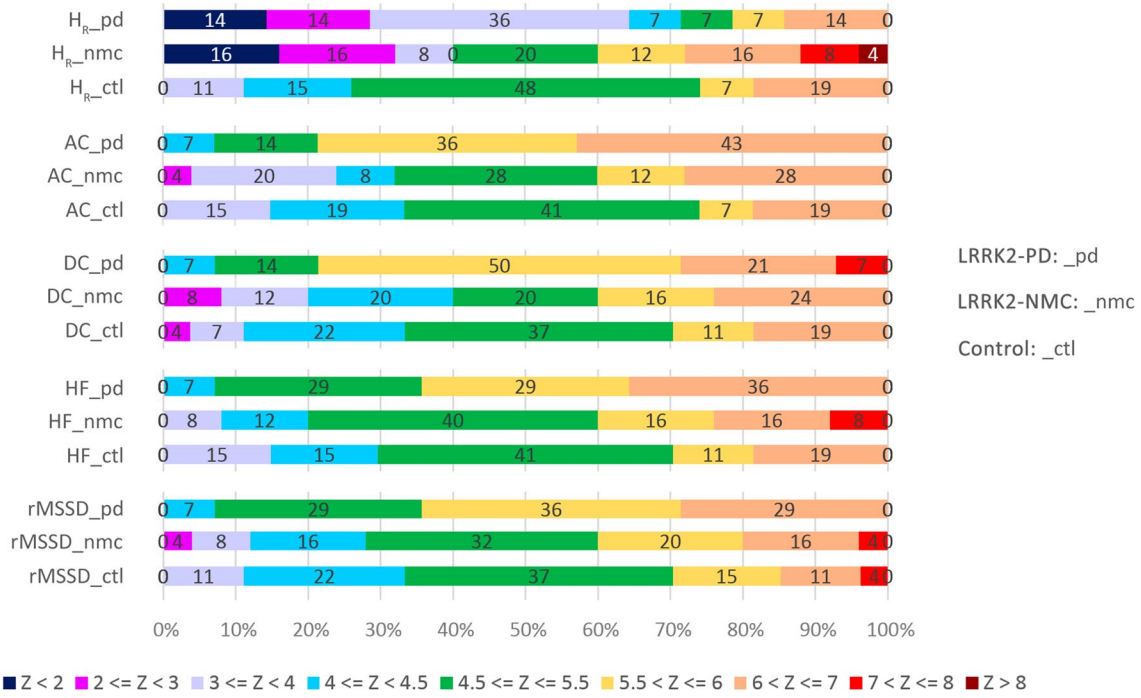

Fig. 3 Standardized distribution of beat-to-beat variability and irregularity measures of heart rate dynamics in LRRK2-non-manifesting carriers (LRRK2-NMC) compared with healthy control individuals (control) and LRRK2-associated Parkinson's disease (LRRK2-PD) patients. The numbers inside the bars represent the percentages of cases in the specific interval. Compared with controls, the mean interval (green bar) for rMSSD, HF, and AC is shortened and shifted to the left in the LRRK2-NMC and LRRK2-PD groups, indicating a greater proportion of values above the mean. For DC and H_R, the mean interval in the LRRK2-NMC group is shortened only, indicating a greater proportion of values below and above the mean. *AC* acceleration capacity of heart rate, *DC* deceleration capacity of heart rate, H_R Rényi entropy, *HF* power spectral density of the high-frequency band (0.15–0.4 Hz), *rMSSD* square root of the mean of the sum of the squares of differences between adjacent normal-to-normal intervals

