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# Noradrenergic alterations in Parkinson's disease: a combined $^{11}\text{C}$ -yohimbine PET/neuromelanin MRI study

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Degeneration of the noradrenergic system is now considered a pathological hallmark of Parkinson's disease, but little is known about its consequences in terms of parkinsonian manifestations. Here, we evaluated two aspects of the noradrenergic system using multimodal *in vivo* imaging in patients with Parkinson's disease and healthy controls: the pigmented cell bodies of the locus coeruleus with neuromelanin sensitive MRI; and the density of  $\alpha 2$ -adrenergic receptors (ARs) with PET using  $^{11}\text{C}$ -yohimbine.

Thirty patients with Parkinson's disease and 30 age- and sex-matched healthy control subjects were included. The characteristics of the patients' symptoms were assessed using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Patients showed reduced neuromelanin signal intensity in the locus coeruleus compared with controls and diminished  $^{11}\text{C}$ -yohimbine binding in widespread cortical regions, including the motor cortex, as well as in the insula, thalamus and putamen. Clinically, locus coeruleus neuronal loss was correlated with motor (bradykinesia, motor fluctuations, tremor) and non-motor (fatigue, apathy, constipation) symptoms. A reduction of  $\alpha 2$ -AR availability in the thalamus was associated with tremor, while a reduction in the putamen, the insula and the superior temporal gyrus was associated with anxiety. These results highlight a multifaceted alteration of the noradrenergic system in Parkinson's disease since locus coeruleus and  $\alpha 2$ -AR degeneration were found to be partly uncoupled. These findings raise important issues about noradrenergic dysfunction that may encourage the search for new drugs targeting this system, including  $\alpha 2$ -ARs, for the treatment of Parkinson's disease.

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## Introduction

Parkinson's disease (PD) is characterized mostly by the loss of dopaminergic neurons in the substantia nigra pars compacta. However, the neurodegenerative process also extends to other neurotransmission systems such as those for serotonin or acetylcholine and noradrenaline, which contribute to motor and non-motor symptoms.<sup>1–4</sup>

The modulations and interactions of the complex interconnected non-dopaminergic networks with dopaminergic circuits are far from being fully understood, and the cascade of perturbations in these interconnected systems and associated circuits is still a central issue. Among these neurotransmitter networks, the noradrenergic system is probably the least well-known.<sup>5,6–8</sup> The direct roles of the noradrenergic system in various cognitive functions are well documented.<sup>9</sup> These include specific functions like vigilance, attention and executive control, as well as more transversal functions like learning, cognitive flexibility and working memory,<sup>8</sup> or even more general roles in adaptive adjustments in gain that serve to optimize performance.<sup>10</sup> It is important to point out that there is a major gap in our understanding of how these modulations apply to the motor circuits.<sup>11</sup> The alteration of these functions might contribute to various parkinsonian manifestations.<sup>8</sup> However, this is often under-recognized, and the association with specific symptoms, in particular with the motor manifestations of PD, is still unclear.

The effect of noradrenergic dysfunction in the manifestations of PD might also be related to its antiparkinsonian and neuroprotective properties.<sup>12</sup> The loss of noradrenergic neurons in the locus coeruleus (LC), the sole source of noradrenaline to the neocortex, hippocampus, cerebellum and thalamus (see Benarroch<sup>13</sup> for a review), which is estimated to be between 20% and 90%, precedes and exceeds the characteristic loss of dopaminergic neurons in the substantia nigra.<sup>14</sup> There is evidence mainly based on animal studies that noradrenergic loss may enhance neurotoxic damage to nigrostriatal dopaminergic neurons,<sup>15,16</sup> and that, conversely, restoration of the damaged LC system positively influences the recovery of degenerated dopaminergic neurons.<sup>17,18</sup> Taken together, these observations suggest that enhancing noradrenergic neurotransmission may facilitate both specific functions affected by the disease and the recovery of dopaminergic neurons.<sup>19</sup> Yet, therapeutic strategies targeting this system in PD are currently limited.<sup>7,20</sup>

The use of  $\alpha 2$ -adrenergic receptor (AR) antagonists has recently been considered a major possible target<sup>21</sup> as it might potentiate noradrenaline availability by blocking presynaptic  $\alpha 2$ -ARs whose normal function is to regulate noradrenaline release.<sup>22–24</sup> However, direct *in vivo* evidence of  $\alpha 2$ -AR alteration in parkinsonian manifestations is still lacking. This critical lack of knowledge, accompanied by substantial controversies about the neurofunctional bases of the noradrenergic system and its alteration in PD,<sup>25,26</sup> is mainly due to the lack of specific *in vivo* molecular imaging tools in humans. To date, *in vivo* imaging studies have only used presynaptic noradrenergic tracers of noradrenergic transporters with <sup>11</sup>C-MeNER. These studies have shown reduced tracer uptake, suggesting a diminished density of noradrenergic terminals, mainly in the thalamus, hypothalamus, LC and raphe nuclei.<sup>2,27</sup> Regarding  $\alpha 2$ -ARs, most of our knowledge derives from animal studies or post-mortem samples of human brains.<sup>28,29</sup> Autoradiography studies suggest an alteration in  $\alpha 2$ -ARs in different brain regions (thalamus,<sup>30</sup> cerebellum,<sup>31</sup> hypothalamus<sup>32</sup> and prefrontal cortex<sup>33</sup>). Here, we take advantage of recent methodological developments,

allowing *in vivo* imaging of the noradrenergic system in humans with the novel PET radiotracer <sup>11</sup>C-yohimbine,<sup>34–36</sup> now available for use in large samples of human subjects to map differences in  $\alpha 2$ -AR distribution between parkinsonian patients and matched controls. <sup>11</sup>C-yohimbine binds with high selectivity to all  $\alpha 2$ -AR subtypes.<sup>37</sup> It is displaced when there is competition at the receptor with endogenous noradrenaline as shown by preclinical studies reporting reduced receptor binding under unlabelled yohimbine challenge, amphetamine administration or acute vagus nerve stimulation in preclinical studies<sup>37–39</sup> and human studies reporting increased receptor binding after clonidine administration.<sup>34</sup>

The objectives of this study were to assess two aspects of noradrenergic neurodegeneration in PD using hybrid MRI/PET imaging: lesions of pigmented cell bodies of the LC with neuromelanin-sensitive MRI and alterations in  $\alpha 2$ -AR density with <sup>11</sup>C-yohimbine PET. Simultaneously assessing noradrenergic terminals (with PET) and LC cell bodies (with MRI) is of primary importance given that their respective deficits may be uncoupled.<sup>40</sup> To inform the disputed pathophysiological mechanisms of the disease, correlations between the observed noradrenergic dysfunctions and the standard clinical measures of PD have been tested systematically.

