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SHORT COMMUNICATION

Parkinson's Disease-Related pattern in isolated REM sleep behaviour disorder as a prodromal progression marker: 8-Year Follow-Up changes assessed at three time points

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Abstract

Background Isolated REM sleep behavior disorder (iRBD) is a prodromal stage of alpha-synucleinopathies. Biomarkers are crucial for predicting and monitoring its progression, warranting long-term neuroimaging studies. While the Parkinson's Disease Related Pattern (PDRP) from ^{18}F-FDG PET is a recognized Parkinson's Disease (PD) biomarker, its role in tracking progression in prodromal PD remains unclear.

Objective To explore PDRP expression across three time points using ^{18}F-FDG PET over an 8-year follow-up in iRBD.

Methods Thirteen iRBD subjects underwent ^{18}F-FDG PET brain scans at baseline (BL), follow-up 1 (FU1, 4 years), and follow-up 2 (FU2, 8 years). Among them, four developed PD, one Dementia with Lewy Bodies (DLB), three showed subthreshold parkinsonism, and five showed no progression. PDRP z-scores were analyzed within and between groups (converters vs. non-converters) using a two-way repeated measures ANOVA. Similar analyses were conducted for motor scores (Unified Parkinson's Disease Rating Scale part three, UPDRS-III).

Results There was a significant main effect of group ($p=0.011$), time ($p<0.001$), and a group*time interaction ($p=0.020$), indicating that while PDRP z-scores increased over time in most iRBD subjects, the increase was more pronounced in converters ($n=5$) than in non-converters ($n=8$). Post-hoc tests revealed significantly higher PDRP z-scores in converters compared to non-converters at FU1 ($p=0.042$) and FU2 ($p=0.024$). For UPDRS-III scores we found significant effects of group ($p=0.011$), time ($p<0.001$), and their interaction ($p=0.0003$).

Conclusions Repeated ^{18}F-FDG PET scans may be useful to monitor prodromal disease progression and predict conversion in iRBD patients.

Keywords ^{18}F-FDG PET · PDRP · brain glucose metabolism · iRBD · disease progression

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Introduction

Isolated rapid-eye movement (REM) sleep behavior disorder (iRBD) signifies a prodromal stage of Parkinson's disease (PD), dementia with Lewy bodies (DLB) or (more rarely) multiple system atrophy (MSA) [1]. Biomarkers are essential to predict and monitor the heterogeneous disease progression in iRBD [2], with longitudinal neuroimaging studies showing promise.

The PD-related pattern (PDRP), identified via ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET), reflects increased pallido-thalamic and pontine activity with reduced activity in the premotor cortex, supplementary motor area, and parietal association areas [2]. It

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correlates with motor symptoms and progression, serving as a cross-center validated biomarker for PD severity and treatment response [3]. Previous ^{18}F-FDG PET studies have shown that iRBD subjects express the PDRP [4–7]. We have shown that PDRP subject scores were significantly increased in iRBD subjects compared to controls [8], and increased over a 4-year period, especially in those who converted to PD [9]. These results support the use of serial PDRP expression scores as a prodromal progression marker. However, longitudinal studies with longer follow-up durations are needed for further validation.

In the current study, we report the results of the second follow-up ^{18}F-FDG PET scan in thirteen subjects of our original iRBD cohort, approximately 8 years after inclusion. These patients underwent clinical assessments and ^{18}F-FDG PET brain scans at three time points, at intervals of approximately 4 years. We studied longitudinal changes in PDRP expression scores in converters versus non-converters.

Materials and methods

Study design and participants

This three-part longitudinal study took place at the University Medical Center of Groningen and at the Philipps-University Marburg. Thirteen iRBD subjects (3 Dutch and 10 German) underwent ^{18}F-FDG PET scans, motor, cognitive, and olfactory testing at baseline (BL), follow-up visit 1 (FU1, mean of 3.59 years) and follow-up visit 2 (FU2, mean of 4.94 years). We reported the patients' clinical status (converted or not converted) at the last available follow-up. At both centers, phenoconversion to PD or DLB was determined by the neurologist, according to clinical consensus criteria [9, 10]. Additional study details can be found elsewhere [11, 12]. At each visit, the neurologist reviewed medical history and medication changes. No patients received new diagnoses or medications affecting the ^{18}F-FDG PET scan or clinical exams.

