FDG PET, Dopamine Transporter SPECT, and Olfaction: Combining Biomarkers in REM Sleep Behavior Disorder

Sanne K. Meles, MD,1,∗ David Vadasz, MD,2 Remco J. Renken, PhD,3 Elisabeth Sittig-Wiegand,2 Geert Mayer, MD,2,9 Candan Depboylu, MD,2 Kathrin Reetz, MD,4 Sebastian Overeem, MD, PhD,5 Angelique Pijpers, MD, PhD,5 Fransje E. Reesink, MD,1 Teus van Laar, MD, PhD,1 Lisette Heinen, MD,1 Laura K. Teune, MD, PhD,1 Helmut Höflken, MD,6 Marcus Luster, MD,6 Karl Kesper, PhD,7 Sofie M. Adriaanse, PhD,8 Jan Booij, MD, PhD,8 Klaus L. Leenders, MD, PhD,1,11† and Wolfgang H. Oertel, MD, PhD2,10†

1Department of Neurology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands 2Department of Neurology, Philipps-Universität Marburg, Marburg, Germany 3Neuroimaging Center, Department of Neuroscience, University Groningen, The Netherlands 4Department of Neurology and JARA-BRAIN Institute Molecular Neuroscience and Neuroimaging, Aachen University, Aachen, Germany 5Kempenhaeghe Foundation, Sleep Medicine Centre, Heeze, The Netherlands 6Department of Nuclear Medicine, Philipps-Universität Marburg, Marburg, Germany 7Department of Internal Medicine, Section Respiratory Diseases, Philipps Universität Marburg, Marburg, Germany 8Department of Nuclear Medicine, Academic Medical Center, Amsterdam, The Netherlands 9Hephata Klinik, Schwalmstadt, Germany 10Institute for Neurogenomics, Helmholtz Center for Health and Environment, München, Germany

ABSTRACT

Background: Idiopathic REM sleep behavior disorder is a prodromal stage of Parkinson’s disease and dementia with Lewy bodies. Hyposmia, reduced dopamine transporter binding, and expression of the brain metabolic PD-related pattern were each associated with increased risk of conversion to PD. The objective of this study was to study the relationship between the PD-related pattern, dopamine transporter binding, and olfaction in idiopathic REM sleep behavior disorder.

Methods: In this cross-sectional study, 21 idiopathic REM sleep behavior disorder subjects underwent 18F-fluorodeoxyglucose PET, dopamine transporter imaging, and olfactory testing. For reference, we included 18F-fluorodeoxyglucose PET data of 19 controls, 20 PD patients, and 22 patients with dementia with Lewy bodies. PD-related pattern expression z-scores were computed from all PET scans.

Results: PD-related pattern expression was higher in idiopathic REM sleep behavior disorder subjects compared with controls (P = 0.048), but lower compared with PD (P = 0.001) and dementia with Lewy bodies (P < 0.0001). PD-related pattern expression was higher in idiopathic REM sleep behavior disorder subjects with hyposmia and in subjects with an abnormal dopamine transporter scan (P < 0.05, uncorrected).

Conclusion: PD-related pattern expression, dopamine transporter binding, and olfaction may provide complementary information for predicting phenocconversion.

© 2017 The Authors. Movement Disorders published by Wiley Periodicals, Inc. on behalf of International Parkinson and Movement Disorder Society.

Key Words: idiopathic REM sleep behavior disorder; Parkinson’s disease-related pattern; 18F-FDG-PET; dopamine transporter 123I-FP-CIT SPECT; olfaction

Longitudinal studies have shown that >80% of individuals with idiopathic REM sleep behavior disorder (RBD) developed Parkinson’s disease (PD) or dementia with Lewy bodies (DLB) on long-term follow-up.1-3 RBD subjects represent a suitable group to study the prodromal stage of these disorders and may be crucial for disease-modification trials. However, such trials require biomarkers that can reliably identify at-risk individuals and predict clinical manifestation of PD/DLB.

