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Original Article

Analysing Heart Rate Variability in Parkinson's Disease: A Gender-Based Comparison of Patients with and Without Anxiety Symptoms-A Pilot Study

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ABSTRACT

Background and Aim: Parkinson's Disease (PD) is associated with autonomic dysfunction, and anxiety symptoms may add to this burden. Gender-related differences in autonomic control are well recognised, but how they interact with anxiety in PD is unclear. This pilot study examined gender-related autonomic responses to stress, assessed through Heart Rate Variability (HRV), in patients with PD with and without anxiety symptoms and in healthy controls. **Materials and Methods:** HRV was recorded in 52 participants (24 healthy controls, 14 PD patients without anxiety and 14 PD patients with anxiety) during supine rest and a mental arithmetic stress task. Time-domain (Standard Deviation of NN Intervals [SDNN], Root Mean Square of Successive Differences [RMSSD]) and frequency-domain (Low-Frequency [Low Frequency (LF)] power, High-Frequency [High Frequency (HF)] power, LF/HF ratio) measures were analysed with a two-way repeated measures ANOVA (Group, with six groups defined by gender and clinical status, × Condition, rest vs. stress), followed by Sidak-corrected *post hoc* comparisons. Significance was set at $p < 0.05$. **Results:** Stress had significant main effects on LF power ($p = 0.0015$), HF power ($p = 0.0100$) and the LF/HF ratio ($p = 0.0037$), whereas SDNN and RMSSD did not change. Group and Group × Condition effects were not significant. In *post hoc* comparisons, male PD patients without anxiety showed a significant fall in HF power, indicating vagal withdrawal ($p = 0.0469$); female PD patients without anxiety showed a significant rise in LF power ($p = 0.0248$); and female PD patients with anxiety showed a significant rise in the LF/HF ratio, indicating a shift towards sympathetic dominance ($p = 0.0259$). Healthy controls showed minimal changes. **Conclusion:** In this exploratory pilot study, autonomic stress responses in PD differed by gender: male patients showed vagal withdrawal, whereas female patients showed sympathetic activation, most marked in women with anxiety symptoms. Because the Group × Condition interactions were not significant and the female subgroups were small, these findings are hypothesis-generating and require confirmation in larger, gender-balanced samples.

Keywords: Anxiety Symptoms, Autonomic Dysfunction, Gender Differences, Heart Rate Variability, Parkinson's Disease.

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INTRODUCTION

Parkinson's Disease (PD) is a progressive neurodegenerative disorder characterised by motor symptoms and a range of non-motor symptoms, including autonomic dysfunction and anxiety. Anxiety disorders are estimated to affect about 31% of patients.[1,2] Heart Rate Variability (HRV), the beat-to-beat variation in heart rate, is a non-invasive index of Autonomic Nervous System (ANS) function that reflects the balance between sympathetic ("fight-or-flight") and parasympathetic ("rest-and-digest") influences on the heart.[3,4] Reduced HRV has been reported in PD.[5] Cardiac sympathetic denervation is well documented in the disease,[6,7] and cardiovascular autonomic dysfunction may appear early, even before the onset of motor symptoms.[8–10] These changes are attributed to Lewy-body pathology in cardiac autonomic nerve fibres and brainstem autonomic nuclei, together with disruption

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of central autonomic networks, and autonomic dysfunction has been linked to the burden of motor and non-motor symptoms.[11–13]

Anxiety disorders are among the most common psychiatric conditions[14] and are themselves associated with autonomic dysregulation. Functional imaging studies implicate amygdala hyperactivity in anxiety,[15] and anxiety disorders are associated with reduced HRV, particularly reduced vagally mediated (high-frequency) activity.[16,17] The neurovisceral integration model proposes that weakened prefrontal inhibitory control of the amygdala disinhibits sympathoexcitatory pathways while suppressing vagal output,[18,19] and dysregulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis may also contribute.[20] The relationship between anxiety and PD is bidirectional: an anxious personality has been associated with a higher risk of later PD,[21] while in established PD, autonomic dysfunction has been related to non-motor symptoms, including anxiety.[12]

Gender is a further source of variation in autonomic control. In healthy adults, women tend to show higher vagally mediated HRV than men, whereas men tend to show relatively greater Low Frequency (LF) modulation,[22] and HRV declines with age in both sexes.[23] Sex hormones have been proposed to contribute to these differences, but whether gender-related patterns are preserved, exaggerated or lost in PD, and how anxiety modifies them, has received little attention. To our knowledge, no previous study has compared HRV between men and women with PD with and without anxiety symptoms.

