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Slave to the rhythm: Seasonal differences in non-motor symptoms in Parkinson's disease

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ABSTRACT

Introduction: Although circadian variation of (motor) symptoms in Parkinson disease (PD) patients has been described, it remains unclear what effect seasonal variation may have on non-motor symptoms (NMS).
Methods: Cross-sectional retrospective study on 372 consecutive PD patients taking part in the Non-motor Longitudinal International Study at King's College Hospital London between November 2011 and July 2018. Patients were divided into three groups based on their date of assessment, using a simplified seasonal model: group 1: November–February (n = 107); group 2: March-15 June (n = 107); and group 3: 16 June–October (n = 158). Primary outcome was a seasonal difference in NMS scale (NMSS) total scores (higher scores reflecting greater disability). We hypothesized that PD patients exhibit circannual NMS burden patterns.
Results: All groups were identical concerning disease onset and duration, HY stage, Levodopa equivalent dose, and gender. There was a seasonal difference in NMSS total scores (p = 0.040), with the highest scores (57.1 ± 42.5) in season 1 (winter months) and the lowest (45.1 ± 34.4) in season 3 (summer months) (p = 0.037). Seasonal differences were observed in NMSS domain 1 (cardiovascular symptoms) (p = 0.011), domain 4 (perceptual problems) (p = 0.017) and domain 9 (miscellaneous symptoms) (p = 0.009). A trend was observed for domain 2 (sleep) (p = 0.057).
Conclusion: NMS in PD fluctuate throughout the year, with worsening of symptoms in the winter months compared to the summer months suggestive of dysfunction of the body's master clock, the suprachiasmatic nuclei. Such variations must be accommodated in daily care to ascertain appropriate changes in medication regimes and in clinical trials for the interpretation of outcomes.

1. Introduction

Diurnal fluctuations in Parkinson disease (PD) are well-recognised, mainly in relation to motor symptoms. For example, patterns of daily activity differ significantly between patients with PD and healthy elderly people. There is a notable decrease in morning peak activity with flattened overall daily activity, both strongly correlating with disease severity [1,2]. Responsiveness of motor symptoms to L-dopa treatment also seems to decrease throughout the day, without significant alterations in pharmacokinetics, indicating a possible circadian system involvement [3,4]. A similarly altered diurnal regulation of non–motor symptoms has also been reported for autonomic functions (blood pressure, heart rate), psychiatric symptoms (hallucinations) and sleep impairment. Specifically, patients with PD may experience a disappearance of circadian rhythmicity in blood pressure regulation manifesting with postprandial hypotension, nocturnal hypertension and increased diurnal blood pressure variability and decreased hearth rate variability [5–11]. Likewise, 24-h electrocardiography monitoring revealed loss of circadian heart rate variability, a decrease of sympathetic activity during the day and lack of sympathetic morning peak increase in heart rate as well as a diminished low versus high heart rate frequency ratio reflecting a flattening of circadian modulation [12–14].

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Table 1
Demographics and seasonal variations for Non-motor Symptom Scale (NMSS) scores and other non-motor symptoms.