## Materials and methods

### Participants

The demographics and clinical characteristics of the participants are listed in [Table 1](#). We enrolled 30 PD patients and 30 healthy controls matched for age, gender and global cognitive functioning using the Montreal Cognitive Assessment (MoCA) score. Patients had been diagnosed with PD for at least 1 year in accordance with Movement Disorder Society (MDS) criteria.<sup>41</sup> The MDS Revised Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was used to assess PD symptoms, including separate assessments of non-motor symptoms (UPDRS-I), daily activity (UPDRS-II), motor symptoms (UPDRS-III) and motor complications (UPDRS-IV).<sup>42</sup> In addition, the 39-item Parkinson's Disease Questionnaire (PDQ-39) was used to evaluate quality of life.<sup>43</sup> All patients were assessed in the 'ON' state with their usual antiparkinsonian medication. Levodopa equivalent daily dose (LEDD) was calculated according to previously published conversion rules.<sup>44</sup> Most of the patients with PD were in the early and middle stage of their disease with a mean Hoehn and Yahr score of 1.8 and MDS-UPDRS-III score in the 'ON' state of 17.7 ( $\pm 12.3$ ). Exclusion criteria were medications that interfere with the noradrenergic system, a diagnosis of other neurological or psychiatric disorders and the presence of major dyskinesia or tremor for technical imaging purposes. The study was conducted in accordance with the Declaration of Helsinki and approved by the local Ethical Committee in Biomedical Research (No. CPP 19\_01\_02/No. EudraCT 2018-003999-13). Written informed consent was obtained from all subjects before the study.

### MRI

MRI data were acquired on a Biograph mMR (hybrid MRI/PET) including a whole brain high-resolution anatomical 3D T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sequence in the sagittal plane (matrix size 256  $\times$  256  $\times$  176, voxel size 1  $\times$  1  $\times$  1 mm<sup>3</sup>) and a 2D axial turbo spin-echo (TSE) sequence (in plane resolution 0.4  $\times$  0.4 mm<sup>2</sup>, slice thickness 3 mm, matrix size 464  $\times$  512  $\times$  15), which provided a neuromelanin-sensitive MRI.

**Table 1 Demographics and clinical characteristics of participants**

	Healthy controls	Parkinsonian patients	Statistics
<i>n</i>	30	30	
Sex, female/male	12/18	12/18	
Age, years	60.3 ± 8	60.1 ± 7.5	ns <sup>a</sup>
MoCA	27.9 ± 1.5	27.9 ± 2	ns <sup>b</sup>
<b>Parkinson's disease characteristics</b>			
Disease duration, years	–	6.5 ± 4	–
LEDD, mg/day	–	1006 ± 703	–
Hoehn and Yahr	–	1.8 ± 0.4	–
PDQ39	–	39.6 ± 22.1	–
MDS-UPDRS I	–	8.5 ± 5.1	–
MDS-UPDRS II	–	7.1 ± 4.3	–
MDS-UPDRS III	–	17.7 ± 12.3	–
MDS-UPDRS IV	–	2.3 ± 3	–

Data are presented as mean ± standard deviation. LEDD = levodopa equivalent daily dose; MDS = Movement Disorder Society; MoCA = Montreal Cognitive Assessment; ns = not significant; PDQ = Parkinson's Disease Questionnaire; UPDRS = Unified Parkinson's Disease Rating Scale.

<sup>a</sup>Parametric test (Student's *t*-test).

<sup>b</sup>Non-parametric test (Wilcoxon test).

### Voxel-based morphometry analysis

To exclude the possibility that structural degeneration affects the results of <sup>11</sup>C-yohimbine binding, voxel-based morphometry (VBM) analysis was conducted. The standard VBM preprocessing protocol of the Computational Anatomy Toolbox (CAT12, <http://www.neuro.uni-jena.de/cat/>) running on Statistical Parametric Mapping (SPM12; Welcome Trust Centre for Neuroimaging, University College, London, UK) was employed. Briefly, each 3D T1-weighted image was bias-corrected and segmented into grey matter, white matter and CSF tissue classes using SPM's unified segmentation function. The grey matter segmentation probability maps were spatially transformed to Montreal Neurological Institute (MNI) standard space using the International Consortium for Brain Mapping (ICBM)-152 template according to the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) approach with default settings in 1.5 mm cubic resolution and then smoothed with a Gaussian kernel of 8 mm full-width at half-maximum. Lastly, to correct for individual differences in brain size, total intracranial volume (TIV) was estimated for each subject using a Computational Anatomy Toolbox (CAT)12 interface (Statistical Analyses—Estimate TIV) as the sum of the grey matter, white matter and CSF volumes.

### Neuromelanin-sensitive MRI analysis

To calculate signal intensity in the LC, an approach similar to that published by García-Lorenzo and colleagues<sup>6</sup> was implemented. First, two regions were drawn manually on the T1 MRI high-resolution MNI template using FSleyes (FSL v5.0.11, FMRIB, Oxford, UK). These two regions (one for each side) were defined as large 3D bounding boxes and placed around the hyperintense voxels at the lateral border of the fourth ventricle so that they included the LC but excluded the substantia nigra, which also contains neuromelanin.<sup>45</sup> In addition, we used the central reference mask freely available to normalize the intensity of the LC.<sup>46</sup> These three regions were then wrapped and resampled onto the subject's neuromelanin-sensitive T1 image using SPM12. Using FSL functions, the LC was defined as

the area of the 10 voxels with the brightest intensity within each bounding box. We considered the intensity of the LC as the average of the intensities of the 10-voxel region (Fig. 1). The contrast-to-noise ratio (CNR) was calculated for each LC (right and left) as  $CNR_{LC} = (S_{LC} - S_{REF}) / S_{REF}$ , where  $S_{LC}$  and  $S_{REF}$  correspond to the mean signal intensity of the LC and the reference region, respectively. Normalization of the LC signal to a central reference region (pons) to calculate the CNR by relative difference has been the most commonly used and recommended method in previous studies.<sup>47</sup>

### <sup>11</sup>C-yohimbine PET

Radiosynthesis of <sup>11</sup>C-yohimbine was performed as previously described.<sup>37</sup> The radiochemical purities of syntheses used for the study were greater than 95%, with molar activities of 85 ± 30 GBq/μmol at the end of synthesis. All subjects received an intravenous bolus injection of 370 MBq ± 10% of <sup>11</sup>C-yohimbine. List-mode PET data were acquired over the 90 min from the injection of the tracer. MRI data were acquired simultaneously.

