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Four-Year Follow-up of [¹⁸F] Fluorodeoxyglucose Positron Emission Tomography–Based Parkinson’s Disease–Related Pattern Expression in 20 Patients With Isolated Rapid Eye Movement Sleep Behavior Disorder Shows Prodromal Progression

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Rosalie V. Kogan, Annette Janzen, Klaus L. Leenders, and Wolfgang H. Oertel share first and last authorship.

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ABSTRACT: Background: Isolated rapid eye movement sleep behavior disorder is known to be prodromal for alpha-synucleinopathies, such as Parkinson’s disease (PD) and dementia with Lewy bodies. The [¹⁸F]fluorodeoxyglucose-positron emission tomography (PET)–based PD-related brain pattern can be used to monitor disease progression.

Objective: We longitudinally investigated PD-related brain pattern expression changes in 20 subjects with isolated rapid eye movement sleep behavior disorder to investigate whether this may be a suitable technique to study prodromal PD progression in these patients and to identify potential phenoconverters.

Methods: Subjects underwent two [¹⁸F]fluorodeoxyglucose-PET brain scans ~3.7 years apart, along with baseline and repeated motor, cognitive, and olfactory testing within roughly the same time frame.

Results: At baseline, 8 of 20 (40%) subjects significantly expressed the PD-related brain pattern (with z scores above the receiver operating characteristic–determined threshold). At follow-up, six additional subjects exhibited significant PD-related brain pattern expression (70% in total). PD-related brain pattern expression increased in all subjects ($P = 0.00008$). Four subjects (20%), all with significant baseline PD-related brain pattern expression, phenoconverted to clinical PD.

Conclusions: Suprathreshold PD-related brain pattern expression and greater score rate of change may signify greater shorter-term risk for phenoconversion. Our results support the use of serial PD-related brain pattern expression measurements as a prodromal PD progression biomarker in patients with isolated rapid eye movement sleep behavior disorder. © 2020 The Authors. *Movement Disorders* published by Wiley Periodicals LLC. on behalf of International Parkinson and Movement Disorder Society.

Key Words: [¹⁸F]FDG-PET; rapid eye movement sleep behavior disorder; Parkinson’s disease–related pattern; neuroimaging; prodromal progression biomarker

Isolated or idiopathic rapid eye movement sleep behavior disorder (iRBD) is known to be prodromal for alpha-synucleinopathies, such as Parkinson’s disease (PD), dementia with Lewy bodies (DLB), or more rarely, multiple system atrophy (MSA) in >80% of cases.^{1–3} As such, patients with iRBD are critical for the

study of prodromal PD development and will likely be key to disease-modifying drug trials.

However, this necessitates the availability of reliable biomarkers for the tracking and prediction of disease progression and phenoconversion to manifest alpha-synucleinopathies. Equally important, these biomarkers must be able to identify those who will *not* phenoconvert.

Accordingly, this study focuses on the longitudinal change in expression of a characteristic pattern of [^{18}F] fluorodeoxyglucose positron emission tomography ([^{18}F]FDG-PET)-based abnormal cerebral glucose metabolism known as the “PD-related pattern” (PDRP) in subjects with iRBD. The PDRP is defined by the Scaled Subprofile Model Principal Component Analysis (SSM/PCA) method,^{4,5} and it has been widely used in the study of parkinsonian syndromes.⁶ Previous reports have demonstrated that PDRP expression precedes onset of motor symptoms by several years in prodromal patients,^{7–9} and that in manifest PD, pattern expression increases with disease progression¹⁰ and decreases with effective symptomatic treatment.¹¹

Repeated longitudinal measurements of [^{18}F]FDG-PET-based disease-related metabolic brain pattern expression in patients with iRBD have not been performed before. We therefore studied 20 subjects with iRBD with glucose metabolic brain imaging, as well as motor, cognitive, and olfactory testing two times approximately 4 years apart. Our primary purpose was to investigate whether serial PDRP expression measurements may be a suitable technique to study prodromal PD progression in patients with iRBD.

Methods

Study Design and Participants

This prospective, two-part longitudinal pilot study took place at the University Medical Center of Groningen in Groningen, the Netherlands, and at the Philipps-Universität Marburg in Marburg, Germany. Study protocols for the baseline and follow-up investigations were approved by the institutional review boards of both institutions, and voluntary informed consent was obtained from each subject at baseline and follow-up after verbal and written explanation of the study, in accordance with the Declaration of Helsinki.