	Group 1 (Nov–Feb) (n = 107)	Group 2 (Mar-15 Jun) (n = 107)	Group 3 (16 Jun–Oct) (n = 158)	p	Post-hoc analysis
Demographics					
Onset (years)	57.8 (12.1)	58.4 (11.7)	58.3 (11.8)	0.91	–
Duration (years)	6.7 (6.2)	5.2 (4.9)	5.4 (5.1)	0.10	–
Hoehn & Yahr	2.3 (0.9)	2.4 (1.0)	2.3 (0.9)	0.49	–
Sex (M/F)	68/39 (64% M)	71/36 (66% M)	110/48 (70% M)	0.58	–
LEDD	644.0 (552.8)	521.8 (421.3)	596.0 (506.9)	0.20	–
NMSS total	57.1 (42.5)	50.7 (38.2)	45.1 (34.4)	**0.040**	0.035 (season 1–3)
Domain 1	2.7 (3.8)	2.2 (3.1)	1.5 (2.7)	**0.011**	0.009 (season 1–3)
Domain 2	12.2 (10.3)	9.5 (9.0)	9.7 (9.0)	0.057	–
Domain 3	10.0 (13.9)	9.7 (12.4)	7.6 (11.3)	0.21	–
Domain 4	2.0 (4.2)	1.3 (3.0)	3.1 (2.4)	**0.017**	0.014 (season 1–3)
Domain 5	5.5 (7.0)	5.1 (6.1)	4.6 (6.4)	0.54	–
Domain 6	4.6 (5.5)	4.6 (5.7)	4.4 (5.7)	0.95	–
Domain 7	8.7 (9.4)	6.4 (8.1)	7.7 (9.3)	0.17	–
Domain 8	2.9 (5.9)	2.9 (4.8)	2.4 (5.0)	0.65	–
Domain 9	8.5 (8.1)	9.0 (7.7)	6.3 (7.1)	**0.009**	0.015 (season 2–3)
Pain	2.2 (3.4)	2.7 (3.8)	2.0 (3.3)	0.25	–
Smell	3.7 (4.3)	4.0 (4.4)	2.3 (3.5)	**0.002**	0.024 (season 1–3) and 0.004 (season 2–3)
Weight loss	1.2 (2.9)	0.6 (1.8)	0.9 (2.4)	0.13	–
Sweating	1.4 (3.2)	1.7 (3.4)	1.0 (2.5)	0.19	–
HADS	11.5 (6.6)	12.8 (7.4)	11.8 (7.1)	0.40	–
Depression	6.0 (3.8)	6.6 (4.3)	6.4 (4.3)	0.62	–
Anxiety	5.5 (3.6)	6.1 (4.0)	5.4 (3.9)	0.28	–
PDSS	103.0 (27.8)	104.8 (28.4)	106.4 (27.2)	0.61	–
ESS	8.3 (5.4)	8.5 (5.6)	7.3 (4.8)	0.19	–

LEDD: levodopa equivalent dose; NMSS: non-motor symptom scale; HADS: hospital anxiety and depression scale; PDSS: Parkinson's disease sleep scale; ESS: Epworth sleepiness scale; M: male; F: female; a: Pearson Chi-Square test. All statistical analyses were performed using one-way ANOVA. Domain 1: cardiovascular and falls; domain 2: sleep/fatigue; domain 3: mood/cognition; domain 4: perceptual problems/hallucinations; domain 5: attention/memory; domain 6: gastrointestinal tract; domain 7: urinary; domain 8: sexual function; domain 9: miscellaneous.
Bold: A p-value of ≤ 0.05 was considered statistically significant.

Moreover, circadian disruption in patients with PD experiencing hallucinations is associated with greater intra-daily variability of rest-activity cycles, decreased amplitude of activity and increased night-time activity compared to non-hallucinators [15].

In clinical practice, we have also observed that the severity of symptoms in PD patients may alter with change of seasons. Symptoms appear to be less pronounced when the climate is warmer in summer months and worse in winter (when there is also less daylight). However, clear evidence for seasonal fluctuations in PD symptoms is lacking, and only a handful of studies have explored the possibility of circannual fluctuations in PD. In a study with 546 PD patients, no difference in UPDRS motor scores was observed over the four seasons of the year [16]. In another study determining the seasonal effect on hallucinations, again no effect of the seasons was observed [17]. For other non-motor symptoms, no studies are available. We therefore set out to determine the seasonal effect on non-motor symptoms in PD.

2. Methods

In this cross-sectional analysis, all consecutive patients between November 2011 and July 2018 with a diagnosis of probable idiopathic PD who participated in the Non-motor Longitudinal International Study (NILS) and had a first assessment at King's College Hospital London (NHS Foundation Trust) were included. The NILS Study is the world's first comprehensive study addressing non-motor profiling of PD and the natural history of non-motor symptoms together with treatment response and clinico-pathological correlations. The study involves 14 centres across Europe, but for the current study only patients who had a baseline assessment at King's College Hospital were included. NILS has been adopted as a national study by the National Institute of Health Research in the UK (UKCRN No: 10084). The study was authorized by local ethics committees (NRES SouthEast London REC3, 10084, 10/H0808/141). All patients gave written consent prior to study procedures in accordance with the Declaration of Helsinki.