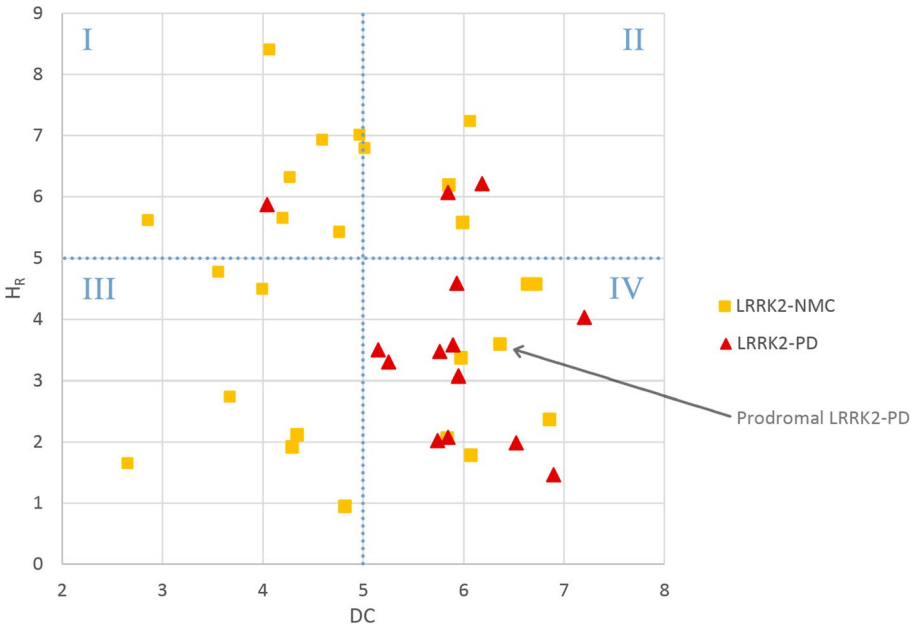

Fig. 4 Subgroup of LRRK2-non-manifesting carriers (LRRK2-NMC) overlapping with the LRRK2-associated Parkinson's disease (LRRK2-PD) group. The subgroup of LRRK2-NMC with the highest DC and the lowest H_R standardized values overlaps with the LRRK2-PD group in quadrant IV. *DC* deceleration capacity of heart rate, H_R Rényi entropy

suggest an overactive vagal system [22]. These results are consistent with the findings of a previous study, where a significant increase in both diurnal and nocturnal HF power was reported in a cohort of eight Sardinian LRRK2-PD patients [10]. Yet, in previous work reporting on a partially overlapping sample, we found no significant differences in rMSSD or HF power when comparing 20 LRRK2-PD patients with controls [9], although mean values for these measures were greater than controls in 10 of the LRRK2-PD patients [23]. Some of us recently described two distinct clinicopathological subtypes of G2019S-associated PD, one with typical Lewy pathology and the other devoid of this brain synucleinopathy [24]. The latter patients also exhibited evidence of less severe autonomic dysfunction. Consistent with this earlier finding, we now report that among LRRK2-PD patients, a higher prevalence of autonomic symptoms (SCOPA-AUT score) is associated with lower values in the HRV markers of cardiac vagal activity (DC, AC, and HF power). Hence, discrepancies across the HRV findings from LRRK2-PD studies could reflect the neuropathological heterogeneity of G2019S-associated PD.

We extended our previous findings by integrating novel approaches in HRV analysis. DC and RE were both significantly increased in the LRRK2-PD group compared with controls. In fact, the two measures in combination facilitated the identification of five LRRK2-PD patients with abnormally high values of beat-to-beat variability and irregularity of HR. Furthermore, DC and RE values tended to cluster towards both sides of their distribution in LRRK2-NMC, consistent with the existence of LRRK2-NMC subgroups as previously suggested [25]. Since LRRK2-PD is characterized by incomplete penetrance, the LRRK2-NMC subgroup with higher DC and irregularity of HR might represent those in a preclinical stage and thus at greater risk of developing PD, as was seen for the prodromal subject. DC has previously been shown to identify patients at higher risk of mortality following myocardial infarction [11]. Although this hypothesis needs testing in longitudinal studies, our results suggest that DC and RE are promising biomarkers that could provide prognostic information in LRRK2-NMC, potentially adding to the list of clinical conditions in which these features have proven useful [11, 13].