Twenty subjects with iRBD (3 Dutch and 17 German) were evaluated with baseline and follow-up [^{18}F]FDG-PET imaging, as well as motor, cognitive, and olfactory testing (see Table 1 for demographics). At baseline, subjects with iRBD with a clinical diagnosis of parkinsonism, dementia, or history of psychotropic medication use before or during iRBD onset were excluded.

In addition, 16 age- and gender-matched healthy control subjects (HCs) (13 male/3 female, age

63.1 \pm 6.7 years) underwent baseline [^{18}F]FDG-PET imaging to z -transform the iRBD PDRP scores.

Exclusion criteria for all subjects at baseline included a history of (other) neurological diseases, diabetes mellitus, hyperthyroidism or hypothyroidism, stroke, significant head trauma, or other relevant comorbidities.

At both centers, phenoconversion to PD or DLB was determined by the neurologist performing the motor examination, according to the UK Parkinson’s Disease Society Brain Bank diagnostic criteria or the DLB Consortium consensus criteria.^{12,13} In addition, at Philipps-Universität Marburg, a neurologist confirmed the presence of PD/DLB twice, 3 months apart, in phenoconverted German subjects.

[^{18}F]FDG-PET

Twenty RBD Screening Questionnaire–screened and video polysomnographically confirmed iRBD patients underwent baseline and follow-up [^{18}F]FDG-PET imaging an average of 3.7 \pm 0.6 years apart. Sixteen HCs underwent baseline [^{18}F]FDG-PET imaging as well. All baseline and follow-up scans were performed on a Siemens Biograph mCT64 or mCT40 PET/CT camera (Siemens, Munich, Germany) at the University Medical Center of Groningen. Images were reconstructed with OSEM3D (3 iterations, 21 subsets), time-of-flight, point-spread-function, Gaussian 8-mm full-width-at-half-maximum spatial filter, and matrix size 256 (corresponding to a voxel size of 2 mm \times 3.18 mm \times 3.18 mm).

Central nervous system depressants and any iRBD-related medications (ie, melatonin or clonazepam) were discontinued in all HCs and subjects with iRBD for at least 24 hours before baseline and follow-up imaging.

All iRBD and HC images were spatially normalized to an [^{18}F]FDG-PET template in Montreal Neurological Institute brain space¹⁴ using SPM12 software (Wellcome Centre for Human Neuroimaging, London, UK) implemented in MATLAB (version R2019a; MathWorks, Natick, MA, USA).

A PDRP based on 16 HCs and 14 patients with PD was defined with the SSM/PCA⁴ method using data prepared to the same specifications as the earlier iRBD and HC data (see Supporting Information Fig. S1) (notably, these 16 HCs are a separate cohort from the one described earlier).

PDRP expression in subjects with iRBD and HCs was calculated using in-house code. PDRP subject scores were z -transformed to HCs such that the mean HC PDRP z score was 0, with a standard deviation of ± 1 . A receiver operating characteristic (ROC) analysis was performed to best differentiate between HCs and patients with PD, which determined a z score cutoff of 1.98 (specificity 100%, sensitivity 85.7%; high specificity will be an important consideration for drug trials to

TABLE 1. Results are ordered from lowest to highest follow-up PDRP expression z score

