Sommerauer M, Hansen AK, Parbo P, Fedorova TD, Knudsen K, Frederiksen Y,
Nahimi A, Brooks DJ, Borghammer P.

[Decreased noradrenaline transporter density in the motor cortex of
Parkinson's disease patients.](#)

Movement Disorders 2018

DOI: <https://doi.org/10.1002/mds.27411>

Copyright:

This is the peer reviewed version of the following article, which has been published in final form at <https://doi.org/10.1002/mds.27411>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

Date deposited:

23/03/2018

Embargo release date:

24 May 2019

Decreased noradrenaline transporter density in the motor cortex of Parkinson's disease patients

Michael Sommerauer^{1,2*}, MD, Allan K Hansen¹, MD, Peter Parbo¹, MD, Tatyana D Fedorova¹, Karoline Knudsen¹, MSc, Yoon Frederiksen³, PhD, Adjmal Nahimi¹, MD, PhD, David J Brooks^{1,4,5}, MD, DSc FRCP(UK), FMed Sci (UK), and Per Borghammer¹, MD, PhD

¹Aarhus University Hospital, Department of Nuclear Medicine and PET Centre, Aarhus, Denmark

²Department of Neurology, University Hospital Cologne, Cologne, Germany

³Aarhus University, Department of Clinical Medicine & Department of Psychology, Aarhus, Denmark

⁴Division of Neuroscience, Department of Medicine, Imperial College London, London, UK

⁵Division of Neuroscience, Newcastle University, Newcastle, UK

*Corresponding author: Michael Sommerauer
Email: Michael.sommerauer@clin.au.dk
Department of Neurology
University Hospital Cologne
Kerpener Straße 62
50937 Köln
Germany

Running title: Cortical noradrenaline transporter

Keywords: Parkinson's disease, noradrenaline, motor cortex

Conflict of interest: The authors declare no conflict of interest.

Funding sources for study: Lundbeck foundation, Parkinsonforeningen, Swiss National Science Foundation

Word count: Abstract: 150
Manuscript: 1421
Figures / tables: 2
References: 30

Abstract

Background: Reduced noradrenaline levels have been reported to occur in the motor cortex of PD patients at *post-mortem*. Imaging techniques have recently become available to specifically study noradrenergic terminal function *in vivo* using PET.

Methods: 30 PD patients and 12 healthy control subjects, comparable across age, sex, and cognitive performance underwent PET imaging with ^{11}C -MeNER, a specific ligand of the noradrenaline transporter (NAT). Cortical NAT binding was compared at a voxel level using Statistical Parametric Mapping while cortical thickness was assessed using FreeSurfer software with MRI.

Results: PD patients showed reduced ^{11}C -MeNER binding in the primary motor cortex unrelated to cortical thickness; other cortical regions did not differ between groups. In a subgroup analysis, patients with higher Hoehn & Yahr stage exhibited more pronounced ^{11}C -MeNER binding reductions.

Conclusion: Loss of cortical noradrenergic projections to the primary motor cortex occurs in PD associated with disease stage.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder affecting several major neurotransmitter systems. In particular, *post-mortem* studies have reported considerable degeneration of the locus coeruleus (LC), which supplies the cortex with noradrenaline.¹ At *post-mortem*, multiple brain regions were reported to exhibit reduced levels of noradrenaline, including cerebellar cortex, thalamus, and cerebral cortex including primary motor cortex.²⁻⁵ *In vivo* imaging using positron emission tomography (PET) with ¹⁸F-DOPA is a marker of aromatic aminoacid decarboxylase activity in monoaminergic terminals, including those of dopaminergic, serotonergic and noradrenergic neurons. Moore and colleagues reported a decreased signal specifically in PD motor cortex.⁶ Newer PET ligands based on a reboxetine structure, such as ¹¹C-MeNER, provide a specific marker of noradrenaline transporter function,^{7,8} and a recently proposed MeNER PET analytical approach allowed *in vivo* estimation of cortical noradrenaline transporter availability in healthy subjects.⁹

The objective of this ¹¹C-MeNER PET study was to examine the hypothesis that noradrenaline transporter function is decreased in cortical regions of PD patients compared to matched healthy control (HC) subjects.