Neurodegenerative disorders are characterized by disease-specific patterns of altered brain glucose metabolism on 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) brain imaging. Such patterns can be extracted from 18F-FDG-PET data.
with scaled subprofile model and principal component analysis (SSM PCA). With SSM PCA, a PD-related pattern (PDRP) has been identified in multiple cohorts.\textsuperscript{7-10} The degree to which the PDRP is present in a new \textsuperscript{18}F-FDG-PET scan can be quantified, resulting in a subject score. PDRP subject scores increase with disease progression and decrease with effective therapy.\textsuperscript{10,11}

To date, 2 groups have reported that RBD subjects have higher PDRP subject scores compared with controls.\textsuperscript{12,13} In a longitudinal study of 17 RBD subjects, baseline PDRP expression was associated with a high risk of developing PD or DLB within 5 years.\textsuperscript{12}

Other markers have also been considered. Loss of striatal dopamine transporter (DAT) binding on single photon emission computed tomography (DAT-SPECT) indicates imminent phenoconversion.\textsuperscript{14,15} In addition, RBD subjects with baseline hyposmia have a high risk of developing PD/DLB within 5 years of follow-up.\textsuperscript{16,17}

The PDRP has potential as a disease biomarker in prodromal subjects, but further validation by an independent research group is essential. Moreover, direct comparisons between PDRP expression, DAT binding, and olfaction in the same RBD subjects have never been made. We therefore studied these 3 markers in 21 RBD patients.

**Methods**

Twenty-one subjects with RBD (polysomnographically confirmed\textsuperscript{18}) were evaluated with \textsuperscript{18}F-FDG-PET, DAT-SPECT, and olfactory testing. Per inclusion criteria, RBD subjects did not have parkinsonism\textsuperscript{19} or DLB\textsuperscript{20} at the time of the study. Participants with a history of psychotropic medication use before the onset of RBD were excluded.\textsuperscript{21}

Nineteen age-matched healthy controls were studied with \textsuperscript{18}F-FDG-PET and olfactory testing. Controls did not have RBD (score < 5 on the RBD screening questionnaire\textsuperscript{22}) and furthermore had no first-degree family members with a neurodegenerative disease.

RBD subjects and controls were investigated with the Unified Parkinson’s Disease Rating Scale (UPDRS, version 2003\textsuperscript{23}) and the Montreal Cognitive Assessment (MoCA).\textsuperscript{24} Olfactory function was assessed with Sniffin’ Sticks.\textsuperscript{15,16,25} Total olfaction scores (TDI) were obtained by summing the threshold (T), discrimination (D), and identification (I) subscores. Five olfactory stages were defined as follows: anosmia, TDI ≤ 15; severe hyposmia, 15 < TDI ≤ 20); moderate hyposmia, 20 < TDI ≤ 25; mild hyposmia, 25 < TDI ≤ 30; and normosmia, TDI > 30. In a previous study, it was determined that a baseline TDI score < 18 was associated with increased risk of phenoconversion to PD/DLB within 5 years of follow-up.\textsuperscript{16} We therefore divided RBD patients into 2 groups: patients with TDI scores < 18 and patients with TDI scores ≥ 18.

For reference, we studied the \textsuperscript{18}F-FDG-PET scans of retrospectively-included patients with clinical diagnoses of “probable PD” (n = 20, nondemented, aged 67.5 ± 8.6 years; 16 men; median disease duration, 2 years; interquartile range, 1-7 years) and “probable DLB” (n = 22, aged 73.7 ± 7 years; 17 men; median disease duration, 3 years; interquartile range, 1-4 years) according to consensus criteria.\textsuperscript{19,20}

Exclusion criteria for all subjects included a history of (other) neurological diseases, diabetes mellitus, stroke, significant head trauma, or other relevant comorbidities. The study was approved by local institutional review boards. Voluntary written informed consent was obtained from each subject after verbal and written explanation of the study, in accordance with the Declaration of Helsinki.

All subjects underwent static \textsuperscript{18}F-FDG-PET imaging on a Siemens Biograph mCT-64 PET/CT camera (Siemens, Munich, Germany) at the University Medical Center Groningen, the Netherlands. Images were reconstructed with OSEM3D, including point-spread function and time-of-flight modeling, and smoothed with a Gaussian 8-mm full-width at half-maximum filter. Central nervous system depressants were discontinued in all subjects for at least 24 hours before each scan. In RBD patients, all RBD-related medications (eg, melatonin or clonazepam) were discontinued for at least 48 hours prescan. In PD and DLB patients, dopaminimetics were not withheld.