A further novel interpretation of the current findings is a differential involvement of the cholinergic and noradrenergic systems in LRRK2-PD and iPD. The novel HRV measures of vagal modulation, DC and AC, were both significantly elevated in LRRK2-PD compared with iPD and controls, whereas LF power, which reflects both vagal and sympathetic contributions to HR modulation, was similar in LRRK2-PD compared with controls, but greater compared with iPD patients, who actually showed a significant reduction in LF power compared with controls. These chronotropic alterations were associated with a greater global HRV and HR irregularity in LRRK2-PD compared with iPD, further suggesting pathophysiological differences for the development of cardiovascular autonomic neuropathy between the two types of PD.

Postganglionic noradrenergic lesions affecting α-adrenergic and β-adrenergic functions are the main cause of alterations in cardiac and vascular sympathetic modulation in iPD, both of which may occur in patients even in the absence of orthostatic hypotension and symptoms of orthostatic intolerance [26, 27]. Impairment of central vagal feedback loops, though, may account for the cardiac

chronotropic modulation disturbances found in LRRK2-PD. However, cardiac sympathetic denervation has also been reported in LRRK2-PD [28]. Consistent with our results, decreased HRV and sympathetic involvement have both been found in iPD compared with LRRK2-PD [8, 9]. Furthermore, increased cholinergic activity was recently reported in the brains of 14 LRRK2-PD and 16 LRRK2-NMC individuals using positron emission tomography [29]. However, we found that the prevalence of autonomic symptoms in LRRK2-PD was associated with lower values of the HRV markers of vagal modulation. Interestingly, sensory stimulation of the feet has been proposed to promote a mild enhancement of cardiac parasympathetic modulation [30]. Our findings suggest that applying pharmacological or non-pharmacological approaches to improve cardiac vagal modulation may be of value to further compensate for LRRK2-related dysfunction.

Animal studies have provided evidence for pro-inflammatory cytokine activation of vagal afferent signaling, which leads to excitatory synaptic transmission in the nucleus tractus solitarius and subsequent synaptic activation of efferent vagal pathways originating in the nucleus ambiguus [31], the main source of preganglionic parasympathetic cardiac motoneurons [32]. Elevated peripheral pro-inflammatory markers have been reported in *LRRK2* G2019S mutation carriers [25, 33], whereas a central microglial pro-inflammatory response has also been associated with *LRRK2* mutations [34]. Previous studies have shown involvement of the vagus nerve in attenuating release of cytokines and down-regulating systemic tumor necrosis factor production, providing evidence for a cholinergic anti-inflammatory pathway [35]. Increased peripheral cholinergic drive, as was observed in LRRK2-NMC and LRRK2-PD individuals, might therefore represent an early and sustained compensatory mechanism to counterbalance the inflammation reported in these cohorts.

The loss of integration of complex physiological feedback loops may result in abnormalities in cardiac autonomic control that manifest as random variations in the HR dynamics (erratic sinus rhythm), as have been described for older adults and for patients with cardiovascular disease [21, 22, 36]. This sinus arrhythmia of non-respiratory origin may be associated with an increased magnitude of beat-to-beat HR changes (e.g., increased rMSSD and HF power), even in the presence of reduced parasympathetic control of HR. However, we did not observe the abnormal patterns of HR variations characteristic of erratic sinus rhythm in the LRRK2-PD patients in our study. Furthermore, we found increased the short-term complexity of HR dynamics (decreased $H_R(-\alpha, 8)$) in these patients, and an enhanced sinus rhythm ability to slow the HR (increased DC).