Methods

Study design and participants

We recruited 30 PD patients for imaging with ^{11}C -MeNER PET. Inclusion criteria were: diagnosis of PD according to the Movement Disorder Society (MDS) consensus criteria,¹⁰ age 50 - 85 years, a geriatric depression scale (GDS-15) score <6 , and Montreal cognitive assessment (MoCA) score >22 . Exclusion criteria were: a diagnosis of dementia, receiving medication acting on the noradrenergic transporter, and significant white matter lesions. Total levodopa-equivalent daily doses (LEDD) were calculated as previously recommended.¹¹ Olfaction was tested with the 16-item *Sniffin' Sticks* battery. Motor symptoms were scored using the MDS Unified PD Rating Scale part III (MDS-UPDRS III) after 12 hours of medication abstinence. Clinical disease duration and modified Hoehn & Yahr stage were recorded. Presence of REM sleep behavior disorder (RBD) was assessed with overnight polysomnography and a clinical interview for features of dream enactment.¹² Demography of PD patients was compared to 12 age and sex matched, cognitively normal (MoCA >26) and non-depressed (GDS-15 <6) HC subjects without a history of neurological disorders and with a normal brain MRI (Table 1). A volume of interest analysis of NAT density in subcortical structures of the 42 subjects was previously reported.¹²

The study was approved by the local ethical committee. All subjects gave informed written consent according to the Declaration of Helsinki.

^{11}C -MeNER PET

Details of ^{11}C -MeNER radiosynthesis and image reconstruction and normalization are provided as supplementary material. A 4 mm Gaussian filter was applied to the normalized images before calculation of parametric maps of binding potentials non displaceable (BP_{ND}) using the simplified reference tissue model 2 (SRTM2). Voxel-wise calculations in PXMOD were initiated with time activity curves of the thalamus as a high binding region and the caudate as a low binding region; the efflux constant of the reference region was fixed at $k_2' = 0.021 \text{ min}^{-1}$ as previously published.^{7,9} BP_{ND} values of the left + right precentral and postcentral gyrus were extracted for group comparisons.

MRI

An MPRAGE sequence was acquired on a Siemens Magnetom Tim Trio scanner using a 32 channel headcoil and the following parameters: TR/TI/TE, 960/2420/3.7ms; flipangle, 9 degrees; number of slices, 176; FOV 256x256mm; 1mm isotropic resolution, and an iPAT factor of 2 using grappa. Cortical grey

matter thickness was estimated using the standard presets in FreeSurfer 5.3 (<http://surfer.nmr.mgh.harvard.edu/>).

Statistical parametric mapping (SPM)

All individual parametric maps were non-rigidly transformed to an ^{11}C -MeNER spatial template derived from an averaged image of the 12 HC subjects. Statistical Parametric Mapping 12 (SPM12) in Matlab2015b was used for between group comparisons of ^{11}C -MeNER binding potentials at a voxel level (two-sample t-test between PD patients and HC subjects). Parametric maps were smoothed with a 4 mm Gaussian filter, and an average cortical grey matter mask was used for explicit masking within the SPM software. Voxel-level analysis threshold was $p < 0.005$ (uncorrected) and subsequently a family-wise error (FWE) cluster-level correction at $p < 0.05$ was applied. Surface projections of resulting voxels were overlaid on a rendered brain of one HC subject.

Statistical analysis

We analyzed the data with the Statistical Package for the Social Sciences (SPSS) version 24. Group data were presented as mean $\pm$ standard deviation. Group comparisons were interrogated with the Student's t, Mann-Whitney, and Chi-square statistics as appropriate; a normal distribution of data was assessed with the Shapiro-Wilk test. Volume of interest (VOI) analysis of BP_{ND} values was tested with a repeated measures analysis of variance (ANOVA). Significance was accepted at $p < 0.05$.

Results

Demographic and clinical characteristics of PD patients and HC subjects are summarized in table 1. Groups did not differ with regards to age, sex and MoCA scores. In the voxel-wise comparison, SPM localised lower cortical ^{11}C -MeNER binding in PD patients tracking the primary motor cortex and, to a lesser extent, the primary sensory cortex (Figure 1A). Similarly, VOI analysis of the precentral and postcentral gyrus showed significant reduced ^{11}C -MeNER BP_{ND} values in PD patients (ANOVA, $p = 0.006$; precentral left 0.166 ± 0.081 vs. 0.044 ± 0.123 , $p = 0.003$, precentral right 0.124 ± 0.087 vs. 0.022 ± 0.122 , $p = 0.012$, postcentral left 0.131 ± 0.074 vs. 0.022 ± 0.127 , $p = 0.008$, postcentral right 0.125 ± 0.096 vs. 0.016 ± 0.115 , $p = 0.006$). To correct for potential partial volume effects on binding signals, we compared cortical thickness of the primary motor cortex between groups, which did not differ between PD patients and HC subjects (2.44 ± 0.20 versus 2.43 ± 0.24 mm; $p = 0.80$, and for primary sensory cortex 1.94 ± 0.13 versus 1.95 ± 0.18 mm; $p = 0.76$, respectively). Subgroup analysis of PD patients divided by a cut-off at Hoehn & Yahr stage 2.5 (resulting in $n = 15$ PD subjects in each group), revealed more widespread reductions of ^{11}C -MeNER binding in PD patients with a higher disease stage when contrasted against healthy controls (Figure 1B). However, a direct comparison of mild and more severely affected PD groups revealed no significant NAT cortical binding differences.