All images were spatially normalized onto an \textsuperscript{18}F-FDG-PET template in Montreal Neurological Institute brain space\textsuperscript{26} using SPM12 software (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK) implemented in Matlab (version 2012b; MathWorks, Natick, Massachusetts). Expression of the previously identified PDRP\textsuperscript{8} was calculated in the new \textsuperscript{18}F-FDG-PET data as described previously.\textsuperscript{27} All PDRP subject scores were z-transformed to the controls (n = 19), such that the average PDRP z-score in controls was 0, with a standard deviation of 1.

In future clinical trials of RBD, diagnostic tool specificity will be more important than sensitivity (ie, RBD subjects who will not phenoconvert should be excluded). We therefore reanalyzed the PDRP identification cohort\textsuperscript{4} and selected a cutoff z-score that gave 100% specificity. At PDRP z = 1.8, there was no misclassification of controls in the identification cohort (data not shown). This threshold was applied to the PDRP z scores in the current study (ie, a z score ≥ 1.8 was considered indicative of PD).

RBD subjects underwent DAT imaging with \textsuperscript{123}I-ß-carbomethoxy-ß-(4-iodophenyl)-N-(3-fluoropropyl)-nortropane single photon emission computed tomography. DAT binding in striatal regions was quantified with the Brain Registration & Analysis Software Suite
Our findings underscore the value of the PDRP as a potential disease biomarker in idiopathic RBD. In line with 2 previous studies, RBD subjects significantly scored too low for age, and TDI scores were significantly lower in RBD patients compared with controls. MoCA and olfaction scores were significantly lower in RBD patients (P < 0.01; Supplementary Table).

PDRP subject scores were not significantly different between men (n = 9) and women (n = 10) in the control group (P = 0.75, independent t test). Stepwise increases in PDRP z-scores were observed across groups (ANOVA \(F_{81} = 59.06, P < 0.0001\); Fig. 1). In 12 of 21 RBD subjects (57%), the PDRP z-score surpassed the threshold (\(z \geq 1.8\); Table 1).

In Table 1, PDRP z-scores, putamen DAT-binding ratios, and TDI scores are shown for each RBD patient. This permits identification of several RBD subgroups. Subjects 1-3 have normal values for all 3 markers: subjects 17-21 have abnormal values for all 3 markers: suprathreshold PDRP z-scores, putamen DAT-binding too low for age, and TDI scores < 18. Subjects 15 and 16 have suprathreshold PDRP z-scores and abnormal DAT scans, but TDI scores \(\geq 18\). Of the 9 subjects with abnormal DAT scans, 7 had suprathreshold PDRP z-scores (subjects 15-21). Interestingly, of the 12 subjects with normal DAT scans, 5 (42%) had suprathreshold PDRP z-scores (subjects 10-14).

On average, subjects with abnormal DAT scans (n = 9) had higher PDRP z-scores compared with subjects with normal DAT scans (P = 0.044, uncorrected). Subjects with olfaction scores < 18 (n = 9) had higher PDRP z-scores compared with subjects with olfaction scores \(\geq 18\) (P = 0.032, uncorrected). Putamen DAT-binding ratios were not significantly different between the 2 olfaction groups (P = 0.117). PDRP z-scores, DAT binding, and olfaction were not significantly correlated, but trends were observed (n = 21; Supplementary Fig. 1).

**Results**

UPDRS-III scores were significantly higher in RBD subjects compared with controls. MoCA and olfaction scores were significantly lower in RBD patients (P < 0.01; Supplementary Table).
expressed the PDRP.\textsuperscript{12,13} Although on average, PDRP z-scores were lower in RBD subjects compared with PD/DLB, more than half of the RBD subjects already had a PDRP z-score in the range of PD patients.

This study is the first to directly compare PDRP expression, striatal DAT binding, and olfaction in RBD. Although a trend was observed, PDRP and striatal DAT binding were not significantly correlated. Previous studies in PD have shown that PDRP expression shows only modest correlation to DAT binding.\textsuperscript{10,28,29} This may indicate a partly nondopaminergic genesis of the PDRP. Remarkably, 5 of 12 RBD patients with normal striatal DAT binding had suprathreshold PDRP z-scores. In 2 of these cases, \textsuperscript{18}F-FDG-PET was performed before DAT-SPECT. It has been shown that some DLB patients may initially have unremarkable DAT scans.\textsuperscript{30} It is possible that RBD subjects with significant PDRP expression but normal DAT binding will eventually develop DLB. Longitudinal imaging studies of RBD subjects are needed to further investigate the relationship between PDRP expression and loss of DAT binding in relation to the final clinical diagnosis.