Clinical, motor and global cognitive variables

At each timepoint, patients were evaluated with motor (Unified Parkinson's Disease Rating Scale part three - 2003 version, (UPDRS-III) and/or Movement Disorders Society UPDRS part three, (MDS-UPDRS- III)), cognitive (Montreal Cognitive Assessment, MoCA) and olfactory (identification sub-score of the Sniffin' Sticks Test) testing. Motor evaluation at baseline, FU1 and FU2 was performed using the UPDRS-III (2003 version). At FU2, a newer version, The MDS-UPDRS-III, was also applied. Because MDS-UPDRS-III was not available at baseline and FU1, the 2003 version of UPDRS-III was used for statistical analyses (Appendix **S1** and Table S1).

The MDS recommends a cut-off score of 6 on the MDS-UPDRS-III for defining subthreshold parkinsonism [13]. We included an additional category for patients who exhibited subtle motor dysfunction on clinical examination and had an MDS-UPDRS-III > 6 (excluding postural tremor) in the absence of cardinal symptoms at FU3. This category of 'subthreshold parkinsonism' was included solely for graphical representation, as the small sample size precluded meaningful comparisons with other groups (see Table S2 and Figure S1). For the main statistical analyses, we considered individuals with subthreshold parkinsonism as part of the non-converter group.

^{18}F-FDG PET imaging and PDRP z-scores

Acquisition and preprocessing of ^{18}F-FDG PET is described in Appendix **S2**. The PDRP was previously identified in ^{18}F-FDG PET scans of 17 controls (12 male, age 61.5 ± 7.5 years) and 19 PD patients (13 male, age 63.9 ± 7.8), in the off-levodopa state [14]. PDRP subject scores were calculated for each scan as described previously [8, 11]. PDRP subject scores were z-scored to a cohort of 12 age- and sex-matched controls (10 male, age 65.96 ± 6.21 years). These controls only underwent baseline ^{18}F-FDG PET imaging.

Statistical analyses

We computed the yearly change (Δ) for UPDRS-III (2003 version), MoCA, olfaction and PDRP z-scores for two intervals according to:

$$\Delta BL\ to\ FU1 = \frac{score\ at\ FU1 - score\ at\ BL}{time\ between\ BL\ and\ FU1\ in\ years}$$

and

$$\Delta FU1\ to\ FU2 = \frac{score\ at\ FU2 - score\ at\ FU1}{time\ between\ FU1\ and\ FU2\ in\ years}$$

A two-way repeated measures ANOVA was used to investigate whether changes in PDRP z-scores and clinical variables (UPDRS-III, MoCA, and olfactory impairments) across the three time points differed between individuals who later developed PD/DLB (converters) and those who did not (non-converters and subthreshold parkinsonism). Time was the within-subjects factor, and conversion status was the between-subjects factor (see Appendix S3). As a post-hoc exploratory analysis, we repeated the same model, excluding individuals with subthreshold parkinsonism from the non-converter group. Correlation analyses were

conducted between ΔPDRP and ΔUPDRS-III between BL to FU1 and FU1 to FU2. Additionally, we examined the correlation between PDRP z-scores and age at the three time points. We also examined the correlation between PDRP expression and age in our in-house large cohort of healthy controls ($n=69$, age range: 20–80 years) who underwent ^{18}F-FDG PET (**Appendix S5**). This cohort includes the 12 controls selected for the z-scoring procedure in this study. A Bonferroni correction was applied to adjust for multiple comparisons, with statistical significance set at $p<0.05$. Analyses were conducted using R Studio (version RStudio 2023.06.0).

Results

Five subjects converted during the follow-up period: four to PD and one to DLB. Of these, three converted between BL and the FU1, one between FU1 and FU2, and one at FU2. Among the eight non-converters, three exhibited subthreshold parkinsonism (MDS-UPDRS-III > 6) (Table 1 and Table S2).

PDRP z-scores - A significant main effect of group ($p=0.011$) and time (pGG < 0.001, GGε = 0.586) was observed, along with a significant interaction effect between group and time (pGG = 0.020, GGε = 0.586). Post-hoc tests revealed significantly higher PDRP z-scores in converters compared to non-converters at FU1 ($p=0.042$) and FU2 ($p=0.024$). When comparing PDRP z-scores between time points within each group, converters showed significant differences between BL and FU1 ($p=0.0002$) and FU1 and FU2 ($p=0.0001$). The non-converters also showed significant differences between BL and FU1 ($p=0.007$) and FU1 and FU2 ($p=0.002$) (Table 2; Figs. 1 and 2).