This pilot study aimed to address this gap. Its aims were to:

1. Compare HRV parameters (SDNN, Root Mean Square of Successive Differences (RMSSD), LF power, High Frequency (HF) power and LF/HF ratio) at rest and during mental stress between PD patients with anxiety symptoms (PD-A), PD patients without anxiety symptoms (PD-NA) and healthy controls.

2. Investigate gender-related differences in these HRV responses.

3. Explore the combined influence of PD, anxiety symptoms and gender on autonomic function.

We hypothesised that PD-A patients would show greater autonomic dysfunction than PD-NA patients (lower HRV and a greater shift towards sympathetic dominance during stress), and that men and women would show different HRV patterns.

MATERIALS AND METHODS

This cross-sectional pilot study recruited 72 participants; data from 52 are reported here because data collection was limited by the study period. The sample size was estimated with G*Power using an effect size of 2.12 from previous literature, $\alpha = 0.05$ and power = 0.95. Participants were recruited from the outpatient neurology department of the National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru. The sample comprised 24 Healthy Controls (HC; 12 men, 12 women) and 28 PD patients, divided by anxiety status into 14 PD patients without anxiety symptoms (PD-NA; 12 men, 2 women) and 14 PD patients with anxiety symptoms (PD-A; 9 men, 5 women). Inclusion criteria were age 30-60 years, literacy, and the ability to give informed consent and to perform the mental arithmetic task. The age range was restricted to reduce the confounding effect of age-related autonomic decline, which becomes more marked after 60 years, and to avoid early-onset PD in younger adults, which may have a distinct pathophysiology. Exclusion criteria were conditions that confound HRV interpretation: cardiac arrhythmia, diabetes mellitus, other neurodegenerative or psychiatric disorders, a pacemaker, severe cognitive impairment (MMSE < 24), pregnancy or lactation, and use of medications that modify autonomic function.[4,5] Healthy controls were screened for psychiatric morbidity with the Modified Mini Screen (MMS). Anxiety was assessed with the Hamilton Anxiety Rating Scale (HAM-A), with a score of ≥ 10 used as the threshold for clinically relevant anxiety symptoms, and cognition was assessed with the Mini-Mental State Examination (MMSE; cut-off ≥ 24).

A clinical psychologist administered the HAM-A (symptoms over the preceding two weeks) and the MMSE. For autonomic assessment, two 5-min segments of short-term HRV were recorded with a three-lead ECG, in line with Task Force recommendations:[4,24] (1) supine rest and (2) a Mental Arithmetic Task (MAT) as the stressor, consisting of serial subtractions, additions, multiplications and divisions with a time limit of 5 sec per sum. Participants abstained from caffeine, nicotine and vigorous activity for 12 hr before testing, and the testing room was temperature-controlled (22-24 °C).

ECG data were pre-processed with LabChart Pro HRV software (version 8.1.30), using a Poincaré plot filter to identify and remove artefacts. The following HRV measures were derived:

Time-Domain Measurements

1. SDNN (ms; standard deviation of NN intervals): Global Autonomic Variability.[25]

2. RMSSD (ms; root mean square of successive differences): Vagally Mediated Variability.[4]

Frequency-Domain Measurements

- **LF power (nu; 0.04-0.15 Hz):** mixed sympathetic and baroreflex-mediated activity; it is not a pure index of sympathetic tone.[26]
- **HF power (nu; 0.15-0.40 Hz):** respiratory sinus arrhythmia, an index of vagal modulation.[27]
- **LF/HF ratio:** an index of sympathovagal balance, interpreted with the same caution as LF power.[26]

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Frequency-domain measures are expressed in normalised units (nu), which minimise inter-individual variability.

Statistical analyses were performed with GraphPad Prism (version 8.4). For each HRV parameter (SDNN, RMSSD, LF power, HF power and LF/HF ratio), a two-way repeated measures ANOVA tested the effects of Condition (rest vs. MAT; within-subject factor), Group (six groups: male and female healthy controls, PD-NA and PD-A; between-subject factor) and their interaction, treating subject variability as a random factor. *post hoc* comparisons of rest versus MAT within each group used Sidak's correction. Results are reported as mean differences with 95% confidence intervals and adjusted p values. Between-group differences in HAM-A scores were assessed with the Mann-Whitney U test. Statistical significance was set at ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$).