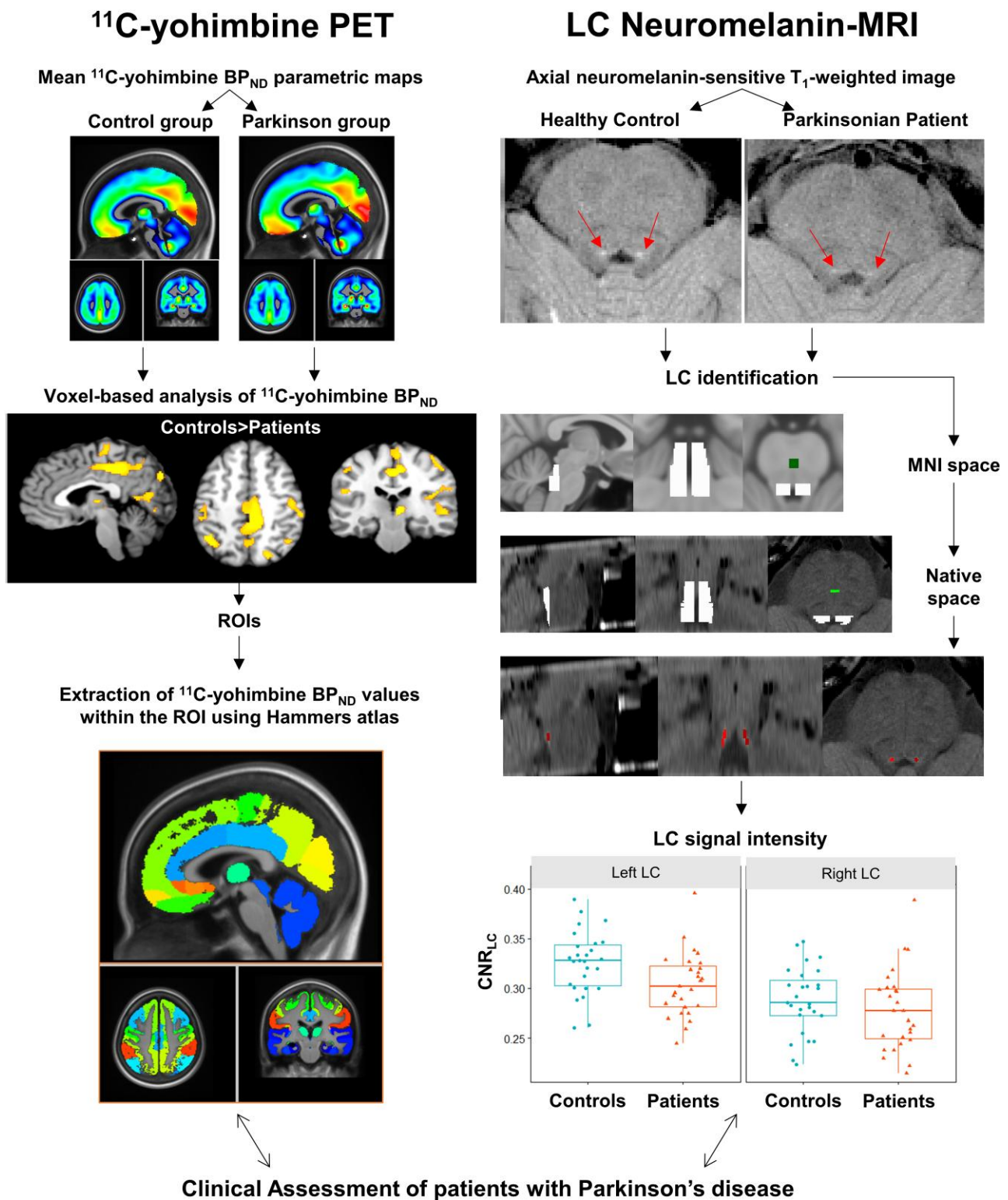
Raw PET data were corrected for motion<sup>48</sup> and then rebinned into 24 time-frame (variable length frames: 8 × 15 s, 3 × 60 s, 5 × 120 s, 1 × 300 s, 7 × 600 s) sinograms for dynamic reconstruction. Sinograms were corrected for scatter, randoms, normalization and attenuation.<sup>49</sup> Images were reconstructed using 3D ordinary Poisson-ordered subsets expectation maximization (OP-OSEM 3D), incorporating the system point spread function using three iterations of 21 subsets. Reconstructions were performed with a zoom of 2 in a matrix of 172 × 172 voxels, yielding a voxel size of 2.03 × 2.03 × 2.08 mm<sup>3</sup>, with 4 mm 3D post-reconstruction Gaussian filtering. Regional time activity curves were extracted based on labelling of structural brain regions obtained with multi-atlas propagation with enhanced registration (MAPER)<sup>50</sup> methodology and the 83-region Hammers atlas.<sup>51</sup> <sup>11</sup>C-yohimbine non-displaceable binding potential (BP<sub>ND</sub>) parametric maps were then generated using the simplified reference tissue model (SRTM), with the corpus callosum as reference region.<sup>34</sup> PET parametric images were spatially normalized to the MNI space with parameters derived from the individual T1 MRI.