Data extracted from the NILS database concerned sex, disease onset and duration (in years), Hoehn and Yahr stage, Levodopa equivalent dose (LEDD) and Non-motor Symptom Scale (NMSS), Hospital Anxiety and Depression Scale (HADS), Parkinson Disease Sleep Scale (PDSS) and Epworth Sleepiness Scale (ESS) scores. The NMSS addresses NMS that have occurred during the previous four weeks [18,19]. We used the following NMSS domains: cardiovascular and falls (domain 1), sleep/fatigue (domain 2), mood/cognition (domain 3), perceptual problems/hallucinations (domain 4), attention/memory (domain 5), gastrointestinal tract (domain 6), urinary (domain 7), sexual function (domain 8) and miscellaneous (domain 9).

The date when the NILS baseline assessment took place was recorded. Subsequently, patients were then assigned to one of three groups which were defined based on the ecological seasons, rather than the classical four seasons. The ecological seasons were defined as follows: 1) Prevernal: March and April; 2) Vernal: May – 15 June; 3) Estival: 16 June – 15 August; 4) Serotinal: 16 August – 15 September; 5) Autumnal: 16 September–October and 6) Hibernal: November–February. To obtain an equal distribution across the year and to reduce the impact of multiple testing these ecological seasons were merged into three groups: 1) winter months: November until February; 2) spring months: March until 15 June; 3) summer months: 16 June until October. Similar rearrangement methods for seasons in order to control for the effect of daytime light duration, by grouping months with similar daytime light duration together, have been described before [20].

The primary outcome was the seasonal difference in NMSS total scores. Secondary outcomes were NMSS subscores, PDSS, ESS and HADS scores. For analysis of the outcomes we used a one-way analysis of variance (ANOVA). A formal Bonferroni correction was used to correct for multiple testing for the secondary outcomes. To test for gender differences, Pearson Chi-Square analysis was used. All data was analyzed using SPSS Version 24 (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.).

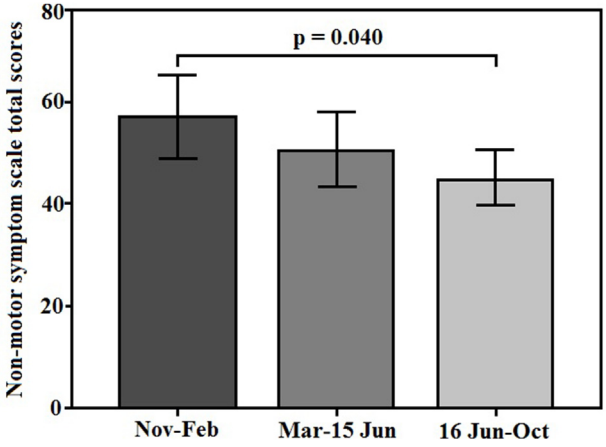

Fig. 1. Non-motor symptom scales (NMSS) total scores grouped according to three parts of the year. Group 1: patients assessed in November through February (winter months); group 2: patients assessed in March through 15 June (spring months); and group 3: patients assessed in 16 June through October (summer months).

3. Results

A total of 372 patients who had a baseline assessment were included: 107 patients were allocated to group 1 (November–February), 107 to group 2 (March - 15 June) and 158 to group 3 (16 June–October). All groups were identical concerning disease onset and duration, Hoehn and Yahr stage, Levodopa equivalent dose (LEDD), and distribution of sex ($p > 0.10$) (Table 1). Six patients (1.6%) used antidepressant medication.

For the primary outcome, there was a statistically significant group difference with high NMS burden (57.1 ± 42.5) in season 1 (November–February) and lower NMS burden (45.1 ± 34.4) in season 3 (16 June–October) (one-way ANOVA, $p = 0.040$) (Fig. 1). For the secondary outcomes, we observed significant seasonal differences in NMSS domain 1 (cardiovascular and falls; $p = 0.011$), domain 4 (perceptual problems; $p = 0.017$) and domain 9 (miscellaneous; $p = 0.009$). A trend was observed for domain 2 (sleep and fatigue; $p = 0.057$) (Table 1). No difference was observed in the remaining NMSS domains ($p > 0.13$), nor in PDSS, HADS and ESS scores ($p > 0.19$).