Subject no.	Gender	Age (yr)	Age of iRBD onset (yr)	Duration of iRBD (yr)	Baseline PDRP z score	Follow-up PDRP z score category	Follow-up PDRP z score (change from baseline)	PDRP change per year	Sniffin' Sticks Identification Test (change from baseline)	UPDRS-III (change from baseline)	MoCA (change from baseline)
1	M	60.4	52.8	7.6	-1.56	<1.98	-0.77 (+0.80)	0.31	10 (-2) ^a	0 (-1)	27 (-1)
2	M	61.2	55.0	6.2	-2.19		-0.72 (+1.47)	0.40	13 (+4)	3 (-3)	29 (+2)
3	M	61.4	52.4	9.0	-0.47		0.70 (+1.18)	0.30	12 (-1)	1 (-3)	28 (-2)
4	M	58.0	48.0	10.0	-0.08		0.93 (+1.01)	0.25	13 (+2)	7 (+3) ^{ab}	27 (+1)
5	M	67.1	54.1	13.0	-0.59		1.40 (+1.98)	0.50	7 (-2) ^a	2 (0)	29 (0)
6	M	70.1	42.1	28.0	1.42		1.77 (+0.35)	0.12	8 (+2) ^a	0 (0)	28 (0)
7	F	72.5	62.3	10.3	-0.85	≥1.98	2.07 (+2.92) ^{ac}	0.68	14 (0)	2 (0)	30 (+7)
8	M	69.9	63.9	6.0	1.00		2.44 (+1.44) ^{ac}	0.48	12 (+2)	4 (+2)	27 (0)
9	M	67.5	62.5	5.0	-0.71		2.60 (+3.30) ^{ac}	1.10	6 (-2) ^a	4 (+2)	29 (+3)
10	M	69.9	60.4	9.4	1.23		2.74 (+1.52) ^{ac}	0.44	5 (-2) ^a	4 (+1)	26 (-1)
11	M	64.1	57.5	6.6	0.35		3.02 (+2.67) ^{ac}	1.04	5 (-1) ^a	0 (0)	30 (+3)
12	M	69.1	59.4	9.7	2.76 ^a		3.72 (+0.97) ^a	0.26	2 (-3) ^a	2 (-4)	28 (+1)
13	M	68.1	50.0	18.0	0.60		4.16 (+3.56) ^{ac}	0.88	12 (0)	3 (-1)	27 (-1)
14	F	74.7	67.1	7.6	2.18 ^a		4.41 (+2.23) ^a	0.48	3 (-2) ^a	3 (-1)	30 (+2)
15	M	65.1	60.1	5.0	3.13 ^a		4.46 (+1.33) ^a	0.35	4 (-4) ^a	1 (+1)	26 (-2)
16*	M	66.6	61.6	5.0	2.10 ^a		5.25 (+3.15) ^a	0.79	11 (+3)	7 (+7) ^a	27 (-2)
17	M	70.6	64.6	6.0	4.32 ^a		6.19 (+1.87) ^a	0.48	0 (0) ^a	3 (-2)	29 (+7)
18*	M	69.9	53.9	16.0	2.64 ^a		6.30 (+3.66) ^a	0.94	6 (-2) ^a	9 (+7) ^a	28 (+2)
19*	M	67.2	59.2	8.0	4.68 ^a		7.67 (+2.99) ^a	0.74	0 (0) ^a	7 (+6) ^a	28 (0)
20*	M	53.9	45.9	8.0	4.73 ^a		9.11 (+4.37) ^a	1.08	2 (0) ^a	15 (+14) ^a	25 (+1) ^a
Mean ± SD		66.37 ± 5.17	56.64 ± 6.70	9.72 ± 5.55	1.23 ± 2.05		3.37 ± 2.63 (+2.14 ± 1.12)	0.58 ± 0.30	7.3 ± 4.6 (-0.4 ± 2.1)	3.7 ± 3.2 (+1.3 ± 3.9)	27.9 ± 1.4 (+1.0 ± 2.6)

Underlines denote subjects scanned on the Siemens Biograph mCT40 PET/CT scanner (the rest were scanned on the mCT64 system). Boldface and asterisk by subject number denote the four phenoconverted subjects. Given age and duration of iRBD are for the time of follow-up [¹⁸F]fluorodeoxyglucose positron emission tomography [¹⁸F]FDG-PET scan.

^aDenotes pathological results.

^bSubject 4 has an artificially elevated UPDRS motor score because of unrelated back problems.

^cSubjects 7–11 and 13 had subthreshold PDRP expression at baseline but suprathreshold scores at follow-up [¹⁸F]FDG-PET imaging.

Abbreviations: PDRP, Parkinson's disease-related pattern; iRBD, isolated or idiopathic rapid eye movement sleep behavior disorder; UPDRS-III, Unified Parkinson's Disease Rating Scale, Part III; MoCA, Montreal Cognitive Assessment; M, male; F, female; SD, standard deviation.

take into account to minimize misclassification of nonphenoconverters).

A Hoffman 3D Brain Phantom allowed for linear correction of raw PDRP score offsets between the mCT40 and mCT64 scanners (see Supporting Information).