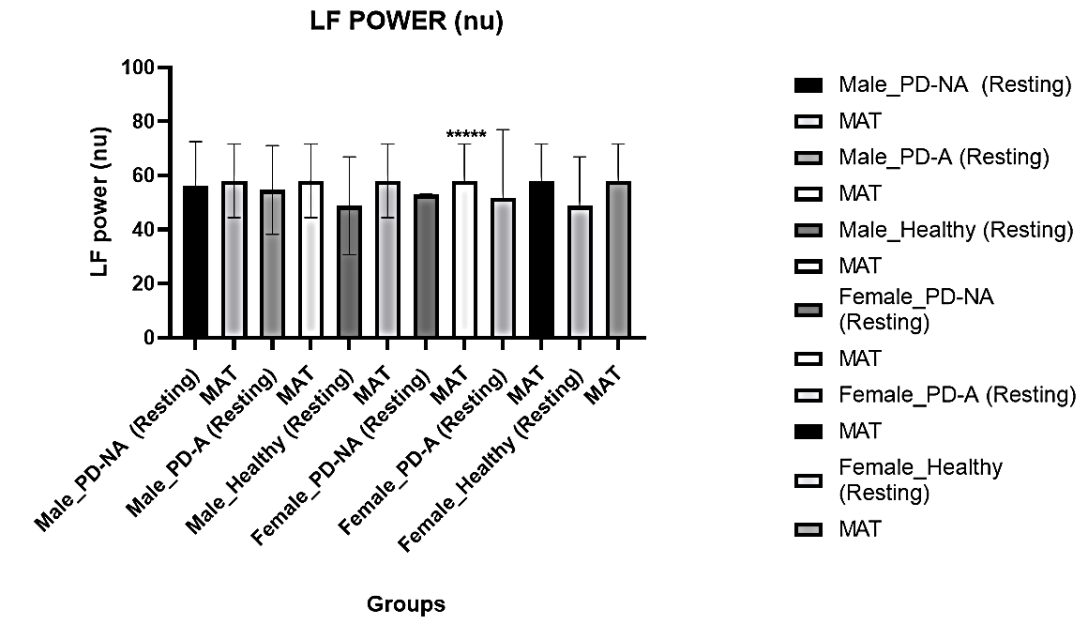

Figure 1: Low Frequency (LF) power at rest and during Mental Arithmetic Task (MAT). Data are presented as mean±SD. Female Parkinson's disease patients without anxiety symptoms (Female_PD-NA) showed a significant increase in LF power during stress ($^{**}p = 0.0248$, Sidak's multiple comparisons test). PD-NA: Parkinson's disease without anxiety; PD-A: Parkinson's disease with anxiety; nu: normalized units.

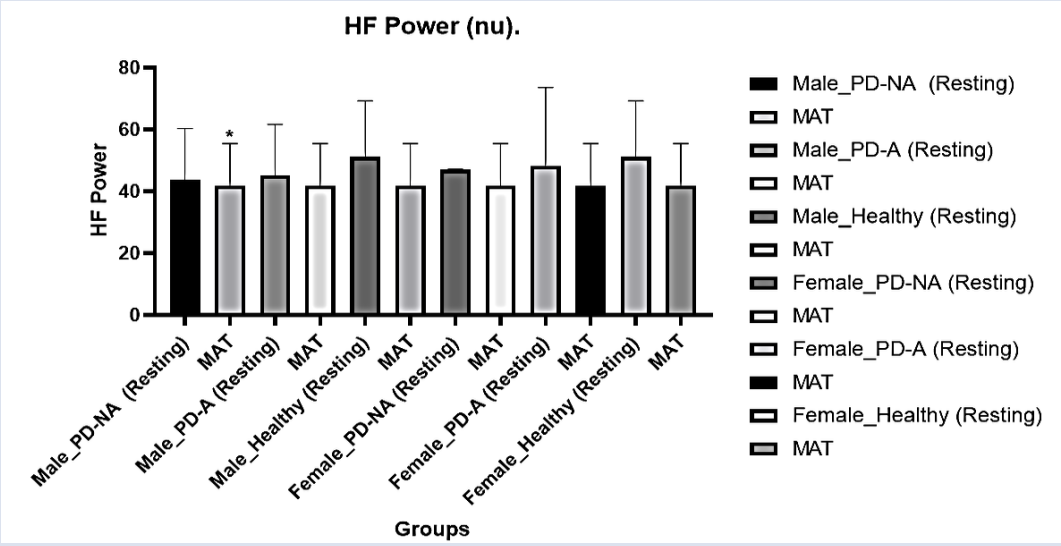

Figure 2: Data are expressed as mean±SD. Male Parkinson's disease patients without anxiety (Male_PD-NA) demonstrated a significant reduction in HF power during stress ($^{*}p = 0.0469$, Sidak's multiple comparison test). PD-NA: Parkinson's disease without anxiety; PD-A: Parkinson's disease with anxiety; nu: normalized units.