Discussion

Previous ^{11}C -MeNER studies on PD patients from our group targeted subcortical high binding areas of MeNER and revealed a reduced ^{11}C -MeNER signal in the thalamus and hypothalamus as well as brainstem nuclei.^{8,12} Using the recently proposed imaging analysis approach for cortical MeNER uptake from Moriguchi and colleagues,⁹ we here report first *in vivo* evidence of impaired noradrenergic function in the primary motor cortex in PD patients using a specific PET ligand for noradrenergic transporter binding. Additionally, we show that patients with more advanced clinical disease have a greater decline of ^{11}C -MeNER uptake in the primary motor cortex.

Growing evidence suggest an involvement of multiple neurotransmitters in PD and, in line with the results from the present study, point to significant dysfunction of the noradrenergic system associated with more severe motor disability.^{4,13,14} The LC is affected by alpha synuclein aggregates in Braak stage 2 of PD during its trajectory which precedes and may even surpass later involvement of the substantia nigra.^{15,16} Evidence from animal studies has implicated noradrenergic dysfunction in the appearance and aggravation of motor symptoms. Several studies reported that deficient noradrenergic innervation accompanied dopaminergic cell loss in toxin-derived PD models.¹⁷⁻¹⁹ In mice with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) induced dopaminergic lesions, the PD-like motor phenotype is only manifested when there is also noradrenergic co-deficiency.²⁰ Noradrenaline deficits also attenuated beneficial levodopa replacement effects on motor symptoms in rats lesioned with 6-hydroxydopamine.¹⁴ Additionally, amphetamines could restore locomotor activity in a dopamine-independent way in a novel PD mouse model.²¹ Data on manipulation of the noradrenergic system to improve motor function in human PD is scarce. One small scale, open-label study trialled duloxetine, a combined serotonin and noradrenaline reuptake inhibitor (SNRI), and reported beneficial effects on motor symptoms in PD.²² Of note, paroxetine, which is a selective serotonin reuptake inhibitor (SSRI), did not improve motor symptoms.²³ Methylphenidate, which is a dual dopamine and noradrenaline reuptake inhibitor, showed beneficial effects on motor symptoms in PD; however, its effects became insignificant with co-administration of high doses of levodopa.^{24,25} The noradrenergic prodrug droxidopa is approved for orthostatic hypotension in PD and was reported to improve UPDRS III scores in one study.²⁶

PD is pathologically characterized not only by perturbed function of the substantia nigra and basal ganglia circuitry, but also of cortical networks, including dysfunction of primary motor cortex connections.²⁷⁻³⁰ Neural plasticity of the primary motor cortex is altered in PD,³¹ and facilitation of its excitability by transcranial direct current stimulation has shown to improve motor performance in PD patients.³² Concordantly, abnormal suppression of electroencephalographic activity during a motor task was observed in PD patients.³³ Using ^{18}F -DOPA PET, Moore and colleagues reported that the primary motor cortex exhibited a monoaminergic deficit in early PD which then spread anteriorly and laterally with disease

progression.⁶ A cortical deficit of the noradrenergic system has also been reported in a *post-mortem* study.² Our *in vivo* results confirm a noradrenergic influence on motor symptoms and altered functioning of the primary motor cortex in PD.