We performed a separate analysis for domain 9 (miscellaneous) for the separate questions in this domain (pain, smell, weight loss and sweating). This revealed that smell was better in the summer months (16 June–October) compared to the winter (November–February) and spring months (March – 15 June) ($p = 0.008$ and 0.024, respectively; Table 1).

4. Discussion

This is the first comprehensive study showing seasonal differences in NMS in PD patients. In line with the subjective impression of patients and health care professionals, we observed significant seasonal differences in NMS in PD patients, with mostly higher scores (i.e. more complaints) during the winter months and lower scores during the summer months. The change of NMS scores between seasons in patients was determined by changes in the cardiovascular and falls, hallucinations and perceptual problems and miscellaneous domains of the NMSS. A trend was observed for sleep and fatigue. Remarkably, depression scores, which could potentially explain these differences, did not carry with the seasons.

Seasonal variations in NMS can be accounted for by several factors. A prime factor is the influence of the biological clock located in the suprachiasmatic nuclei (SCN) within the hypothalamus. The involvement of the circadian system in PD has been shown in several studies [21,22]. For example, decreased expression of melatonergic receptors (MT_1 and $MT_{2)}$ has been observed in the amygdala and substantia nigra [23]. In addition, circulating melatonin levels are affected in PD patients compared to the healthy elderly population [24,25] and these changes correspond with a disruption in slow wave and REM sleep [26]. Here, light therapy is a promising strategy to realign circadian output and potentially improve fluctuating (both circadian and seasonal) symptoms [27–29].

The role of depression, which is known to fluctuate in severity across seasons, being worse in winter and autumn compared to the other seasons [30], could explain the differences. Depressed patients might be inclined to answer globally more negative to all questions. In our study group, however, we did not observe a change in depression scores across the different seasons, making it unlikely that fluctuation of depression scores explains the seasonal variations in NMS. The absent fluctuation of depressive symptoms might be related to the use of the HADS which is normally used as a screening tool and not to make a formal diagnosis of depression. In PD, the HADS is not recommended for scoring severity of depressive symptoms [31]. Moreover, a recent study has shown that the depression subsection of the HADS shows an item bias for several items influencing group differences between e.g. age groups [32]. The NMSS is also a global tool for addressing the burden of NMS as a while and includes cognition, dysautonomia, sleep and pain and it is likely that changes could have been missed in this specific domain because of the composite nature of this scale [18,19].

The main limitation of the current study relates to the cross-sectional nature (use of single measurements in individual patients), rather than follow-up scores at different times during the year within individual patients. Preferably, a similar study should be conducted with several assessments throughout the year within the same patients. We feel, however, that our current results are still meaningful, considering there was no difference between the three groups concerning disease duration, Hoehn and Yahr stages, LEDD and sex which in themselves can also influence NMS burden. It is therefore likely that the observed results are indeed due to seasonal changes.

In conclusion, we observed seasonal differences in total NMS scores in PD patients – with highest scores during the winter months and lower scores during the summer months. These changes might be explained by altered circannual regulation in PD due to pathology of the body's master clock, as was shown in previous studies. The current results should be replicated in further prospective cohorts, with analyses preferably aimed at repeated measurements in patients for longer periods of time. The seasonal variation of NMS in PD need to be taken into account to ascertain appropriate changes in medication regimes. Also, adjustment for cyclical variation of NMS could be important in the interpretation of clinical trials.