Clinical features - Two-way repeated measures ANOVA did not show any effect of group, time or interaction (group*time) on MoCA scores. Only the main effect of time was significant for the olfactory scores ($p=0.007$). For UPDRS-III, a significant main effect of group ($p=0.011$), time ($p<0.001$), and interaction effect of group*time ($p=0.0003$) were found. Post-hoc tests showed significantly different UPDRS-III scores in converters compared to non-converters at FU2 ($p=0.027$) (Table 2; Fig. 1).

Correlation between PDRP and clinical variables

In the total iRBD group, there was a significant correlation between ΔPDRP and ΔUPDRS-III only from BL to FU1 ($r=0.697$, $p_{Bonferroni}=0.049$). Age and PDRP z-scores were not significantly correlated at any of the timepoints in iRBD or in the HC cohort ($n=69$, age range: 20–80 years) (See Figure S2 and S5).

Table 1 Clinical, motor and global cognitive features over time

	Non-converters $N=8$	Converters $N=5$	Total $N=13$
Baseline			
Sex	M	M	M
Age at onset iRBD	57.30 ± 5.53	55.38 ± 5.85	56.54 ± 5.49
Age at time of conversion	-	66.40 ± 8.24	-
Age at BL	62.20 ± 3.21	61.43 ± 6.78	61.92 ± 4.64
RBD symptom duration at BL	13.60 ± 4.74	6.05 ± 3.50	5.38 ± 4.06
UPDRS-III at BL	2.00 ± 1.41	1.20 ± 1.09	1.69 ± 4.06
Sniffin' Sticks Test (identification subscore) at BL	8.75 ± 4.10	4.60 ± 3.44	7.15 ± 4.26
MoCA at BL	27.40 ± 2.50	26.40 ± 1.52	27.00 ± 2.16
PDRP z-score at BL	1.55 ± 0.67	2.99 ± 1.68	2.10 ± 1.31
Follow-up 1			
Age at FU1	65.80 ± 3.43	64.98 ± 6.66	65.51 ± 4.67
Follow-up duration (BL-FU1)	3.61 ± 0.55	3.55 ± 0.62	3.59 ± 0.56
UPDRS-III at FU1	1.88 ± 1.81	5.20 ± 4.66	3.15 ± 3.46
Sniffin' Sticks Test (identification subscore) at FU1	7.75 ± 4.30	3.60 ± 2.51	6.15 ± 4.16
MoCA at FU1	27.80 ± 1.16	27.40 ± 1.95	27.60 ± 1.45
PDRP z-scores at FU1	2.95 ± 1.24	5.75 ± 2.28	4.03 ± 2.16
Follow-up 2			
Age at FU2	70.90 ± 3.41	69.79 ± 6.88	70.45 ± 4.78
Follow-up duration (FU1-FU2)	5.02 ± 0.34	4.89 ± 0.35	4.94 ± 0.33
UPDRS-III at FU2	5.38 ± 5.15	16.00 ± 7.11	9.46 ± 7.83
Sniffin' Sticks Test (identification subscore) at FU2	6.62 ± 3.74	2.40 ± 2.88	5.00 ± 3.94
MoCA at FU2	27.40 ± 1.41	26.40 ± 1.14	27.00 ± 1.35
PDRP z-score at FU2	4.12 ± 1.96	7.85 ± 2.12	5.56 ± 2.70

Abbreviations: N: Number; BL: baseline; UPDRS: Unified Parkinson's Disease Rating Scale; MoCA: Montreal cognitive assessment; PDRP: Parkinson disease related pattern; FU: follow-up