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Table 1: Descriptive Data.

Parameter	Condition	Male_PD-NA ($n = 12$)	Male_PD-A ($n = 9$)	Male_Healthy ($n = 12$)	Female_PD-NA ($n = 2$)	Female_PD-A ($n = 5$)	Female_Healthy ($n = 12$)	*p* value (Condition)	*p* value (Group × Condition)
SDNN (ms)	Rest	40.55±22.2331.73 (23.69-53.05)	35.46±27.0223.89 (18.33-47.19)	35.75±19.9731.98 (19.53-54.33)	18.00±5.1918.00 (14.33-21.67)	26.39±22.4012.25 (9.20-50.65)	35.79±19.8527.01 (19.29-52.81)	0.8100	0.2375
	MAT	35.13±30.3224.90 (10.92-46.58)	31.76±28.4321.55 (10.75-47.78)	29.11±23.5620.50 (11.28-48.40)	12.55±1.1812.55 (11.72-13.39)	24.29±27.348.73 (3.42-52.95)	29.78±18.7029.07 (12.90-44.40)		
RMSSD (ms)	Rest	39.52±13.8138.67 (25.66-53.42)	38.84±13.8534.22 (28.41-52.65)	35.31±12.4036.44 (25.92-44.32)	18.00±5.1918.00 (14.33-21.67)	26.39±22.4012.25 (9.20-50.65)	35.79±19.8527.01 (19.29-52.81)	0.4618	0.4330
	MAT	35.31±12.4036.44 (25.92-44.32)	35.31±12.4036.44 (25.92-44.32)	29.11±23.5620.50 (11.28-48.40)	12.55±1.1812.55 (11.72-13.39)	24.29±27.348.73 (3.42-52.95)	29.78±18.7029.07 (12.90-44.40)		
LF (nu)	Rest	56.09±16.4657.91 (38.57-72.55)	54.69±16.3859.96 (37.24-69.99)	48.80±18.0853.01 (31.12-65.41)	52.99±0.3852.99 (52.72-53.26)	51.66±25.3146.30 (28.28-77.71)	48.80±18.0853.01 (31.12-65.41)	0.0015**	0.4715
	MAT	58.07±13.6059.67 (49.00-71.71)	58.07±13.6059.67 (49.00-71.71)	58.07±13.6059.67 (49.00-71.71)	58.07±13.6059.67 (49.00-71.71)	58.07±13.6059.67 (49.00-71.71)	58.07±13.6059.67 (49.00-71.71)		
HF (nu)	Rest	43.91±16.4642.09 (27.45-61.43)	45.31±16.3840.04 (30.01-62.76)	51.20±18.0846.99 (34.59-68.88)	47.01±0.3847.01 (46.74-47.28)	48.34±25.3153.70 (22.29-71.72)	51.20±18.0846.99 (34.59-68.88)	0.0100*	0.5085
	MAT	41.93±13.6040.33 (28.29-51.00)	41.93±13.6040.33 (28.29-51.00)	41.93±13.6040.33 (28.29-51.00)	41.93±13.6040.33 (28.29-51.00)	41.93±13.6040.33 (28.29-51.00)	41.93±13.6040.33 (28.29-51.00)		
LF/HF Ratio	Rest	1.89±1.151.59 (0.93-2.92)	2.02±1.271.93 (0.75-2.81)	1.54±0.551.61 (0.96-1.86)	1.41±0.301.41 (1.20-1.62)	3.25±3.101.75 (0.75-6.50)	1.54±0.551.61 (0.96-1.86)	0.0037**	0.1565
	MAT	2.11±1.331.60 (1.31-2.87)	2.11±1.331.60 (1.31-2.87)	2.11±1.331.60 (1.31-2.87)	2.11±1.331.60 (1.31-2.87)	2.11±1.331.60 (1.31-2.87)	2.11±1.331.60 (1.31-2.87)		

Data presented as mean±standard deviation (upper row) and median (interquartile range) (lower row). PD-NA: Parkinson's disease without anxiety; PD-A: Parkinson's disease with anxiety; MAT: Mental Arithmetic Task; nu: normalised units. *p* values from repeated measures ANOVA (rmANOVA). Bold values indicate statistical significance ($p < 0.05$).