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References

[1] J.J. van Hilten, J.F. Kabel, H.A. Middelkoop, C.G. Kramer, G.A. Kerkhof, R.A. Roos, Assessment of response fluctuations in Parkinson's disease by ambulatory wrist activity monitoring, Acta Neurol. Scand. 87 (1993) 171–177.
[2] J.J. van Hilten, H.A. Middelkoop, G.A. Kerkhof, R.A. Roos, A new approach in the assessment of motor activity in Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 54 (1991) 976–979.
[3] U. Bonuccelli, P. del Dotto, C. Lucetti, L. Petrozzi, S. Bernardini, G. Gambaccini, G. Rossi, P. Piccini, Diurnal motor variations to repeated doses of levodopa in Parkinson's disease, Clin. Neuropharmacol. 23 (2000) 28–33.
[4] D. Nyholm, H. Lennernas, A. Johansson, M. Estrada, S.M. Aquilonius, Circadian rhythmicity in levodopa pharmacokinetics in patients with Parkinson disease, Clin. Neuropharmacol. 33 (2010) 181–185.
[5] M. Plaschke, P. Trenkwalder, H. Dahlheim, C. Lechner, C. Trenkwalder, Twenty-four-hour blood pressure profile and blood pressure responses to head-up tilt tests in Parkinson's disease and multiple system atrophy, J. Hypertens. 16 (1998) 1433–1441.
[6] J.M. Senard, B. Chamontin, A. Rascol, J.L. Montastruc, Ambulatory blood pressure in patients with Parkinson's disease without and with orthostatic hypotension, Clin. Auton. Res. 2 (1992) 99–104.
[7] L. Chen, G. Yang, Recent advances in circadian rhythms in cardiovascular system, Front. Pharmacol. 6 (2015) 132.
[8] Y.S. Oh, J.S. Kim, I.S. Park, I.U. Song, Y.M. Son, J.W. Park, D.W. Yang, H.T. Kim, K.S. Lee, Association between nocturnal/supine hypertension and restless legs syndrome in patients with Parkinson's disease, J. Neurol. Sci. 344 (2014) 186–189.
[9] T. Umehara, A. Nakahara, H. Matsuno, C. Toyoda, H. Oka, Predictors of post-prandial hypotension in elderly patients with de novo Parkinson's disease, J. Neural. Transm. 123 (2016) 1331–1339.
[10] S. Sommer, B. Aral-Becher, W. Jost, Nondipping in Parkinson's disease, Parkinsons Dis. 2011 (2011) 897586.
[11] H. Kanegusuku, C. Silva-Batista, T. Pecanha T, N. Silva-Junior, A. Queiroz, L. Costa, M. Mello, M. Piemonte, C. Ugrinowitsch, C. Forjaz, Patients with Parkinson disease present high ambulatory blood pressure variability, Clin. Physiol. Funct. Imaging 37 (2017) 530–535.
[12] A.A. Ejaz, I.S. Sekhon, S. Munjal, Characteristic findings on 24-h ambulatory blood pressure monitoring in a series of patients with Parkinson's disease, Eur. J. Intern. Med. 17 (2006) 417–420.
[13] D. Devos, M. Kroumova, R. Bordet, H. Vodougnon, J.D. Guieu, C. Libersa, A. Destee, Heart rate variability and Parkinson's disease severity, J. Neural. Transm. 110 (2003) 997–1011.
[14] F. Niwa N. Kuriyama, M. Nakagawa, J. Imanishi, Circadian rhythm of rest activity and autonomic nervous system activity at different stages in Parkinson's disease, Auton. Neurosci. 165 (2011) 195–200.
[15] D.L. Whitehead, A.D. Davies, J.R. Playfer, C.J. Turnbull, Circadian rest-activity rhythm is altered in Parkinson's disease patients with hallucinations, Mov. Disord. 23 (2008) 1137–1145.
[16] R.B. Postuma, T. Arenovich, A.E. Lang, Does severity of Parkinson's disease vary according to season? Mov. Disord. 20 (4) (2005) 476–479.
[17] C.G. Goetz, J.M. Li, J. Wuu, S. Leurgans, Does seasonal variation affect hallucinations in PD? A longitudinal study, Mov. Disord. 21 (6) (2006) 863–865.