Several limitations of our study have to be mentioned. Cortical binding potentials of ¹¹C-MeNER tend to be low, lowering statistical power.⁹ However, we recruited a relatively robust number of 42 subjects for PET and employed corrected SPM analyses as well as VOI based statistics. As specific binding was very low in the cortex of PD patients, we also minimized subgroup analysis to avoid low statistical power. Larger sample sizes and future noradrenergic PET ligands with higher signal to noise properties may be able to detect more subtle deficits in PD and might facilitate analysis of specific PD subgroups and their association to cortical noradrenergic innervation. These studies should also address laterality of PD symptoms and its correlation to cortical noradrenergic innervation. We also did not assess potential reductions of other monoamines. Future studies using multi-tracer approaches are needed for quantifying and comparing deficits of specific monoamines in the motor cortex of PD.⁶

In conclusion, this study provides *in vivo* evidence for altered noradrenergic transmission in the motor cortex in PD patients, which is associated with greater disease severity. Thus, our results suggest that noradrenergic dysfunction make a contribution to the motor deterioration in PD.

Acknowledgment

We thank all study participants, Karen Østergaard, Mette Møller, Erik Danielsen, and Jacob Geday (Aarhus University Hospital, Department of Neurology, Aarhus, Denmark), and Lorenz Oppel (Aalborg University Hospital, Department of Neurology, Aalborg, Denmark) for contacting patients, and biomedical laboratory scientists and radiochemists (Department of Nuclear Medicine and PET Centre, Aarhus University Hospital, Denmark) for technical assistance.

Contributors

Research project: A. Conception: MS, PB, DJB; B. Organization: MS, PB, DJB, YF; C. Execution: MS, PB, AKH, TDF, KK, YF, AN

Statistical Analysis: A. Design: MS, PB, DJB; B. Execution: MS, PB; C. Review and Critique: all authors

Manuscript: A. Writing of the first draft: MS, PB; B. Review and Critique: all authors.

Financial disclosures

Dr. Sommerauer reports grants from Swiss National Science Foundation, during the conduct of the study; Dr. Hansen reports grants from Lundbeck Foundation, during the conduct of the study; Dr. Brooks reports grants from Lundbeck Foundation, grants from Danish Council for Independent Research, grants from Danish Parkinson's Society, outside the submitted work; Dr. Borghammer reports grants from Lundbeck Foundation, during the conduct of the study; all other authors have nothing to disclose.

References

1. Braak E, Sandmann-Keil D, Rub U, et al. alpha-synuclein immunopositive Parkinson's disease-related inclusion bodies in lower brain stem nuclei. *Acta Neuropathol* 2001; **101**(3): 195-201.
2. Gaspar P, Duyckaerts C, Alvarez C, Javoy-Agid F, Berger B. Alterations of dopaminergic and noradrenergic innervations in motor cortex in Parkinson's disease. *Ann Neurol* 1991; **30**(3): 365-74.
3. Scatton B, Javoy-Agid F, Rouquier L, Dubois B, Agid Y. Reduction of cortical dopamine, noradrenaline, serotonin and their metabolites in Parkinson's disease. *Brain Res* 1983; **275**(2): 321-8.
4. Pifl C, Kish SJ, Hornykiewicz O. Thalamic noradrenaline in Parkinson's disease: deficits suggest role in motor and non-motor symptoms. *Mov Disord* 2012; **27**(13): 1618-24.
5. Kish SJ, Shannak KS, Rajput AH, Gilbert JJ, Hornykiewicz O. Cerebellar norepinephrine in patients with Parkinson's disease and control subjects. *Arch Neurol* 1984; **41**(6): 612-4.
6. Moore RY, Whone AL, Brooks DJ. Extrastriatal monoamine neuron function in Parkinson's disease: an 18F-dopa PET study. *Neurobiol Dis* 2008; **29**(3): 381-90.
7. Pietrzak RH, Gallezot JD, Ding YS, et al. Association of posttraumatic stress disorder with reduced in vivo norepinephrine transporter availability in the locus coeruleus. *JAMA Psychiatry* 2013; **70**(11): 1199-205.
8. Nahimi A, Sommerauer M, Kinnerup MB, et al. Noradrenergic deficits in Parkinson's disease imaged with 11C-MeNER. *J Nucl Med* 2017.
9. Moriguchi S, Kimura Y, Ichise M, et al. PET Quantification of the Norepinephrine Transporter in Human Brain with (S,S)-18F-FMeNER-D2. *J Nucl Med* 2017; **58**(7): 1140-5.
10. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord* 2015; **30**(12): 1591-601.
11. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord* 2010; **25**(15): 2649-53.
12. Sommerauer M, Fedorova TD, Hansen AK, et al. Evaluation of the noradrenergic system in Parkinson's disease: an 11C-MeNER PET and neuromelanin MRI study. *Brain* 2018; **141**(2): 496-504.
13. Espay AJ, LeWitt PA, Kaufmann H. Norepinephrine deficiency in Parkinson's disease: the case for noradrenergic enhancement. *Mov Disord* 2014; **29**(14): 1710-9.
14. Ostock CY, Lindenbach D, Goldenberg AA, Kampton E, Bishop C. Effects of noradrenergic denervation by anti-DBH-saporin on behavioral responsivity to L-DOPA in the hemi-parkinsonian rat. *Behav Brain Res* 2014; **270**: 75-85.
15. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003; **24**(2): 197-211.