That there was no direct significant correlation between PDRP z-scores, DAT binding, and olfaction could indicate that the 3 markers provide complementary information. For example, 2 cases had suprathreshold PDRP z-scores and abnormal DAT scans, but TDI scores \(\geq 18\). These subjects would have been considered at low risk of phenoconversion if the olfaction scores alone had been considered.\textsuperscript{16} We also identified 3 subjects with normal values for all 3 markers. These individuals may have a low risk of converting to PD/DLB. In contrast, 5 subjects had suprathreshold PDRP z-scores, putamen DAT binding too low for age, and TDI scores \(< 18\); these subjects may be considered to have a particularly high risk of conversion within the next 5 years.

The data presented in this report are cross-sectional. A longitudinal study of our RBD cohort is ongoing. Follow-up data will be essential to elucidate if DAT-SPECT-negative DLB cases, and perhaps subjects who later developed multiple system atrophy, contributed to the aforementioned findings. We expect that the PDRP will be especially informative, because in contrast to olfaction,\textsuperscript{31} the PDRP is a progression marker.\textsuperscript{11} Moreover, PDRP expression is useful in the differential diagnosis of parkinsonian disorders,\textsuperscript{32} whereas DAT imaging is not.\textsuperscript{13}

\textbf{Acknowledgments:} We thank R.V. Kogan for proofreading the manuscript. W.H. Öertel, MD, PhD, is Hertie-Senior-Research Professor, supported by the Charitable Hertie Foundation, Frankfurt/Main, Germany.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|c|c|c|}
\hline
PDRP z score category & DAT scan category & RBD subject & PDRP z score & Lowest putamen DAT-binding ratio & Total olfaction score (TDI) & Sex & Age & RBD duration (years) & Age at onset RBD & MoCA & UPDRS-III \\
\hline
<1.8 & Normal & 1 & 1.7 & 2.0\textsuperscript{c} & 33.8 & Male & 57.4 & 5.0 & 52.4 & 30.0 & 4.0 \\
2 & 1.0 & 2.3 & 33.5 & Female & 58.9 & 7.0 & 51.9 & 27.0 & 0.0 \\
3 & -0.3 & 2.5 & 33.5 & Female & 68.3 & 6.0 & 62.3 & 23.0 & 2.0 \\
4 & 1.1 & 2.5 & 29.5 & Male & 54.0 & 6.0 & 48.0 & 26.0 & 4.0 \\
5 & 0.9 & 2.4 & 26.0 & Male & 56.4 & 6.0 & 56.4 & 27.0 & 1.0 \\
6 & 0.2 & 2.2 & 19.5 & Male & 67.1 & 25.0 & 42.1 & 28.0 & 0.0 \\
7 & 0.4 & 2.9 & 0.0 & Male & 56.0 & 9.0 & 47.0 & 25.0 & 1.0 \\
\hline
Abnormal & 8 & 0.3 & 1.2 & 19.0 & Male & 65.9 & 12.0 & 53.9 & 26.0 & 2.0 \\
9 & 1.1 & 1.0 & 13.0 & Male & 66.4 & 6.0 & 60.4 & 27.0 & 3.0 \\
\hline
\geq 1.8 & Normal & 10 & 2.2 & 2.5 & 29.0 & Male & 57.8 & 5.0 & 52.8 & 28.0 & 1.0 \\
11 & 2.2 & 2.3 & 23.5 & Male & 62.6 & 14.0 & 48.6 & 24.0 & 5.0 \\
12 & 3.0 & 2.5 & 20.5 & Male & 57.5 & 2.5 & 55.0 & 27.0 & 6.0 \\
13 & 1.9 & 2.3 & 16.5 & Male & 64.5 & 2.0 & 62.5 & 26.0 & 2.0 \\
14 & 2.5 & 2.0\textsuperscript{c} & 15.5 & Female & 70.1 & 3.0 & 67.1 & 28.0 & 4.0 \\
\hline
Abnormal & 15 & 2.2 & 1.7 & 27.5 & Male & 64.0 & 14.0 & 50.0 & 28.0 & 4.0 \\
16 & 1.8 & 1.6 & 25.8 & Male & 66.9 & 3.0 & 63.9 & 27.0 & 2.0 \\
17 & 3.4 & 0.9 & 17.0 & Male & 61.5 & 4.0 & 57.5 & 27.0 & 0.0 \\
18 & 3.1 & 1.7 & 13.0 & Male & 65.4 & 6.0 & 59.4 & 27.0 & 6.0 \\
19 & 4.2 & 2.0\textsuperscript{c} & 2.0 & Male & 49.9 & 4.0 & 45.9 & 24.0 & 1.0 \\
20 & 5.7 & 1.2 & 0.0 & Male & 63.2 & 4.0 & 59.2 & 28.0 & 1.0 \\
21 & 1.9 & 1.8 & 0.0 & Male & 66.6 & 2.0 & 64.6 & 22.0 & 5.0 \\
\hline
\end{tabular}
\caption{Clinical and imaging characteristics of the 21 RBD subjects}
\end{table}
References