### Statistics

Statistical analyses of demographic data were performed using Rstudio (<https://github.com/rstudio/rstudio>). All data were tested for normal distribution using the Shapiro–Wilk test and the Levene test for homogeneity of variance. Independent samples *t*-tests or Wilcoxon tests, as appropriate, were used to compare demographic group mean differences. We assessed group differences in the CNR<sub>LC</sub> with an analysis of covariance accounting for age and sex as covariates. A two-tailed *t*-test was generated in the SPM12 toolbox to assess between-group differences in grey matter concentration using family-wise error (FWE) correction with a threshold of  $P < 0.05$ . The extend threshold was set to 100 voxels and total intracranial volume was used as covariate of no interest.

SPM12 in MATLAB 2020a was used for between-group comparisons of <sup>11</sup>C-yohimbine BP<sub>ND</sub> at the voxel level (two-sample *t*-test) controlling for age and gender. Spatially normalized parametric images were smoothed with an 8-mm Gaussian filter, and an average cortical grey-matter mask was used for explicit masking within the SPM software. The voxel-level analysis threshold was  $P < 0.001$  (uncorrected), and subsequently a FWE cluster-level correction at  $P < 0.05$  was applied.

We assessed the association of MRI and PET signals and interrogated non-parametric (partial) correlations between CNR<sub>LC</sub> and <sup>11</sup>C-yohimbine BP<sub>ND</sub> values extracted from the regions of interest



**Figure 1 Data pipeline.**  $^{11}\text{C}$ -yohimbine and locus coeruleus (LC) neuromelanin data were acquired simultaneously from hybrid PET/MRI. *Left:*  $^{11}\text{C}$ -yohimbine non-displaceable binding potential ( $\text{BP}_{\text{ND}}$ ) parametric maps were used for contrasting the healthy control and Parkinson's disease groups. The outcome of the voxel-based analysis allowed the identification of four significant clusters that provided the region of interest (ROI) for analysing the links between  $^{11}\text{C}$ -yohimbine  $\text{BP}_{\text{ND}}$  and clinical scores in patients. *Right:* LC identification was performed for each individual from neuromelanin-sensitive  $\text{T}_1$  images with a three-step procedure. First, the ROIs were drawn manually as large 3D bounding boxes in Montreal Neurological Institute (MNI) space, then wrapped and resampled onto the subject's native space. Finally, the clusters of connected voxels with the highest signal intensity were selected to define LC areas. The contrast-to-noise ratio (CNR) between the LC and the reference region was calculated to estimate LC signal intensity, and these values were referred to the clinical scores of the PD patients.

(ROIs) employing the Spearman correlation test adjusted for age and sex.

We assessed the links between both noradrenergic markers and specific clinical characteristics within our group of PD patients using partial correlation coefficients adjusted for age and sex. Indeed, it is known that both variables influence the phenotypic expression of PD,<sup>52</sup> that healthy ageing influences neuromelanin accumulation in the LC<sup>53</sup> and <sup>11</sup>C-yohimbine BP<sub>ND</sub> might be influenced by gender.<sup>36</sup> All correlations were two-sided and significance was set to  $P < 0.05$ .

## Results

### Altered locus coeruleus integrity in patients with Parkinson's disease

PD patients had lower CNR<sub>LC</sub> than healthy controls [ $0.29 \pm 0.04$  versus  $0.31 \pm 0.04$ , respectively;  $F(1,99) = 5.72$ ,  $P = 0.019$ ]. The CNR was higher in the left than right LC [ $0.32 \pm 0.03$  versus  $0.28 \pm 0.04$ , respectively;  $F(1,99) = 22.02$ ,  $P < 0.001$ ]. No significant effect of gender and no interaction were found ( $P > 0.3$ ). Because of the effect related to side, all other analyses were conducted for both sides separately.

### Reduced <sup>11</sup>C-yohimbine binding in Parkinson's disease patients

Reduced binding of <sup>11</sup>C-yohimbine was observed in the PD group compared with the healthy controls and found in four significant clusters, including mainly cortical regions across all lobes and the insula, the putamen and the thalamus (Table 2 and Fig. 2). VBM was additionally employed to assess grey matter volume loss in PD patients compared with controls as a potential confounding factor within the ROI. No significant effect was found between the two groups using FWE with a corrected  $P$ -value  $< 0.05$  in the t-test.

### Correlation between $\alpha 2$ -adrenergic receptor availability and locus coeruleus MRI data

No significant correlation was found between regional <sup>11</sup>C-yohimbine BP<sub>ND</sub> values and CNR<sub>LC</sub> (all  $P > 0.1$ ).

### Correlation of neuromelanin MRI data with clinical scores in Parkinson's disease

#### Clinical characteristics

CNR<sub>LC</sub> correlated negatively with LEDD (right:  $r = -0.52$ ,  $P = 0.011$  and left:  $r = -0.49$ ,  $P = 0.017$ ).

#### Non-motor scores

CNR<sub>LC</sub> correlated negatively with UPDRS-I total score (right:  $r = -0.43$ ,  $P = 0.035$  and left:  $r = -0.47$ ,  $P = 0.02$ ). Within this scale, we investigated which items mostly drove this effect and found that the apathy sub-score was negatively correlated with the right and left CNR<sub>LC</sub> ( $r = -0.48$ ,  $P = 0.018$  and  $r = -0.46$ ,  $P = 0.025$ , respectively), constipation and light-headedness on standing sub-scores correlated negatively with the left CNR<sub>LC</sub> ( $r = -0.52$ ,  $P = 0.008$  and  $r = -0.47$ ,  $P = 0.02$ , respectively), and the fatigue sub-score showed significant negative correlation with the right CNR<sub>LC</sub> ( $r = -0.48$ ,  $P = 0.017$ ).