Motor, Cognitive, and Olfactory Assessment

All 20 subjects with iRBD were additionally assessed using the Unified Parkinson's Disease Rating Scale, Part III (UPDRS-III; motor examination),^{15,16} the Montreal Cognitive Assessment (MoCA),¹⁷ and the Sniffin' Sticks 16-item olfactory odor identification test¹⁸ at baseline and follow-up. A 5-point change in the UPDRS-III was considered to be clinically significant.¹⁹ MoCA scores ≤ 25 out of 30, and Sniffin' Sticks identification score ≤ 10 out of 16 were considered to be pathological.^{17,18}

Statistical Analysis

Variables were tested for normality of distribution with the Shapiro-Wilk test, and PDRP z scores and age were subsequently considered to be distributed parametrically.⁷

The rest of the variables (UPDRS-III, MoCA, and olfactory scores; years duration of iRBD; and variables' rates of change) were considered to be non-parametrically distributed. Correlations between these

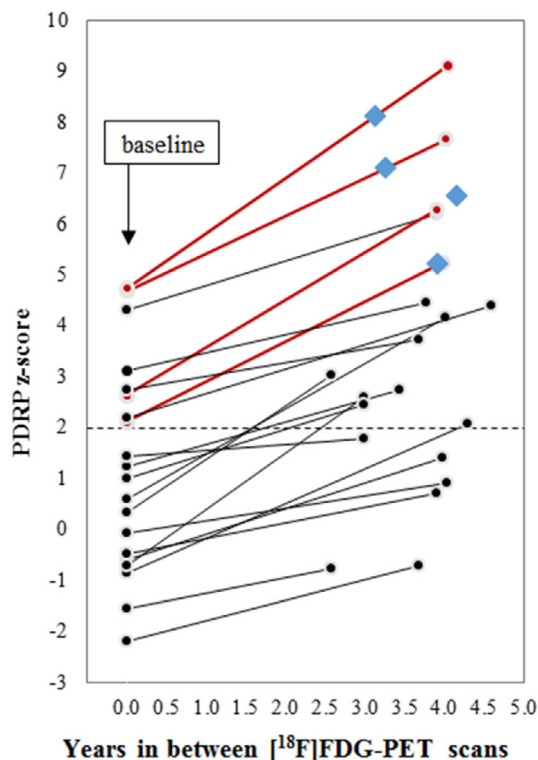


FIG 1. PDRP expression changes between baseline and follow-up [¹⁸F]FDG-PET imaging. Burgundy lines denote phenoconverted subjects; diamonds denote point of clinical phenoconversion.

and PDRP z scores were compared with a two-sided Spearman rank correlation coefficient.

A one-sample Wilcoxon signed rank test was used to examine PDRP z score change per year, UPDRS-III score change per year, MoCA score change per year, and olfactory score change per year. A Spearman rank correlation coefficient was used to compare PDRP z score change per year with UPDRS-III score change per year, MoCA score change per year, and olfactory score change per year.

These analyses were not corrected for multiple comparisons. Correlations were considered to be significant at $P < 0.05$ (uncorrected). All analyses were performed using SPSS v.24 (SPSS Inc., Chicago, IL).

Due to small subgroup sizes, we did not run statistical analyses based on phenoconversion status. Instead, these results are described qualitatively.

This study is registered with the Netherlands Trial Register, number NL8057.

Results

Between 2014 and 2015, 20 patients with iRBD underwent baseline [¹⁸F]FDG-PET imaging, as well as motor, cognitive, and olfactory testing (see Table 1).

At baseline, 8 of 20 (40%) subjects with iRBD expressed a PDRP z score above the ROC-determined threshold of 1.98. At follow-up, six additional subjects with iRBD exhibited suprathreshold PDRP z scores, for a total of 14 of 20 (70%). PDRP expression increased among all 20 (100%) subjects between baseline and follow-up (see Fig. 1). At the group level, PDRP expression was significantly higher at follow-up than at baseline (Wilcoxon $P = 0.00008$). The average absolute z score increase was by 2.1 ± 1.1 points, with an average z score increase of 0.6 ± 0.3 point per year.

UPDRS-III, MoCA, and olfactory scores did not change significantly between baseline and follow-up testing (Wilcoxon $P < 0.33$, 0.48 , and 0.26 , respectively). However, olfactory scores correlated significantly with PDRP z scores at baseline and follow-up (Spearman $P < 0.0005$ and $P = 0.001$, respectively; see Supporting Information Fig. S2), although olfactory score change per year did not correlate to PDRP scores or PDRP change per year. UPDRS motor scores correlated with PDRP z scores at follow-up, but not at baseline (Spearman $P = 0.017$ vs. 0.099). In addition, UPDRS-III score change per year did correlate significantly with PDRP z score change per year (Spearman $P = 0.024$; see Supporting Information Fig. S3). MoCA scores and MoCA change per year did not correlate to PDRP z scores or PDRP change per year. In fact, all follow-up MoCA scores were within the normal range except for one (25), which was from a phenoconverted

subject with the highest PDRP z score of the entire iRBD cohort (9.11).