The study was approved by the Institutional Ethics Committee of NIMHANS, Bengaluru, and written informed consent was obtained from all participants before inclusion.

RESULTS

HRV was analysed in 52 participants: 28 PD patients (14 PD-A and 14 PD-NA) and 24 healthy controls, all aged 30-60 years (Table 1). Gender distribution was balanced in the healthy controls (12 men, 12 women) but male-predominant in both PD groups (PD-NA: 12 men, 2 women; PD-A: 9 men, 5 women). The PD-A group had significantly higher HAM-A scores (median 13.50, IQR 11.50-18.50) than the PD-NA group (median 4.50, IQR 3.00-6.50; Mann-Whitney U = 0, $p < 0.0001$), confirming a clear distinction between anxious and non-anxious patients. All participants scored within the normal range on the MMSE (≥24). HRV at rest and during the MAT is summarised in Table 1, the ANOVA results are given in Table 2, and the significant *post hoc* comparisons in Table 3.

SDNN: There were no significant main effects of group ($p = 0.7327$) or condition ($p = 0.8100$) and no significant Group × Condition interaction ($p = 0.2375$) (Table 2). *Post hoc* comparisons showed no significant difference between rest and stress in any group (all adjusted $p > 0.05$). Thus, overall autonomic variability, as measured by SDNN, did not differ between groups or conditions in this sample.

RMSSD: There were no significant main effects of group ($p = 0.5737$) or condition ($p = 0.4618$) and no significant Group × Condition interaction ($p = 0.4330$) (Table 2). No pairwise comparison between rest and stress was significant in any group (all adjusted $p > 0.05$). A numerical decline in RMSSD under stress in the Male_PD-A group did not reach significance (adjusted $p = 0.2575$). Overall, vagally mediated variability measured by RMSSD did not differ significantly between groups or conditions.

LF power: There was a significant main effect of condition ($p = 0.0015$; partial $\eta^2 \approx 0.20$), showing that the mental arithmetic task elicited an autonomic response with an overall increase in LF

Table 2: rmANOVA DATA.

Parameter	Effect	SS	DF	MS	F	*p* value	Significance
SDNN	Condition	23.85	1,46	23.85	0.0585	0.8100	ns
	Group	2664	5,46	532.8	0.5564	0.7327	ns
	Condition × Group	2881	5,46	576.2	1.413	0.2375	ns
RMSSD	Condition	322.4	1,46	322.4	0.5507	0.4618	ns
	Group	2256	5,46	451.2	0.7732	0.5737	ns
	Condition × Group	2904	5,46	580.9	0.9922	0.4330	ns
LF Power	Condition	1143	1,46	1143	11.42	0.0015	**
	Group	1219	5,46	243.8	0.4211	0.8316	ns
	Condition × Group	464.4	5,46	92.87	0.9282	0.4715	ns
HF Power	Condition	958.1	1,46	958.1	7.227	0.0100	*
	Group	440.6	5,46	88.12	0.2381	0.9436	ns
	Condition × Group	576.7	5,46	115.3	0.8700	0.5085	ns
LF/HF Ratio	Condition	12.06	1,46	12.06	9.354	0.0037	**
	Group	22.54	5,46	4.508	1.168	0.3392	ns
	Condition × Group	10.88	5,46	2.177	1.688	0.1565	ns

Abbreviations: SS=Sum of Squares; DF=Degrees of Freedom; MS=Mean Square; F=*F* statistic. Bold values indicate statistical significance. **$p < 0.05$; **$p < 0.01$; ns=not significant.*

Table 3: Significant *post hoc* Comparisons (Sidak's Multiple Comparisons Test).