16. Zarow C, Lyness SA, Mortimer JA, Chui HC. Neuronal loss is greater in the locus coeruleus than nucleus basalis and substantia nigra in Alzheimer and Parkinson diseases. *Arch Neurol* 2003; **60**(3): 337-41.
17. Mavridis M, Degryse AD, Lategan AJ, Marien MR, Colpaert FC. Effects of locus coeruleus lesions on parkinsonian signs, striatal dopamine and substantia nigra cell loss after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in monkeys: a possible role for the locus coeruleus in the progression of Parkinson's disease. *Neuroscience* 1991; **41**(2-3): 507-23.
18. Fornai F, Bassi L, Bonaccorsi I, Giorgi F, Corsini GU. Noradrenaline loss selectivity exacerbates nigrostriatal toxicity in different species of rodents. *Funct Neurol* 1997; **12**(3-4): 193-8.
19. Yao N, Wu Y, Zhou Y, et al. Lesion of the locus coeruleus aggravates dopaminergic neuron degeneration by modulating microglial function in mouse models of Parkinson's disease. *Brain Res* 2015; **1625**: 255-74.
20. Rommelfanger KS, Edwards GL, Freeman KG, Liles LC, Miller GW, Weinshenker D. Norepinephrine loss produces more profound motor deficits than MPTP treatment in mice. *Proc Natl Acad Sci U S A* 2007; **104**(34): 13804-9.
21. Arai A, Tomiyama M, Kannari K, et al. Reuptake of L-DOPA-derived extracellular DA in the striatum of a rodent model of Parkinson's disease via norepinephrine transporter. *Synapse* 2008; **62**(8): 632-5.
22. Nishijima H, Ueno T, Kon T, et al. Effects of duloxetine on motor and mood symptoms in Parkinson's disease: An open-label clinical experience. *J Neurol Sci* 2017; **375**: 186-9.
23. Chung KA, Carlson NE, Nutt JG. Short-term paroxetine treatment does not alter the motor response to levodopa in PD. *Neurology* 2005; **64**(10): 1797-8.
24. Moreau C, Delval A, Defebvre L, et al. Methylphenidate for gait hypokinesia and freezing in patients with Parkinson's disease undergoing subthalamic stimulation: a multicentre, parallel, randomised, placebo-controlled trial. *Lancet Neurol* 2012; **11**(7): 589-96.
25. Espay AJ, Dwivedi AK, Payne M, et al. Methylphenidate for gait impairment in Parkinson disease: a randomized clinical trial. *Neurology* 2011; **76**(14): 1256-62.
26. Zhao S, Cheng R, Zheng J, et al. A randomized, double-blind, controlled trial of add-on therapy in moderate-to-severe Parkinson's disease. *Parkinsonism Relat Disord* 2015; **21**(10): 1214-8.
27. Xu T, Wang S, Lalchandani RR, Ding JB. Motor learning in animal models of Parkinson's disease: Aberrant synaptic plasticity in the motor cortex. *Mov Disord* 2017; **32**(4): 487-97.
28. Tomse P, Jensterle L, Grmek M, et al. Abnormal metabolic brain network associated with Parkinson's disease: replication on a new European sample. *Neuroradiology* 2017; **59**(5): 507-15.
29. Pasquereau B, DeLong MR, Turner RS. Primary motor cortex of the parkinsonian monkey: altered encoding of active movement. *Brain* 2016; **139**(Pt 1): 127-43.