#### Motor scores

Although we did not observe any significant correlation between CNR<sub>LC</sub> and UPDRS-II and -III total scores (all  $P > 0.1$ ), we also

specifically explored the relationship between CNR<sub>LC</sub> and rest tremor, rigidity and bradykinesia. Those were calculated using the following items for MDS-UPDRS-III: rest tremor, 3.17; rigidity, 3.3; bradykinesia, 3.4–3.8. Interestingly, the left CNR<sub>LC</sub> correlated negatively with the bradykinesia sub-score ( $r = -0.42$ ,  $P = 0.043$ ), while a trend in the right side was also observed ( $r = -0.39$ ,  $P = 0.056$ ) and the right CNR<sub>LC</sub> correlated positively with the tremor sub-score ( $r = 0.45$ ,  $P = 0.026$ ). Finally, we also found that the left CNR<sub>LC</sub> correlated negatively with the UPDRS-IV score ( $r = -0.44$ ,  $P = 0.03$ ) with a trend in the right side ( $r = -0.38$ ,  $P = 0.069$ ). Interestingly, this effect was driven mostly by the motor fluctuation sub-score (sum of items 4.3 and 4.4), which showed a significant negative correlation with the left and right CNR<sub>LC</sub> ( $r = -0.43$ ,  $P = 0.035$  and  $r = -0.41$ ,  $P = 0.044$ , respectively), while such correlations were not observed for the dyskinesia sub-score (sum of items 4.1 and 4.2) (all  $P > 0.1$ ).

### Correlation of $\alpha 2$ -adrenergic receptor PET data with clinical scores in Parkinson's disease

We found no correlation between <sup>11</sup>C-yohimbine BP<sub>ND</sub> values in the ROI derived from the between-group SPM contrast and the total scores of the MDS-UPDRS scales. However, significant correlations were found with sub-scores within the different sections of the scale.

#### Non-motor scores

The item assessing anxiety in the UPDRS-I part correlated negatively with <sup>11</sup>C-yohimbine BP<sub>ND</sub> values in three regions within the right hemisphere: the putamen ( $r = -0.50$ ,  $P = 0.008$ ), the insula ( $r = -0.44$ ,  $P = 0.02$ ) and the superior temporal gyrus ( $r = -0.41$ ,  $P = 0.034$ ).

#### Motor scores

The item assessing rest tremor in the UPDRS-III part correlated negatively with <sup>11</sup>C-yohimbine BP<sub>ND</sub> values in the right thalamus ( $r = -0.46$ ,  $P = 0.015$ ). In other words, the lower the binding in the thalamus, the more the patients suffered from tremor.

## Discussion

In the present study, we investigated two aspects of the noradrenergic system using multimodal *in vivo* imaging in PD patients and healthy controls with hybrid MRI/PET: the density of pigmented cell bodies of the LC with neuromelanin sensitive MRI and the availability of the  $\alpha 2$ -ARs with <sup>11</sup>C-yohimbine PET. Both show marked reductions in signal intensity in patients, confirming that noradrenergic damage is profound and widespread in PD. Clinical, behavioural and anatomical data suggest, however, that noradrenergic dysfunction is multifaceted and may involve different circuits underlying specific motor and non-motor symptoms.

### Noradrenergic system integrity in Parkinson's disease

The reduction in signal intensity within the LC in PD patients confirmed previous MRI studies<sup>2,40,54–57</sup> and provided a robust and replicable *in vivo* indication of the loss of pigmented LC neurons previously suggested in post-mortem histological studies.<sup>58–60</sup> On the contrary, there has been only very sparse evidence about the loss of  $\alpha 2$ -ARs in PD patients reported, including only one *in vitro* autoradiography study reporting a decrease in density of the prefrontal cortex<sup>33</sup> and one preliminary *in vivo* study using

Table 2 Statistical parametric mapping results of the two samples t-test on <sup>11</sup>C-yohimbine binding

Areas	BA	Side	MNI coordinates			t-value	P corr cluster	Cluster size
			x	y	z			
<b>Reduced <sup>11</sup>C-yohimbine binding in Parkinson's disease patients versus healthy controls</b>								
Angular gyrus	40	R	46	−38	52	5.37	0.000	3775
Superior temporal gyrus	22	R	52	−12	0	5.08	–	–
Postcentral gyrus (opercular)	48	R	50	−8	16	5.06	–	–
Inferior frontal gyrus (pars opercularis)	44	R	46	14	10	4.22	–	–
Insula	13	R	36	−12	6	4.18	–	–
Precentral gyrus	4	R	40	−26	58	3.97	–	–
Putamen	–	R	30	−10	6	3.90	–	–
Postcentral gyrus	3	R	52	−14	30	3.73	–	–
Thalamus (PuM)	–	R	6	−24	4	5.18	0.000	1354
Insula	13	L	−32	−6	16	4.59	–	–
Precentral gyrus (premotor cortex)	6	L	−48	−4	12	3.84	–	–
Posterior cingulate cortex (dorsal)	31	R	2	−36	40	4.95	0.000	3836
Superior parietal cortex	7	R	18	−76	40	4.55	–	–
Lateral occipital cortex	19	L	−10	−82	36	4.43	–	–
Cuneus	18	R	4	−80	34	4.41	–	–
Posterior cingulate cortex (ventral)	23	R	8	−52	10	4.37	–	–
Posterior cingulate cortex (mid cingulate)	23	R	8	−20	46	4.28	–	–
Lateral occipital cortex	19	R	32	−80	26	4.27	–	–
Lingual gyrus	18	L	−6	−72	0	4.07	–	–
Precentral gyrus	6	R	4	−22	60	3.89	–	–
Lingual gyrus	17	R	4	−66	12	3.87	–	–
Precuneus	31	L	−6	−52	38	3.80	–	–
Precuneus	31	R	2	−56	42	3.80	–	–
Superior parietal cortex	7	L	−32	−50	56	4.41	0.013	614
Angular gyrus	40	L	−42	−52	46	4.23	–	–
Postcentral gyrus	3	L	−50	−14	38	3.76	–	–
Postcentral gyrus	4	L	−36	−28	56	3.66	–	–

BA = Brodmann area; L = left; MNI = Montreal Neurological Institute; PuM = medial pulvinar nucleus; P corr = corrected P-value; R = right.