Parameter	Group	Mean Difference (Rest – MAT)	95% CI of Difference	Adjusted *p* value	Significance
LF Power	Female_PD-NA	-14.21	-27.18 to -1.252	0.0248	*
HF Power	Male_PD-NA	+13.04	0.1170 to 25.96	0.0469	*
LF/HF Ratio	Female_PD-A	-2.15	-4.128 to -0.1792	0.0259	*
LF Power	Male_PD-NA	-11.01	-22.24 to 0.2148	0.0571	+
LF/HF Ratio	Male_PD-A	-1.392	-2.864 to 0.07922	0.0725	+

Sidak's multiple comparisons test data. CI stands for confidence interval; a positive difference denotes a higher value at rest, whereas a negative difference denotes a higher value during MAT. *$p < 0.05$; + $p < 0.10$ (borderline significance).

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power. The main effect of group (p = 0.8316) and the Group × Condition interaction (p = 0.4715) were not significant (Table 2). *post hoc* testing showed a significant increase in LF power from rest to stress in the Female_PD-NA group (increase of 14.21 nu; adjusted p = 0.0248; Figure 1, Table 3). The Male_PD-NA group showed a borderline increase (11.01 nu; adjusted p = 0.0571). No significant change was found in the Male_PD-A, Male_Healthy, Female_PD-A or Female_Healthy groups (all adjusted $p > 0.05$). Thus, the stress task increased LF power overall, with the clearest group-level increase in female PD-NA patients, although this group comprised only two women.

HF power: There was a significant main effect of condition (p = 0.0100; partial $\eta^2 \approx 0.14$), indicating an overall reduction in HF power, and hence vagal modulation, during stress. The main effect of group (p = 0.9436) and the Group × Condition interaction (p = 0.5085) were not significant (Table 2). *Post hoc* testing showed a significant decrease in HF power during stress in the Male_PD-NA group (decrease of 13.04 nu; adjusted p = 0.0469; Figure 2, Table 3), indicating vagal withdrawal. The Male_PD-A group showed a similar decrease (13.77 nu) that did not reach significance (adjusted p = 0.0847). Healthy males showed minimal change (1.88 nu; adjusted p = 0.9991), and no female group showed a significant change (all adjusted $p > 0.05$). Thus, vagal withdrawal during stress was evident in men with PD, whereas healthy men showed almost no change in HF power.

LF/HF ratio: There was a significant main effect of condition (p = 0.0037; partial $\eta^2 \approx 0.17$), reflecting an overall shift towards sympathetic dominance during stress. The main effect of group (p = 0.3392) and the Group × Condition interaction (p = 0.1565) were not significant (Table 2). *post hoc* testing showed a significant increase in the LF/HF ratio from rest to stress in the Female_PD-A group (increase of 2.15; adjusted p = 0.0259; Figure 3, Table 3), the largest shift towards sympathetic dominance in any group. The Male_PD-A group showed a borderline increase (1.39; adjusted p = 0.0725). The Male_PD-NA, Male_Healthy, Female_PD-NA and Female_Healthy groups showed no significant change (all adjusted $p > 0.05$). Partial η^2 values for the condition effects were calculated from the F statistics in Table 2.

DISCUSSION

In this pilot study, mental arithmetic stress produced the expected autonomic response across participants, with higher LF power and LF/HF ratio and lower HF power, whereas the time-domain measures (SDNN and RMSSD) did not change. This pattern suggests that frequency-domain indices may be more sensitive than short-term time-domain indices to stress-induced autonomic shifts.[4,25] The Group × Condition interactions were not significant for any parameter, so the gender- and anxiety-related patterns described below derive from exploratory within-group comparisons and should be interpreted cautiously. Within these limits, the groups differed in how they responded. Men with PD without anxiety showed significant vagal withdrawal (a fall in HF power), whereas healthy men showed almost no change. Women with PD without anxiety showed a significant rise in LF power, and women with PD with anxiety showed the largest shift towards sympathetic dominance (rise in LF/HF ratio). Earlier work has documented reduced cardiac sympathetic innervation in PD;[6,7] our findings raise the possibility that, under stress, the