1. Postuma RB, Gagnon JF, Vendette M, Fantini ML, Massicotte-Marquez J, Montplaisir J. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. Neurology 2009;72:1296-1300.

2. Postuma RB, Lang AE, Gagnon JF, Pelletier A, Montplaisir JY. How does parkinsonism start? Prodromal parkinsonism motor changes in idiopathic REM sleep behaviour disorder. Brain 2012;135:1860-1870.

3. Iranzo A, Tolosa E, Gelpi E, et al. Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study. Lancet Neurol 2013;12:443-453.

4. Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of old men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. Sleep Med 2013;14:744-748.

5. Iranzo A, Fernandez-Arcos A, Tolosa E, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. PLoS One 2014;9:e89741.

6. Eidelberg D. Metabolic brain networks in neurodegenerative disorders: a functional imaging approach. Trends Neurosci 2009;32:548-557.

7. Ma Y, Tang C, Spetsiers P, Dhawan V, Eidelberg D. Abnormal metabolic network activity in Parkinson’s disease: test-retest reproducibility. J Cereb Blood Flow Metab 2007;27:397-405.

8. Teune LK, Renken RJ, de Jong BM, et al. Parkinson’s disease-related perfusion and glucose metabolic brain patterns identified with PCASL-MRI and FDG-PET imaging. Neuroimage Clin 2014;5:240-244.

9. Meles SK, Teune LK, de Jong BM, Dierckx RA, Leenders KL. Metabolic imaging in Parkinson disease. J Nucl Med 2017;58:23-28.

10. Niethammer M, Eidelberg D. Metabolic brain networks in translational neurology: Concepts and Applications. Ann Neurol 2012;72(5):635-647.

11. Huang C, Tang C, Feigin A, et al. Changes in network activity with the progression of Parkinson’s disease. Brain 2007;130:1834-1846.

12. Holtbernd F, Gagnon JF, Postuma RB, et al. Abnormal metabolic network activity in REM sleep behavior disorder. Neurology 2014;82:620-627.

13. Wu P, Yu H, Peng S, et al. Consistent abnormalities in metabolic network activity in idiopathic rapid eye movement sleep behaviour disorder. Brain 2014;137:3122-3128.

14. Iranzo A, Lomena F, Stockner H, et al. Decreased striatal dopamine transporter uptake and substantia nigra hyperechogenicity as risk markers of synucleinopathy in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective study [corrected]. Lancet Neurol 2010;9:1070-1077.

15. Stiasny-Kolster K, Mayer G, Schafer S, Moller JC, Heinzel-Gutenbrunner M, Oertel WH. The REM sleep behavior disorder screening questionnaire—a new diagnostic instrument. Mov Disord 2007;22:2386-2393.

16. Movement Disorder Society Task Force on Ratings Scales for Parkinson’s Disease. The Unified Parkinson’s Disease Rating Scale (UPDRS): status and recommendations. Mov Disord 2003;18:738-750.

17. Postuma RB, Jocas S, Desjardins C, Latreille V. The Montreal Cognitive Assessment: a screening tool for mild cognitive impairment in REM sleep behavior disorder. Mov Disord 2010;25:936-940.