Table 2 Within and between subject effects: two-way repeated measure ANOVA

Within subjects	BL	FU1	FU2	BL vs. FU1 *	BL vs. FU2 *	FU1 vs. FU2 *
Converters N*	5	5	5	-	-	-
PDRP z-scores	2.99 (1.68)	5.75 (2.28)	7.85 (2.12)	**0.0002**	**0.0001**	**0.0001**
MoCA	26.40 (1.52)	27.40 (1.95)	26.40 (1.14)	1.000	1.000	0.686
UPDRS-III	1.20 (1.10)	5.20 (4.66)	16.00 (7.11)	0.100	**0.001**	**0.0025**
Sniffin' Sticks Test (identification)	4.60 (3.44)	3.60 (2.51)	2.40 (2.88)	0.689	0.197	0.750
Non-converters N*	8	8	8			
PDRP z-scores	1.55 (0.67)	2.95 (1.24)	4.12 (1.96)	**0.007**	**0.002**	**0.002**
MoCA	27.4 (2.50)	27.8 (1.16)	27.4 (1.41)	1.000	1.000	1.000
UPDRS-III	2.00 (1.41)	1.88 (1.81)	5.38 (5.15)	1.000	0.497	0.266
Sniffin' Sticks Test (identification)	8.75 (4.10)	7.75 (4.30)	6.62 (3.74)	0.408	0.089	0.533
Between subjects	**Converters*N*=5**		**Non-converters*N*=8**		***p*-value raw (*p*-value Bonf. corrected *)**	
Baseline						
PDRP z-scores	2.99 (1.68)		1.55 (0.67)		0.130 (0.390) [a]	
MoCA	26.40 (1.52)		27.4 (2.50)		0.453 (1.000)	
UPDRS-III	1.20 (1.09)		2.00 (1.41)		0.306 (0.918)	
Sniffin' Sticks Test (identification)	4.60 (3.44)		8.75 (4.10)		0.087 (0.261)	
Follow-up 1						
PDRP z-scores	5.75 (2.28)		2.95 (1.24)		**0.014 (0.042)**	
MoCA	27.40 (1.95)		27.8 (1.16)		0.690 (1.000)	
UPDRS-III	5.20 (4.66)		1.88 (1.81)		0.200 (0.600) [b]	
Sniffin' Sticks Test (identification)	3.60 (2.51)		7.75 (4.30)		0.078 (0.234)	
Follow-up 2						
PDRP z-scores	7.85 (2.12)		4.12 (1.96)		**0.0079 (0.024)**	
MoCA	26.40 (1.14)		27.4 (1.41)		0.221 (0.663)	
UPDRS-III	16.00 (7.11)		5.38 (5.15)		**0.009 (0.027)**	
Sniffin' Sticks Test (identification)	2.40 (2.88)		6.62 (3.74)		0.055 (0.165)	

PDRP: Parkinson's Disease-related pattern, MoCA: Montreal Cognitive Assessment; UPDRS: Unified Parkinson's Disease Rating Scale; [a] Welch's t-test - Homogeneity of variance unmet; [b] Wilcoxon test was used for Time 2 due to non-normality distribution of non-converters group; * *P* value adjustment: Bonferroni method for 3 tests

Discussion

This pilot study, involving long-term follow-up with repeated clinical measures and ^{18}F-FDG PET imaging in 13 iRBD patients, provides insights into the potential utility of PDRP expression as a biomarker for disease progression in the prodromal stage of alpha-synucleinopathies. We observed a consistent increase in PDRP expression among both converters and non-converters over the 8-year follow-up period, though at differing rates. Notably, iRBD patients exhibited significantly higher PDRP z-scores than controls across all three time points (Fig. 2). The distinction between converters and non-converters in PDRP z-score expression became significant only at follow-up 1, with no significant differences at baseline (Table 2). These findings imply that relying solely on a single baseline measurement may not be adequate for predicting phenoconversion from iRBD to PD/DLB over an extended period, especially if the measurement is distant from the conversion point. Incorporating repeated ^{18}F-FDG PET scanning could hold promise in monitoring disease progression and potentially predicting clinical phenoconversion. Repeated scanning can be considered safe, especially with the advent of long-axial field of view PET cameras, which allow a similar resolution at a lower burden of radioactivity [15].

Notably, two out of five converters converted before FU1, limiting pre-conversion trajectory data. Patients with subthreshold parkinsonism (n = 3) also displayed consistent increases from FU1 to FU2 (Figure S1). One subject had bradykinesia but lacked rigidity, resting tremor or significant cognitive impairment. Although the MDS-UPDRS-III was high (> 20), the patient had hyposmia and the dopamine transporter (DAT) SPECT brain scan was abnormal, a clinical diagnosis of PD or DLB could not (yet) be made. In the