<sup>11</sup>C-yohimbine in a small group of PD patients reporting a global reduction in <sup>11</sup>C-yohimbine distribution volume in the temporal, parietal and occipital cortices, the insula and the cingulate gyrus.<sup>61</sup> Our data provide a precise mapping of <sup>11</sup>C-yohimbine binding reduction in PD patients (Fig. 2). Within the parietal lobe, the angular gyrus, the superior parietal lobule and the postcentral gyrus are especially affected. The occipital cortex also shows multiple sources of binding differences both in the primary and associative visual cortices. In the frontal lobe, only motor structures (primary motor cortex, supplementary motor area and premotor cortex) and the inferior frontal gyrus revealed binding reduction in patients. The temporal lobe seems also to be relatively preserved, since only one region in the superior temporal gyrus showed group differences. Medially, the posterior cingulate/precuneus region is particularly affected. Finally, binding reduction in PD also concerns the insula, the putamen and the thalamus (Fig. 2). This latter observation was in good agreement with previous post-mortem and animal studies showing severe reductions of noradrenaline levels in almost all subregions of the thalamus.<sup>30,62</sup>

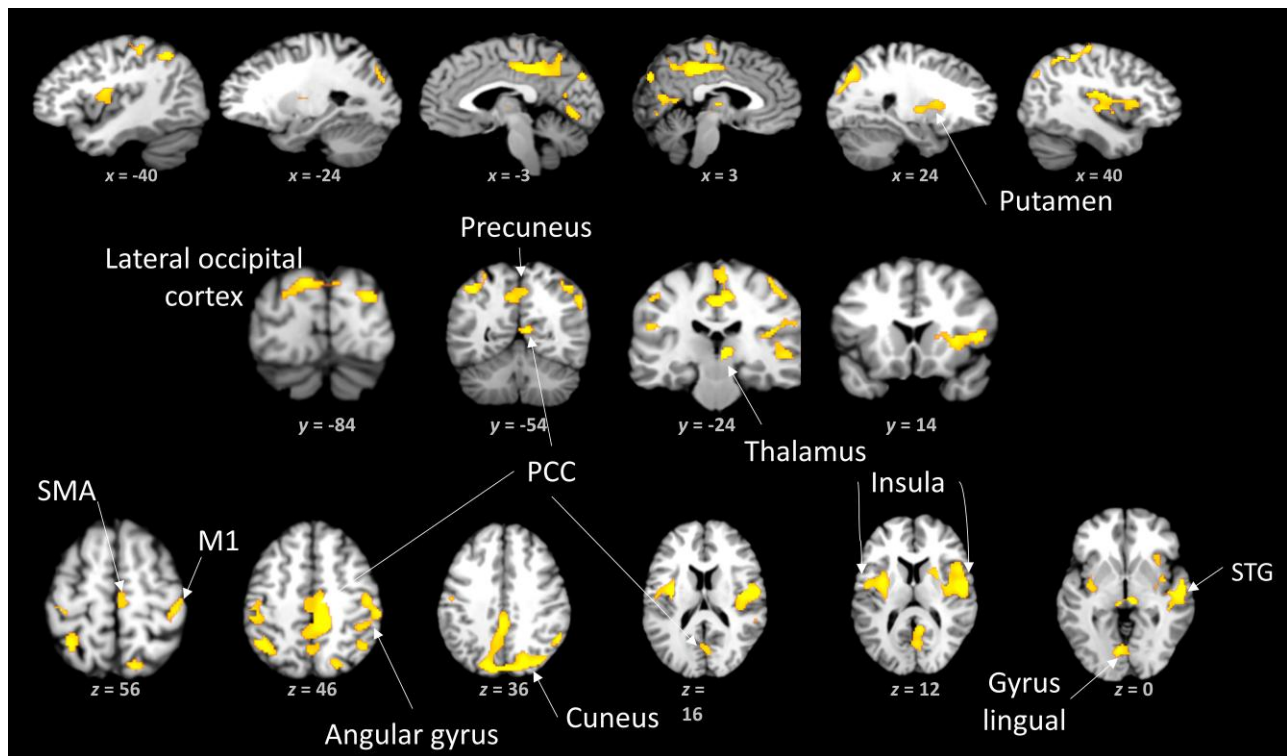
Interpreting <sup>11</sup>C-yohimbine binding reduction is not straightforward. Indeed, as  $\alpha$ 2-ARs are located both pre- and postsynaptically,<sup>63,64</sup> the decrease in <sup>11</sup>C-yohimbine binding could reflect both a reduction of presynaptic  $\alpha$ 2-ARs due to the diminished innervation caused by the degeneration of noradrenergic neurons and/or a reduction in the availability of postsynaptic  $\alpha$ 2-ARs, which can be relatively independent of the degeneration of noradrenergic neurons (as observed for the dopaminergic system).<sup>65</sup> The former hypothesis predicted strong correlations between neuromelanin MRI and <sup>11</sup>C-yohimbine PET signals. Our results were not consistent

with this prediction. They were rather reminiscent of the conclusion obtained from <sup>11</sup>C-MeNER—a marker of noradrenaline transporter availability—PET studies that deficits in noradrenergic terminals and LC cell bodies are partly uncoupled.<sup>2,40</sup> It seems that the number of noradrenergic cells in the LC would be a major determinant of  $\alpha$ 2-AR density only in the LC itself.<sup>66</sup> Our data are in line with the overall hypothesis according to which monoaminergic receptors undergo adaptive changes in PD that make the availability of their receptors non-proportional to the extent of neuronal death of the corresponding cell bodies.<sup>65,67</sup> It is therefore essential to disentangle, within the global clinical picture, the symptoms that might be more related to the loss of  $\alpha$ 2-ARs and/or to the loss of noradrenergic cells in the LC.