No significant correlation was found between age of iRBD onset, age or duration of iRBD at time of follow-up, and any other variable tested in this study.

All four phenoconverters had suprathreshold baseline and follow-up PDRP z scores, as well as greater PDRP score rate of change (see Fig. 1).

Discussion

For the first time, this follow-up study of serial [^{18}F]FDG-PET imaging demonstrates that the expression of abnormal cerebral metabolism in patients with iRBD increases over time. Our results support the use of serial [^{18}F]FDG-PET imaging and PDRP expression measurements as a prodromal disease progression biomarker in patients with iRBD. Previous cross-sectional findings demonstrated that abnormal metabolic expression in iRBD can begin years before motor manifestations of alpha-synucleinopathies.⁷

Motor, cognitive, and olfactory scores did not change significantly between baseline and follow-up. This may be attributable to bias because of the test-retest effect (with the MoCA) or guessing (in the case of the olfaction test).²⁰ Olfaction has previously been reported not to be a disease progression biomarker in iRBD.²¹ In contrast, [^{18}F]FDG-PET showed consistent, significant changes between baseline and follow-up imaging, which corresponded to changes in motor function. Based on the four phenoconverted subjects, we infer that subjects with suprathreshold absolute PDRP expressions and higher PDRP rates of change may be at shorter-term risk for phenoconversion to clinical alpha-synucleinopathy. This study underscores the importance of repeated PDRP measurements for its implementation as a disease progression biomarker.

One of the strengths of this study includes its longitudinal nature. Some of the limitations of this study include small sample size and lack of repeat measurements of the HC cohort for comparison. Investigation of greater numbers of subjects with iRBD will be necessary to confirm or modify the conclusions of this study. In addition, a separate investigation into expressions of the DLB- or MSA-related patterns in this cohort was beyond the scope of this report.^{6,22}

Further longitudinal studies should also examine the relationship between [^{18}F]FDG-PET and other biomarkers, such as dopamine transporter imaging with [^{123}I]N- ω -fluoropropyl-2 β -carbomethoxy-3 β -(4-iodophenyl)nortropane single-photon emission computed tomography ([^{123}I]FP-CIT-SPECT).^{23,24} The latter is a well-studied potential prodromal progression biomarker in alpha-synucleinopathies. However, serial [^{18}F]FDG-PET imaging may have an advantage,

because [^{18}F]FDG-PET allows for quantitative analysis of changes in glucose uptake in all areas of the brain at once, whereas [^{123}I]FP-CIT-SPECT is predominately used to visualize the dopaminergic nigrostriatal tract. [^{18}F]FDG-PET also likely has greater potential to identify which specific parkinsonian disorder will develop in a patient with iRBD.^{6,22} In addition, it is known that some patients with DLB may have initially negative [^{123}I]FP-CIT-SPECT scans.²⁵

One hundred subjects with iRBD are currently being recruited for ongoing multicenter, multinational research within the scope of this project to validate our findings.

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Appendix

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Author Roles

Klaus L. Leenders, Wolfgang H. Oertel, Geert Mayer, Jan Booij, Kathrin Reetz, Sebastiaan Overeem, Angelique Pijpers, and Rosalie V. Kogan assisted in the study protocol and design. Klaus L. Leenders and Wolfgang H. Oertel secured the funding for this project. Annette Janzen, Felix Bernhard, Elisabeth Sittig, Sebastiaan Overeem, and Angelique Pijpers recruited patients. Sanne K. Meles, Laura K. Teune, Fransje E. Reesink, and Jelmer G. Kok recruited HCs. Elisabeth Sittig organized and accompanied German patients on visits to Groningen for [¹⁸F]FDG-PET imaging. Rosalie V. Kogan organized all logistics and imaging appointments for patients in Groningen. Annette Janzen performed all of the neuroclinical assessments with German patients in Marburg, while Rosalie V. Kogan, Vita Gurvits, and Klaus L. Leenders performed the neuroclinical assessments with Dutch patients in Groningen. Rosalie V. Kogan performed all of the statistical analyses with help from Remco J. Renken and put together all of the figures and table with the support of Annette Janzen, with the exception of Supporting Information Fig. S1, which Sanne K. Meles made; Fig. 1 was also made with input from Sanne K. Meles. Remco J. Renken, David Vallez Garca, and Debora E. Peretti wrote the in-house code used. Rosalie V. Kogan drafted the manuscript. All authors contributed commentary for revising the manuscript.

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