18. Hummel T, Sekinger B, Wolf SR, Pauli E, Kohal G. ‘Sniffin’ sticks’: olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem Senses 1997;22:39-52.

19. Della Rosa PA, Cerami C, Gallivanone F, et al. A standardized [18F]-FDG-PET template for spatial normalization in statistical parametric mapping of dementia. Neuroinformatics 2014;12:575-593.

20. Spetsieris PG, Eidelberg D. Scaled subprofile modeling of resting state imaging data in Parkinson’s disease: methodological issues. Neuroimage 2013;54:2899-2914.

21. Holtbernd F, Ma Y, Peng S, et al. Dopaminergic correlates of metabolic network activity in Parkinson’s disease. Hum Brain Mapp 2015;36:3375-3385.

22. Tang CC, Poston KL, Dhawan V, Eidelberg D. Abnormalities in metabolic network activity precede the onset of motor symptoms in Parkinson’s disease. J Neurosci 2010;30:1049-1056.

23. van der Zande JJ, Booij J, Berendse HW. Idiopathic hyposmia as a preclinical sign of Parkinson’s disease: a 16-year update on a previously reported series. Sleep Med 2013;14:744-748.

24. Frauscher B, Jemmou P, Ju YE, et al. Comorbidity and medication in REM sleep behavior disorder: a multicenter case-control study. Neurology 2014;82:1076-1079.

25. Wu P, Yu H, Peng S, et al. Consistent abnormalities in metabolic network activity in idiopathic rapid-eye-movement sleep behaviour disorder: a prospective study [cor-rected]. Lancet Neurol 2010;9:1070-1077.

26. Spetsiers P, Eidelberg D. Scaled subprofile modeling of resting state imaging data in Parkinson’s disease: methodological issues. Neuroimage 2013;54:2899-2914.

27. Holtbernd F, Ma Y, Peng S, et al. Dopaminergic correlates of metabolic network activity in Parkinson’s disease. Hum Brain Mapp 2015;36:3375-3385.

28. Tang CC, Poston KL, Dhawan V, Eidelberg D. Abnormalities in metabolic network activity precede the onset of motor symptoms in Parkinson’s disease. J Neurosci 2010;30:1049-1056.

29. van der Zande JJ, Booij J, Berendse HW. Idiopathic hyposmia as a preclinical sign of Parkinson’s disease: a 16-year update on a previously reported series. Sleep Med 2013;14:744-748.

30. van der Zande JJ, Booij J, Berendse HW. Idiopathic hyposmia as a preclinical sign of Parkinson’s disease: a 16-year update on a previously reported series. Sleep Med 2013;14:744-748.

31. Iranzo A, Serradell M, Vilaseca I, et al. Longitudinal assessment of olfactory function in idiopathic REM sleep behavior disorder. Parkinsonism Relat Disord 2013;19:600-604.

32. Tripathi M, Tang CC, Feigin A, et al. Automated differential diagnosis of early parkinsonism using metabolic brain networks: a validation study. J Nucl Med 2016;57(1):60-68.

33. Stoffers D, Booij J, Bosscher L, Winogrzodka A, Wolters EC, Berendse HW. Early-stage [123I]FP-CIT SPECT scans initially rated as normal became abnormal over time in patients with probable dementia with Lewy bodies. Eur J Nucl Med Mol Imaging 2016;43:1060-1066.

34. Iranzo A, Serradell M, Vilaseca I, et al. Longitudinal assessment of olfactory function in idiopathic REM sleep behavior disorder. Parkinsonism Relat Disord 2013;19:600-604.

35. Tripathi M, Tang CC, Feigin A, et al. Automated differential diagnosis of early parkinsonism using metabolic brain networks: a validation study. J Nucl Med 2016;57(1):60-68.

36. Stoffers D, Booij J, Bosscher L, Winogrzodka A, Wolters EC, Berendse HW. Early-stage [123I]FP-CIT SPECT and long-term clinical follow-up in patients with an initial diagnosis of Parkinson’s disease. Eur J Nucl Med Mol Imaging 2005;32:689-695.

Supporting Data

Additional Supporting information may be found in the online version of this article at the publisher’s website.