## Non-motor symptoms

### Fatigue

Fatigue was found to be associated with LC neuronal loss. This is in line with the idea that fatigue results from the disruption of nondopaminergic pathways, including the noradrenergic system.<sup>68–70</sup> This is not incompatible with the hypothesis that fatigue in PD is also associated with serotonergic dysfunction in prefrontal-basal ganglia and limbic circuits.<sup>71</sup> Indeed, it is well known that there are strong interactions between the noradrenergic and serotonergic systems (mainly through the LC-dorsal raphe nucleus connection),<sup>72–74</sup> suggesting that both are likely to contribute to the appearance of the symptom. However, the argument that fatigue characterizes a specific serotonergic phenotype of PD is based on associations between



**Figure 2** Statistical parametric maps comparing Parkinson's disease patients to control subjects. A decrease in  $^{11}\text{C}$ -yohimbine binding was observed in patients with Parkinson's disease compared with healthy control subjects. M1 = primary motor cortex; PCC = posterior cingulate cortex; SMA = supplementary motor area; STG = superior temporal gyrus.

fatigue and other non-motor symptoms related to the degeneration of serotonergic pathways (apathy, anxiety, sleep problems and daytime sleepiness)<sup>75</sup> that are most often moderate<sup>69</sup> and that are not all reported in the present study, as only apathy was also found to be associated with LC neuronal loss. Anxiety was associated with a reduction of  $\alpha 2$ -AR availability in the putamen, insula and superior temporal gyrus but not with a reduction in signal intensity within the LC. Yet, neither LC neuronal loss nor  $\alpha 2$ -AR availability was found to account for sleep disorders. This observation is in line with several pharmacological studies of physical exercise in healthy humans suggesting that the role of the serotonergic system in central fatigue might be overestimated,<sup>76</sup> while the role of the noradrenergic system might conversely be underestimated.<sup>77</sup> In addition, given that fatigue is a non-dopaminergic symptom, the fact that methylphenidate—a reuptake inhibitor of dopamine and noradrenaline—is proposed as a treatment for fatigue in PD<sup>78,79</sup> is also consistent with the idea that the pathophysiological mechanism leading to fatigue involves the degeneration of the noradrenergic system. Beyond PD, the association of fatigue with a loss of noradrenergic cells in the LC but not with a loss of  $\alpha 2$ -ARs in other specific brain regions is not trivial. It relates the global perception of an internal state of energy to the general function of the noradrenergic system, which is to mobilize the whole brain and body for action from a unique but widely distributed source. This association has not been put forward in current biological theories of fatigue.<sup>69</sup>

### Apathy

Apathy is a complex and multifactorial alteration of the internal and external drives of goal-directed behaviour.<sup>80</sup> It has been associated with dysfunctions of different neural networks supporting

emotional/affective, cognitive and auto-activation circuits,<sup>3,81,82</sup> for which meso-cortico-limbic dopaminergic and serotonergic lesions are thought to play a major role. The present study provides new insight into apathy pathophysiology and suggests that there is a role for noradrenergic alteration since we found a correlation between apathy and LC neuronal loss. This observation is reminiscent of a recent study using pharmacological MRI and testing more specifically predictive processing (i.e. executive functions) of goal-directed behaviour.<sup>83</sup> Although we cannot disentangle cognitive from motivational apathy in the present study, it is tempting to speculate that the noradrenergic dysfunction identified in our empirical observations may be more closely associated with cognitive apathy (which includes dysfunction of a set of executive mechanisms required for achieving a goal) than with motivational apathy.<sup>84</sup> Our results also strengthen the idea that fatigue is associated with apathy (both relying on the general activation function of the LC-noradrenergic system, not on specific losses of  $\alpha 2$ -ARs) but not with anxiety<sup>85</sup> (which does not involve LC neuronal loss in the present study).

### Anxiety

Anxiety is commonly associated with apathy and depression to constitute a behavioural 'non-motor triad' in PD governed by serotonergic and dopaminergic degeneration.<sup>3,86</sup> However, while anxiety symptoms are clearly linked to alterations of limbic cortico-striato-thalamo-cortical circuits, several studies have proposed that basal ganglia and brainstem nuclei could be at the root of such disorders,<sup>87,88</sup> including a loss of noradrenaline innervation in the LC and the limbic system.<sup>87,89</sup> Our data are consistent with the involvement of noradrenergic dysfunction in anxiety, as its severity is associated with a reduction of  $\alpha 2$ -AR



availability in a brain network including the putamen, insula and superior temporal gyrus (but not with a loss of noradrenergic cells in the LC). However, we found no evidence for a common noradrenergic dysfunction of the ‘non-motor triad’ as they all seem to have different origins: anxiety was associated with alteration of noradrenergic terminals and apathy with alteration of LC cell bodies, while depression was not linked to any of these dysfunctions.

### Constipation

Constipation is one of the most common non-motor symptoms that emerge from the very early phase.<sup>90,91</sup> The underlying mechanisms of constipation in PD are still unknown, but neurodegeneration of autonomic centres of both the enteric and central nervous systems are likely.<sup>92</sup> Our observation that constipation is associated with a reduction of signal intensity in the LC fits with the general idea that dysfunction of the noradrenergic system is closely linked to numerous premotor symptoms of PD.<sup>93–96</sup> Most importantly, it is also consistent with rodent studies providing specific evidence that: (i) the LC participates in the regulation of colorectal motility (via activation of  $\alpha 1$ -ARs in the lumbosacral defecation centre)<sup>97</sup>; (ii) noradrenaline plays a major role in regulating colon immune homeostasis<sup>98</sup>; and (iii) the reduction of noradrenaline levels in the intestine causes colon inflammation,  $\alpha$ -synuclein pathology, neuronal loss and ultimately constipation.<sup>98,99</sup>

### Motor symptoms

LC neuronal loss in PD has been associated with the disease but not directly with motor symptoms.<sup>6,100</sup> Here, we provide evidence for a direct link with bradykinesia, rest tremor and motor fluctuations. In contrast, while noradrenergic denervation of the motor areas<sup>101</sup> and noradrenergic transporter density decrease in the motor cortex<sup>102</sup> have been associated with motor cortical dysfunction in PD,<sup>103,104</sup> the substantial reduction of  $\alpha 2$ -AR availability in the motor cortices of PD patients found in the present study revealed no direct relationship with a global motor dysfunction (i.e. neither with the UPDRS-II nor UPDRS-III scores). However, the potential consequences of cortical  $\alpha 2$ -AR loss may be more indirect and specific. Indeed, as  $\alpha 2$ -ARs would be located on inhibitory interneurons, reduced availability could contribute to the broad reduction of intracortical inhibition at rest and to the increase in cortical excitation frequently observed in PD.<sup>105–107</sup> Future studies are needed to clarify this possibly masked relationship.