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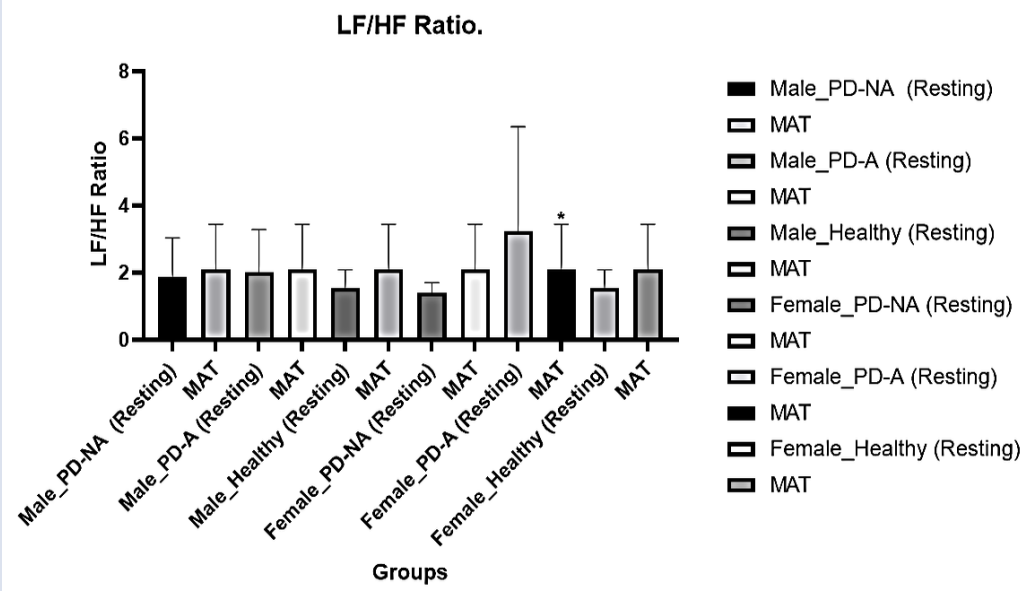

Figure 3: LF/HF ratio at rest and during the Mental Arithmetic Task (MAT). Results are expressed as mean±SD. Female Parkinson's disease patients with anxiety (Female_PD-A) had a significant increase in LF/HF ratio during stress, which indicates the dominance of the sympathetic nervous system. **p = 0.0259, Sidak's multiple comparison test. PD-NA: Parkinson's disease without anxiety; PD-A: Parkinson's disease with anxiety.

direction of autonomic change differs between men and women with PD, but this needs to be tested directly. Because LF power and the LF/HF ratio are not pure measures of sympathetic activity,[26] "sympathetic" interpretations here remain tentative. The condition effects were moderate to large (partial $\eta^2 \approx 0.14$-0.20), but effect sizes from a small pilot sample are imprecise and do not by themselves establish clinical significance.

Anxiety symptoms appeared to modify these responses. Women with PD and anxiety symptoms showed a significant rise in the LF/HF ratio during stress (adjusted $p = 0.0259$), which was not seen in women with PD without anxiety (adjusted $p > 0.05$), and men with PD and anxiety showed a borderline rise (adjusted $p = 0.0725$). Men with PD and anxiety also showed a fall in HF power (13.77 nu) of similar size to that in men without anxiety (13.04 nu), although this did not reach significance (adjusted $p = 0.0847$). These directional trends are compatible with evidence that anxiety is associated with reduced vagal activity and a shift towards sympathetic predominance,[17] and with proposed mechanisms including amygdala hyperactivity,[15] impaired prefrontal inhibition[18,19] and HPA-axis dysregulation,[20] superimposed on brainstem autonomic involvement in PD.[28] However, because the interaction terms were not significant, we cannot conclude that anxiety altered the autonomic response; this requires confirmation in larger samples.

The Gender-Related Patterns Can Be Summarised as Follows

Men with PD without anxiety showed significant vagal withdrawal (HF power fell by 13.04 nu; $p = 0.0469$) and a borderline rise in LF power (11.01 nu; $p = 0.0571$), suggesting a stress response dominated by loss of parasympathetic activity. Men with PD and anxiety showed a similar fall in HF power (13.77 nu; $p = 0.0847$) and a borderline rise in the LF/HF ratio (1.39; $p = 0.0725$). Women with PD without anxiety showed a significant rise in LF power (14.21 nu; $p = 0.0248$) without significant vagal withdrawal, although this group included only two women. Women with PD and anxiety showed the largest sympathovagal shift (LF/HF ratio increased by 2.15; $p = 0.0259$), whereas healthy women showed no significant change. Together, these observations suggest, as a hypothesis, that men with PD respond to stress mainly through vagal withdrawal and women mainly through sympathetic activation, with anxiety most clearly associated with a sympathetic shift in women.