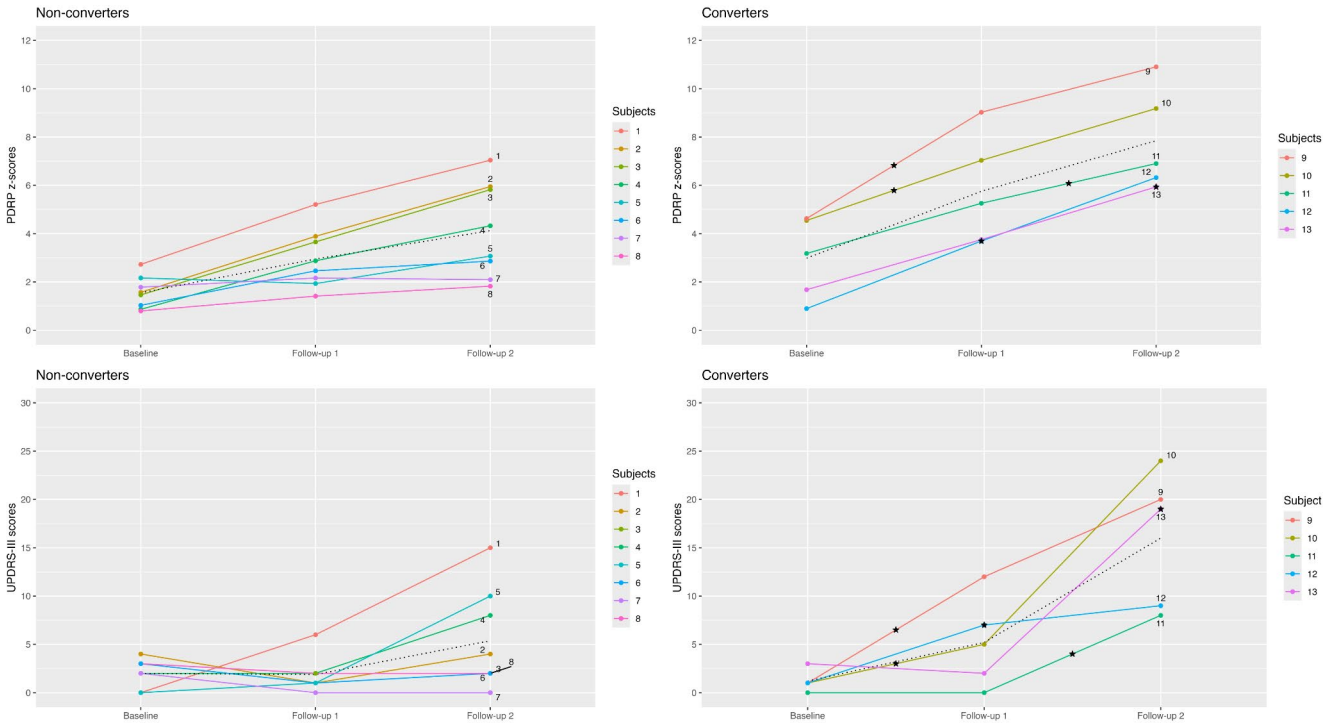

Fig. 1 PDRP z-scores and UPDRS-III scores for each individual at each timepoint. The asterixis indicates the approximate time of conversion for patients who converted to PD (subjects 9, 10, 11, and 12), and DLB (subject 13) during follow-up. The **top row** shows the individual trajectories of PDRP z-scores. All converters showed a steady increase of PDRP z-scores across the three-time points. Subjects categorized as having subthreshold parkinsonism (case 1, 4 and 5) showed consistent increases in PDRP z-scores as well. Of the non-converters, two cases showed consistent increases in PDRP z-scores (case 2 and 3), whereas three cases remained relatively stable (case 6, 7 and 8). Case 7 showed a marginal decrease from z=2.16 (FU1) to z=2.09 (FU2). Case 5 showed a marginal decrease from z=2.17 (BL) to z=1.93 (FU1). These decreases may still fall within the error of measurement and were interpreted as a stable PDRP z-score. The **bottom row** displays the individual trajectories of UPDRS-III scores. Among the converters, two out of five (40%) converted before the FU1 scan, exhibiting a relative increase in UPDRS-III scores from baseline to FU1. One converter converted at FU1 and two converted after FU1 or at FU2, demonstrating a rapid increase in UPDRS-III scores close to the moment of conversion. Amongst non-converters, three were categorized as 'subthreshold parkinsonism' (case 1, 4 and 5). These subjects showed an increase in UPDRS-III scores, particularly from FU1 to FU2, with one individual (Case 1) also exhibiting an increase between BL and FU1. Non-converters displayed consistently low UPDRS-III scores (≤6) across the time points, indicating stability (non-clinically meaningful fluctuations). The dotted line in each figure indicates the mean PDRP z-score or UPDRS-III score for each time-point in that group. Abbreviations: UDRS-III: Unified Parkinson's Disease Rating Scale part three; PDRP: Parkinson disease related pattern

non-converter group excluding subthreshold parkinsonism (n=5), two categories are visible (Figure S1): three patients had stable scores, and two patients showed increasing PDRP z-scores. There were no clear differences in clinical characteristics such as olfactory function between 'stable' and 'rising' non-converters.