30. Lindenbach D, Bishop C. Critical involvement of the motor cortex in the pathophysiology and treatment of Parkinson's disease. *Neurosci Biobehav Rev* 2013; **37**(10 Pt 2): 2737-50.
31. Guo L, Xiong H, Kim JI, et al. Dynamic rewiring of neural circuits in the motor cortex in mouse models of Parkinson's disease. *Nat Neurosci* 2015; **18**(9): 1299-309.
32. Cosentino G, Valentino F, Todisco M, et al. Effects of More-Affected vs. Less-Affected Motor Cortex tDCS in Parkinson's Disease. *Front Hum Neurosci* 2017; **11**: 309.
33. Stegemoller EL, Allen DP, Simuni T, MacKinnon CD. Motor cortical oscillations are abnormally suppressed during repetitive movement in patients with Parkinson's disease. *Clin Neurophysiol* 2016; **127**(1): 664-74.

Figure legend

Figure 1: Reduction of ^{11}C -MeNER binding in the motor cortex of PD patients

Voxels with significantly lower ^{11}C -MeNER binding potentials in PD patients compared to HC subjects are given in purple. Maps were derived with statistical parametric mapping 12 (SPM 12) using a voxel threshold of $p < 0.005$ (uncorrected) and a cluster threshold of $p < 0.05$ with family-wise error correction. **A:** Comparison of all 30 PD patients contrasted against 12 HC subjects. **B:** Subgroup analysis of PD patients with Hoehn & Yahr stage < 2.5 (left; $n = 15$) and patients with Hoehn & Yahr stage ≥ 2.5 (right; $n = 15$) contrasted against 12 HC subjects. In PD patients with Hoehn & Yahr stage < 2.5 , voxels with threshold at $p < 0.005$ (uncorrected) are presented without cluster correction as no cluster survived the family-wise error cluster correction. Abbreviations: HC = healthy control, PD = Parkinson's disease.

Tables

Table 1: Demographics and clinical characteristics

	HC (n=12)	PD (n=30)	P-value
Age	67.3 ± 6.3	66.6 ± 9.1	ns [‡]
Sex (male / female)	9 / 3	22 / 8	ns [§]
Sniffing sticks, correct	11.1 ± 2.8	7.1 ± 2.7	<0.001 [‡]
GDS-15, total	0.2 ± 0.4	1.0 ± 1.4	ns [□]
MoCA, total	28.3 ± 0.9	26.8 ± 2.2	ns [□]
<i>PD characteristics</i>			
Disease duration [years]		6.4 ± 4.3	
Hoehn & Yahr		2.3 ± 0.5	
MDS-UPDRS III, total		36.1 ± 11.5	
LEDD [mg]		620 ± 404	
RBD (yes / no)		16 / 14	

‡ = parametric test (Student's t-test), □ = non-parametric test (Mann-Whitney test), § = χ^2 test. Abbreviations: GDS-15 = Geriatric Depression Scale, HC = healthy control subject, LEDD = levodopa daily equivalent dose, MDS-UPDRS III = Movement Disorder Society Unified Parkinson's disease Rating Scale part III, MoCA = Montreal Cognitive Assessment, ns = not significant, PD = Parkinson's disease, RBD = REM sleep behavior disorder.

Supplementary material

¹¹C-MeNER PET image acquisition and reconstruction

The synthesis of ¹¹C-MeNER was performed accordingly to a previously published protocol.¹ A six minute transmission scan was acquired for attenuation correction prior to each ¹¹C-MeNER emission scan. Radiotracer was intravenously injected and ¹¹C-MeNER doses did not differ between groups (HC, 646.3 ± 119.6, PD, 707.6 ± 106.5 MBq; p = 0.146). Dynamic PET was acquired over 90 minutes in list-mode on a Siemens high-resolution research tomograph (HRRT) and then rebinned into 27 time frames (6 x 30 s, 3 x 60 s, 2 x 120 s, and 16 x 300 s). Image series were reconstructed using 3D OSEM (ordered subsets expectation maximization) and resolution recovery modelling (PSF) with 10 iterations and 16 subsets. Reconstructed images consisted of 207 axial image slices with an isotropic 1.22 mm voxel size. Reconstructed images were processed with PMOD 3.8 and its relevant toolboxes, including time frame realignment for motion correction. All PET images were then normalized into Montreal Neurological Institute (MNI) space including rigid matching of subject's PET to the anatomical magnetic resonance image (MRI), and MRI segmentation using the PNEURO tool. Volumes of interest (VOIs) of the caudate, thalamus and precentral as well postcentral gyrus were extracted from the PMOD built-in atlas.

References:

1. Wilson AA, Johnson DP, Mozley D, et al. Synthesis and in vivo evaluation of novel radiotracers for the in vivo imaging of the norepinephrine transporter. *Nucl Med Biol* 2003; **30**(2): 85-92.