[18] P. Martinez-Martin, C. Rodriguez-Blazquez, K. Abe, K.B. Bhattacharyya, B.R. Bloem, F.J. Carod-Artal, R. Prakash, R.A. Esselink, C. Falup-Pecurariu, M. Gallardo, P. Mir, Y. Naidu, A. Nicoletti, K. Sethi, Y. Tsuboi, J.J. van Hilten, M. Visser, M. Zappia, K.R. Chaudhuri, International study on the psychometric attributes of the Non-Motor Symptoms Scale in Parkinson disease, Neurology 73 (2009) 1584–1591.
[19] K.R. Chaudhuri, P. Martinez-Martin, R.G. Brown, K. Sethi, F. Stocchi, P. Odin, W. Ondo, K. Abe, G. Macphee, D. Macmahon, P. Barone, M. Rabey, A. Forbes, K. Breen, S. Tluk, Y. Naidu, W. Olanow, A.J. Williams, S. Thomas, D. Rye, Y. Tsuboi, A. Hand, A.H. Schapira, The metric properties of a novel non-motor symptoms scale for Parkinson's disease: results from an international pilot study, Mov. Disord. 22 (2007) 1901–1911.
[20] N.C. Thadlow, S. Brown, R. Wardrop, D. Henley, The effects of season, daylight saving and time of sunrise on serum cortisol in a large population, Chronobiol. Int. 31 (2) (2014) 243–251.
[21] A. Videnovic, G.L. Willis, Circadian system - a novel diagnostic and therapeutic target in Parkinson's disease? Mov. Disord. 31 (2016) 260–269.
[22] B. Boutrel, G.F. Koob, What keeps us awake: the neuropharmacology of stimulants and wakefulness promoting medications, Sleep 27 (2004) 1181–1194.
[23] N. Adi, D.C. Mash, Y. Ali, C. Singer, L. Shehadeh, S. Papapetropoulos, Melatonin MT1 and MT2 receptor expression in Parkinson's disease, Med. Sci. Monit. 16 (2010) Br61–67.
[24] D.P. Breen, R. Vuono, U. Nawarathna, K. Fisher, J.M. Shneerson, A.B. Reddy, R.A. Barker, Sleep and circadian rhythm regulation in early Parkinson disease, JAMA Neurol. 71 (2014) 589–595.
[25] R. Bordet, D. Devos, S. Brique, Y. Touitou, J.D. Guieu, C. Libersa, A. Destée, Study of circadian melatonin secretion pattern at different stages of Parkinson's disease, Clin. Neuropharmacol. 26 (2003) 65–72.
[26] D.P. Breen, R.A. Barker, Exogenous melatonin for Parkinson's disease: 'Waking up' to the need for further trials, Park. Relat. Disord. 29 (2016) 121–122.
[27] A. Videnovic, E.B. Klerman, W. Wang, A. Marconi, T. Kuhta, P.C. Zee, Timed light therapy for sleep and daytime sleepiness associated with Parkinson disease: a randomized clinical trial, JAMA Neurol. 74 (4) (2017) 411–418.
[28] S. Paus, T. Schmitz-Hübsch, U. Wüllner, A. Vogel, T. Klockgether, M. Abele, Bright light therapy in Parkinson's disease: a pilot study, Mov. Disord. 22 (10) (2007) 1495–1498.
[29] G.L. Willis, J. Boda, C.B. Freelance, Polychromatic light exposure as a therapeutic in the treatment and management of Parkinson's disease: a controlled exploratory trial, Front. Neurol. (2018), https://doi.org/10.3389/fneur.2018.00741.
[30] A, A. Wirz-Justice, Seasonality in affective disorders, Gen. Comp. Endocrinol. 258 (2018) 244–249.
[31] A. Schrag, P. Barone, R.G. Brown, A.F. Leentjens, W.M. McDonald, S. Starkstein, D. Weintraub, W. Poewe, O. Rascol, C. Sampaio, G.T. Stebbins, C.G. Goetz, Depression rating scales in Parkinson's disease: critique and recommendations, Mov. Disord. 22 (8) (2007) 1077–1092.
[32] M.G.E. Verdam, F.J. Oort, M.A.G. Sprangers, Item bias detection in the Hospital Anxiety and Depression Scale using structural equation modeling: comparison with other item bias detection methods, Qual. Life Res. 26 (6) (2017) 1439–1450.