PDRP z-scores showed modest correlations with motor scores across the three timepoints, confirming previous studies where such correlations were either moderate [5] or even absent [16]. This means that PDRP z-scores and UPDRS-III are not interchangeable. The PDRP captures global functional brain changes, which are not restricted to dopaminergic degeneration [17] or motor function.

This study has some limitations that require cautious interpretation of the results. First, the small sample size and subgroup analysis. Second, repeated ^{18}F-FDG PET measurements were not available for our control cohort. Additionally, all patients were male, which limits the generalizability of the results.

In conclusion, our results indicate that repeated PDRP measurements using ^{18}F-FDG PET could be useful to track disease progression in iRBD towards manifest PD/DLB. A follow-up study in a large, longitudinal, multi-center cohort is currently ongoing.

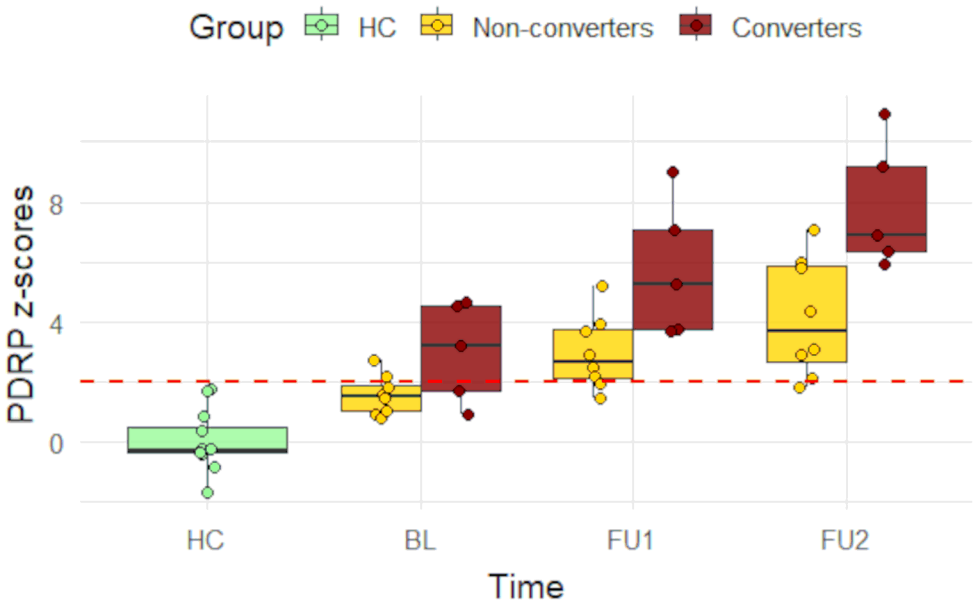

Fig. 2 PDRP expression in iRBD at BL, FU1 and FU2 and 12 HC. Red line at PDRP z-score = 2. Abbreviations: HC: healthy controls; BL: baseline; FU1: follow-up 1; FU2: follow-up 2; PDRP: Parkinson disease related pattern

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00259-025-07260-9.

Author contributions Giulia Carli, Annette Janzen, Klaus L. Leenders, Wolfgang Oertel and Sanne Meles contributed to study conceptualization; Giulia Carli and Anna Dortmond: Data analyses and methodology design; Giulia Carli: writing of the first draft; Eline de Meyer, Annette Janzen and Elisabeth Sittig: data acquisition, database curation and review and critique of the manuscript; Sanne Meles: Supervision, study design and review and critique of the manuscript; Klaus L. Leenders and Wolfgang Oertel: funding acquisition and review and critique of the manuscript.

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Data availability The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Conflict of interest WHO has received honoraria for educational presentations at symposia by AbbVie and Stada Pharma and in his role as a consultant/member of an advisory board for the companies Intrabio, Lario Therapeutics and Modag. He holds stock options of the companies Intrabio and Modag and shares of the companies BioNTech, CureVac, Formycon and Medigene. There is no conflict of interest. S.K. Meles is funded by the Michael J. Fox Foundation (Edmond J. Safra Fellowship in Movement Disorders). All these activities and relations are unrelated to the work submitted.

Ethical approval Study protocols were approved by the institutional review boards of University Medical Center of Groningen and the Philipps-University Marburg, and voluntary informed consent was obtained from each subject after verbal and written explanation of the study, in accordance with the Declaration of Helsinki.

Consent to participate Voluntary informed consent was obtained from each subject after verbal and written explanation of the study.

Clinical trial number Not applicable.

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