Gender differences in HRV are well documented in healthy people.[22,23] Proposed explanations include oestrogen-related protective effects on vagal and brainstem autonomic function and gender differences in Brain-Derived Neurotrophic Factor (BDNF) signalling,[29] but hormonal status was not measured in this study, so any link to our findings is speculative. As a working hypothesis, we propose the term "autonomic rigidity" for a reduced ability to modulate autonomic activity flexibly in response to changing demands, which might present as excessive sympathetic activation in women and excessive vagal withdrawal in men with PD. This idea is conceptually related to the loss of autonomic flexibility described in the neurovisceral integration model,[18] but our data cannot establish it.

Clinical Implications

Condition effects on LF power, HF power and the LF/HF ratio suggest that HRV recorded during a standardised stressor may provide information beyond resting recordings.[25] However, group effects were not significant, and the clinical usefulness of stress-reactivity measures for detecting early autonomic dysfunction in PD needs to be validated in larger studies. If the gender-related patterns are confirmed, they should be considered when designing research and treatment for PD. In particular:

Males: men with PD, who showed predominantly vagal withdrawal, might benefit from approaches that support vagal function, such as HRV biofeedback[30] or vagus nerve stimulation.[28]

Females: women with PD, particularly those with anxiety symptoms, who showed a sympathetic shift, might benefit from stress-reduction techniques and treatment of anxiety. Pharmacological or hormonal approaches would require dedicated study, and gender-specific treatment strategies remain to be developed. Screening and treating anxiety in PD is worthwhile for its psychosocial benefits and may also help autonomic function, although this remains to be shown.

CONCLUSION

This pilot study suggests that autonomic responses to stress in PD may differ by gender. Men with PD showed vagal withdrawal during stress, whereas women with PD showed sympathetic activation, most marked in women with anxiety symptoms. These findings arise from exploratory comparisons in a small sample in which the Group × Condition interactions were not significant, and they should be regarded as hypothesis-generating. If confirmed, they would support gender-specific assessment of autonomic function and anxiety in PD. Larger, gender-balanced studies are needed.

Limitations of the Study

This pilot study has several limitations that should be considered when interpreting the results:

1) The PD-NA group included only two women ($n = 2$), and both PD groups were male-predominant. This limited statistical power for gender comparisons, precludes firm conclusions about women with PD without anxiety, and may have masked additional effects.

2) Although condition effects were significant for LF power, HF power and the LF/HF ratio, the Group × Condition interactions

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were not. The significant gender- and anxiety-related findings come from *post hoc* comparisons within small groups, without correction across the five HRV parameters, so they may include false-positive results, and a significant result in one group and a borderline result in another do not demonstrate a difference between those groups. A larger sample is needed to confirm these findings.

3) The PD-A group included patients with different anxiety presentations and severity (HAM-A median 13.50), and the effects of specific anxiety subtypes or severity levels were not analysed. Clinical characteristics such as disease duration, severity and medication were also not included in the analysis.

4) The 5-min recordings did not allow assessment of very-low-frequency (<0.04 Hz) components or circadian variation; future studies should use longer or ambulatory recordings. In addition, LF power and the LF/HF ratio are not pure measures of sympathetic activity.[26]

5) Healthy males showed little vagal withdrawal under stress, contrary to expectation. This may reflect differences in sample characteristics or variable effects of the MAT in healthy individuals compared with those with PD.

Despite these limitations, this pilot study provides preliminary evidence of gender-related differences in autonomic stress responses in PD and offers effect-size estimates to guide the design of larger, gender-balanced studies of autonomic dysfunction and anxiety in PD.

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ABBREVIATIONS

ANS: Autonomic Nervous System; **BDNF**: Brain-Derived Neurotrophic Factor; **HAM-A**: Hamilton Anxiety Rating Scale; **HF**: High Frequency; **HPA**: Hypothalamic-Pituitary-Adrenal; **HRV**: Heart Rate Variability; **LF**: Low Frequency; **MAT**: Mental Arithmetic Task; **MMS**: Modified Mini Screen; **MMSE**: Mini-Mental State Examination; **NIMHANS**: National Institute of Mental Health and Neurosciences; **nu**: Normalized Units; **PD**: Parkinson's Disease; **PD-A**: Parkinson's Disease with Anxiety; **PD-NA**: Parkinson's Disease Without Anxiety; **PFC**: Prefrontal Cortex; **RMSSD**: Root Mean Square of Successive Differences; **SDNN**: Standard Deviation of NN Intervals;

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

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ETHICAL APPROVAL

The study was carried out with approval from the NIMHANS, Bengaluru Institutional Ethics Committee. Before participation, all subjects provided written informed consent.

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