In summary, our findings are consistent with the results of previous work reporting (i) greater central cholinergic activity in *LRRK2* carriers both manifesting and non-manifesting PD [29], (ii) increased cardiac cholinergic activity in PD patients with the *LRRK2* mutation [10], and (iii) distinct patterns of cardiac autonomic profile among LRRK2-PD and iPD patients [8, 9]. Further study to clarify whether central and peripheral hypercholinergic activity is a G2019S mutation-related mechanism, which operates as a form of prodromal compensation for *LRRK2* immune activation and persists after PD becomes manifest, needs to be addressed.

Limitations

The study patients were receiving L-dopa treatment, which may have affected autonomic regulation, although previous studies have found no significant differences in cardiovascular autonomic function between drug-naïve and dopaminergic drug-treated iPD patients [2, 37]. Although HRV differences between groups were consistent, larger sample sizes are needed to further explore the heterogeneous presentation of PD. Additional information on autonomic modulation of cardiac control might also be gained by using 24-h Holter monitoring. Furthermore, assessment of cardiovascular reflexes by means of noninvasive autonomic tests (active orthostasis, deep breathing, Valsalva maneuver, and physical exercise) may have provided further insight into autonomic regulation of cardiac and vasomotor functions [38, 39]. Longer recording lengths may be more appropriate for analysis, considering the limitations of permutation-based entropies [40].

Conclusions

Our findings extend current knowledge of differences in the non-motor profile of LRRK2-PD and iPD. The *LRRK2* G2019S mutation was found to be associated with significantly increased beat-to-beat HRV, presumably of cardiac cholinergic origin, suggesting that modification of central vagal feedback loops might occur in the preclinical, prodromal, and clinical stages of LRRK2-PD. Cardiac chronotropic modulation alterations distinguished LRRK2-PD from iPD patients, supporting distinct pathological mechanisms underlying both PD types. Our results raise the possibility that Rényi entropy and HRV measures of vagal modulation may be relevant biomarkers of prodromal LRRK2-PD. Further research and longitudinal studies, aimed at performing an integral evaluation of cardiovascular autonomic function in different stages of LRRK2-PD, are needed to understand the full clinical importance of our findings.

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Compliance with ethical standards

Conflict of interest CCN reports employment with Universidad de La Habana, and grants from the International Brain Research Organization, International Parkinson and Movement Disorder Society, and Vrije Universiteit Brussel, Belgium. CM reports consultancies with Acorda Therapeutics; honoraria for teaching from EMD Serono, steering committee for Michael J. Fox Foundation; grants from the Michael J. Fox Foundation, Canadian Institutes of Health Research, International Parkinson and Movement Disorder Society, and National Institutes of Health Research; and employment with University Health Network. NPV reports none. DJC reports none. LS reports none. BS reports none. SMG reports employment with the University of California-San Francisco, San Francisco Veterans Affairs Health Care System, and grants from the Michael J. Fox Foundation, National Institute for Occupational Safety and Health (NIOSH), Biogen, and the U.S. Department of Defense. ME reports none. PKS reports none. AEL has served as an advisor for Abbvie, Acorda, Biogen, Bristol-Myers Squibb, Janssen, Sun Pharma, Kallyope, Merck, Paladin, and Corticobasal Degeneration Solutions; received honoraria from Sun Pharma, Medichem, Medtronic, AbbVie and Sunovion; received grants from Brain Canada, Canadian Institutes of Health Research, Corticobasal Degeneration Solutions, Edmond J. Safra Philanthropic Foundation, Michael J. Fox Foundation, the Ontario Brain Institute, National Parkinson Foundation, Parkinson Society Canada, and W. Garfield Weston Foundation; received publishing royalties from Elsevier, Saunders, Wiley-Blackwell, Johns Hopkins Press, and Cambridge University Press. HFJ reports none. AM reports employment with Universidad de La Habana.

Ethical standards The study protocol was approved by the University Health Network Research Ethics Board (Toronto) and El Camino Hospital Institutional Review Board (Parkinson's Institute). The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent All participants provided written informed consent prior to their inclusion in the study.

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