### Bradykinesia

Bradykinesia is a multifaceted concept including potentially distinct motor abnormalities with discrete pathophysiological backgrounds mixed under a single clinical term.<sup>108</sup> Here, we did not find specific correlates of bradykinesia as assessed by means of UPDRS-III in the <sup>11</sup>C-yohimbine binding data but report a significant association with a global alteration of LC integrity. Although this observation does not address the problem of the ‘bradykinesia complex’,<sup>108</sup> it contributes to the debate about its incomplete response to dopaminergic drugs. Indeed, levodopa improves overall bradykinesia but does not normalize all other abnormal movement parameters.<sup>109</sup> Our data support the suggestions of several studies promoting the role of noradrenaline in the control of motor behaviour<sup>11</sup> and the fact that its depletion results in motor deterioration in PD.<sup>16,19,30,102</sup> It can be assumed that the role of noradrenaline is indirect: first, because it would facilitate nigro-striatal dopamine transmission<sup>110</sup>; and second, because the noradrenergic system

would play a major role in executive functions like response inhibition, the alteration of which might lead to movement control disorders.<sup>111–114</sup> Future work on the noradrenergic bases of movement disorders in PD should include a more detailed clinical evaluation of bradykinesia and its related features.<sup>108</sup>

### Motor fluctuations

The present study pinpoints a correlation between the decrease in LC signal intensity and the severity of levodopa-induced motor complications (UPDRS-IV total score). However, we did not find any relationship with the change in  $\alpha 2$ -AR availability despite previous studies having reported a potent effect of  $\alpha 2$ -AR antagonists on dyskinesia in a monkey model of PD<sup>115–118</sup> as well as in patients with PD when given in combination with levodopa.<sup>119</sup> In addition, although there have been very few investigations into the role of the LC in motor fluctuations, LC denervation in rodents was not found to potentiate levodopa-induced motor complications.<sup>120</sup> These contradictions clearly require further investigation comparing notably PD patients with and without motor fluctuations and dyskinesias. Nevertheless, the present data bring back to the forefront the issue of the links between motor and non-motor fluctuations<sup>121</sup> and suggest that alteration of LC integrity might be a common denominator.

### Rest tremor

Tremor in PD does not closely correlate with nigrostriatal dopaminergic deficits<sup>122</sup> and is not fully restored by dopaminergic medication.<sup>123</sup> Increasing evidence also involves the noradrenergic system in the network dynamics of parkinsonian tremor.<sup>27,122,124</sup> Our data are consistent with this view. Both the amount of neuronal loss in the LC inferred from neuromelanin MRI and  $\alpha 2$ -AR availability in the thalamus inferred from <sup>11</sup>C-yohimbine binding have been associated with tremor level in the present dataset. The direction of the relationship between neuromelanin MRI and clinical data indicated that tremor is higher in patients for whom LC integrity is better preserved, as previously observed in post-mortem analyses comparing tremor-dominant to akinetic-rigid patients<sup>125,126</sup> or in *in vivo* investigations using <sup>11</sup>C-MeNER PET.<sup>124</sup> This relationship was also predicted by prior observations linking the presence of tremor to a more benign course of disease<sup>127</sup> or to a relatively preserved LC-noradrenergic system.<sup>27,124</sup> Our data are in line with a group of studies implicating a cerebello-thalamo-cortical circuit in the genesis of tremor.<sup>128–132</sup> as they provide evidence that  $\alpha 2$ -AR availability in the thalamus decreases with the severity of rest tremor. This is particularly consistent with the recent observation that the distribution volume ratio of noradrenaline transporters in the thalamus correlates with resting tremor amplitude in patients with PD, suggesting that noradrenaline transporter density is relatively preserved in this region for patients with tremor-dominant PD.<sup>124</sup>

### Limitations

Some limitations to this study should be acknowledged. First, due to ethical reasons and the need to reduce movements within the scanner for imaging small brainstem structures like the LC, patients with PD were scanned in the ON medication state. There is evidence from animal studies that administration of levodopa might foster the accumulation of neuromelanin.<sup>133</sup> However, these effects are expected to be relatively long-lasting rather than fluctuating between medication states. In the present study, LEDD in patients did correlate with CNR<sub>LC</sub>, indicating that PD patients with higher dose of dopaminergic treatment were those with lower

signal in the LC. This was observed for both sides of the LC. A second possible effect of the ON medication state is that postsynaptic  $\alpha$ 2-ARs may be downregulated.<sup>134,135</sup> However, we did not find any correlation between LEDD and <sup>11</sup>C-yohimbine BP<sub>ND</sub> at least in the regions sampled.

Second, it was not possible to distinguish the pre- and postsynaptic locations of the  $\alpha$ 2-ARs with <sup>11</sup>C-yohimbine. Future studies should consider multitracer approaches with a specific presynaptic tracer (such as <sup>11</sup>C-MeNER) to assess whether changes in  $\alpha$ 2-ARs with PD occur mainly at the pre- or postsynaptic level (or both). Furthermore, it is also worth mentioning that <sup>11</sup>C-yohimbine does not differentiate between the different subtypes of  $\alpha$ 2-ARs that have been characterized pharmacologically ( $\alpha$ 2A,  $\alpha$ 2B,  $\alpha$ 2C).<sup>136</sup> Therefore, there is still a strong need in the future to pursue the development of specific radiotracers to further investigate this noradrenergic system *in vivo*.

## Conclusions

In conclusion, this work is the first multimodal comparative *in vivo* imaging study to assess the association between PD symptoms and the integrity of two aspects of the noradrenergic system: the distribution of  $\alpha$ 2-ARs in the brain and the density of cell bodies in the LC. Our results highlight the substantial and multimodal alteration of the noradrenergic system in humans and its possible role in the pathophysiology of PD, not only in terms of non-motor impairments (supporting the noradrenergic phenotype recently proposed by Ray Chaudhuri and colleagues<sup>7</sup>) but also with regard to some motor aspects of the disease (bradykinesia, motor fluctuations and rest tremor). Overall, our findings may encourage the search for new drugs targeting the  $\alpha$ 2-AR system for the treatment of PD. However, future studies are warranted to shed more light on the specific role of  $\alpha$ 2-ARs and their different subtypes in the pathophysiology of the disease. In particular, further research is needed to sharpen the clinical picture and better characterize the different phenotypes of this heterogeneous and multisystem disease.

## Data availability

Data are available upon reasonable request.

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## Competing interests

The authors report no competing interests.

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