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Noradrenergic alterations in Parkinson's disease: a combined ¹¹C-yohimbine PET/neuromelanin MRI study

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Abstract

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 evaluate 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 α 2-adrenergic receptors (ARs) with PET using [¹¹C]yohimbine. Thirty patients with Parkinson's disease and thirty age- and sex-matched healthy control subjects were included. Patient's symptoms characteristics were assessed using the MDS-UPDRS scale. Patients showed reduced neuromelanin signal intensity in the locus coeruleus compared to controls, and diminished [¹¹C]yohimbine binding in widespread cortical regions including the motor cortex as well as in the insula, the thalamus and the putamen. Clinically, locus coeruleus neuronal loss was correlated with motor (bradykinesia, motor fluctuations, tremor) and non-motor (fatigue, apathy, constipation) symptoms. A reduction of α 2-ARs 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 findings highlight a multifaceted alteration of the noradrenergic system in Parkinson's disease since locus coeruleus and α 2-ARs degenerations were found to be partly uncoupled. These findings raise important issues about noradrenergic dysfunctions that may encourage the search for new drugs targeting this system, including α 2-ARs, for the treatment of Parkinson's disease.

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16

17 **Keywords:** Parkinson's disease; Noradrenaline; PET/MRI; locus coeruleus; α 2-adrenergic
18 receptors

19 **Abbreviations:** ARs = adrenergic receptors; BP_{ND} = non-displaceable binding potential; CNR =
20 contrast-to-noise ratio; FSL = FMRIB Software Library; FWE = family-wise error; LC = locus
21 coeruleus; LEDD = levodopa equivalent daily doses; MDS = Movement Disorder Society; MNI
22 = Montreal Neurological Institute; MoCA = Montreal Cognitive Assessment; PDQ-39 = 39-item
23 Parkinson's Disease Questionnaire; ROI = region of interest; TSE = turbo spin-echo; UPDRS =
24 Unified Parkinson's disease Rating Scale; VBM = voxel-based morphometry

25

1 Introduction

2 Parkinson's disease is mostly characterized by the loss of dopaminergic neurons in the substantia
3 nigra pars compacta. However, the neurodegenerative process also extends to other
4 neurotransmission systems such as serotonin, or acetylcholine and noradrenaline, which
5 contribute to motor and non-motor symptoms.¹⁻⁴ The modulation and interactions of the complex
6 interconnected non-dopaminergic networks with dopaminergic circuits are far from being fully
7 understood, and the cascade of perturbations in these interconnected systems and associated
8 circuits is still a central issue. Among these neurotransmitters, the noradrenergic system is
9 probably the most least well known.^{5,6-8}

10 Firstly, the direct role of the noradrenergic system in various cognitive functions is well
11 documented.⁹ This includes specific functions like vigilance, attention and executive control, but
12 also more transversal functions like learning, cognitive flexibility and working memory,⁸ or an
13 even more general role in adaptive adjustments in gain that serve to optimize performance.¹⁰ It is
14 important to point out that there is a major gap in our understanding of how these modulations
15 apply to the motor circuits.¹¹ The alteration of these functions might thus contribute to various
16 parkinsonian manifestations.⁸ However, it is often under-recognized and its association with
17 specific symptoms, in particular with the motor manifestations of the disease, is still unclear.
18 Secondly, the effect of noradrenergic dysfunction in the manifestations of the disease might also
19 be related to its antiparkinsonian and neuroprotective properties.¹² The loss of noradrenergic
20 neurons in the locus coeruleus (LC), the sole source of noradrenaline to the neocortex,
21 hippocampus, cerebellum and thalamus (¹³ for review) which is estimated between 20 and 90%,
22 precedes and exceeds the characteristic loss of dopaminergic neurons in the substantia nigra.¹⁴
23 There is evidence mainly based on animal studies that noradrenergic loss may enhance
24 neurotoxic damage to nigrostriatal dopaminergic neurons,^{15,16} and that, conversely, restoration of
25 LC damaged system positively influences the recovery process of degenerated dopaminergic
26 neurons.^{17,18} Taken together, these observations suggest that enhancing noradrenergic
27 neurotransmission may facilitate both specific functions affected by the disease and the recovery
28 process of dopaminergic neurons.¹⁹ Yet, therapeutic strategies targeting this system in
29 Parkinson's disease are still currently limited.^{7,20}

1 The use of $\alpha 2$ -adrenergic receptors (ARs) antagonists has recently been considered as a major
2 possible target²¹ as it might potentiate noradrenaline availability by blocking presynaptic $\alpha 2$ -ARs
3 whose normal function is to regulate noradrenaline release.²²⁻²⁴ However, direct *in vivo* evidence
4 of alteration of $\alpha 2$ -ARs in parkinsonian manifestations is still lacking. This critical lack of
5 knowledge, accompanied by substantial controversies on the neurofunctional bases of the
6 noradrenergic system and its alteration in Parkinson's disease,^{25,26} is mainly due to the lack of
7 specific *in vivo* molecular imaging tools in humans. To date, *in vivo* imaging studies have only
8 used presynaptic noradrenergic tracers of the noradrenergic transporter with [¹¹C]MeNER. These
9 studies have shown reduced tracer uptake, suggesting a diminished density of noradrenergic
10 terminals, mainly in the thalamus, hypothalamus, LC and raphe nuclei.^{2,27} Regarding $\alpha 2$ -ARs,
11 most of our knowledge derives from animal studies or post-mortem samples of human brains.^{28,29}
12 Autoradiography studies suggest an alteration in $\alpha 2$ -ARs in different brain regions (thalamus,³⁰
13 cerebellum,³¹ hypothalamus,³² and prefrontal cortex³³). Here, we take advantage of recent
14 methodological developments allowing *in vivo* imaging of the noradrenergic system in human
15 with the novel PET radiotracer [¹¹C]yohimbine,³⁴⁻³⁶ now available for use in large samples of
16 human subjects to map differences in $\alpha 2$ -ARs distribution between parkinsonian patients and
17 matched controls. The [¹¹C]yohimbine binds with high selectivity to all $\alpha 2$ -ARs subtypes.³⁷ It is
18 displaced when there is competition at the receptor with endogenous noradrenaline, as shown by
19 preclinical studies reporting reduced receptor binding by unlabeled yohimbine challenge,
20 amphetamine administration or acute vagus nerve stimulation in preclinical studies³⁷⁻³⁹ and
21 human studies reporting increased receptor binding after clonidine administration.³⁴

22 The objectives of the present study are to assess two aspects of noradrenergic neurodegeneration
23 in Parkinson's disease by means of hybrid MRI/PET imaging: lesions of pigmented cell bodies
24 of the LC with neuromelanin-sensitive MRI and alterations of $\alpha 2$ -ARs density with
25 [¹¹C]yohimbine PET. Assessing simultaneously noradrenergic terminals (with PET) and LC cell
26 bodies (with MRI) is of primary importance given that their respective deficits may be
27 uncoupled.⁴⁰ To inform the disputed pathophysiological mechanisms of the disease, correlations
28 between the observed noradrenergic dysfunctions and the standard clinical measures of
29 Parkinson's disease have been systematically tested.

30

1 **Materials and methods**

2 **Participants**

3 The demographics and clinical characteristics of the participants are listed in Table 1. We
4 enrolled 30 Parkinson's disease patients and 30 healthy controls matched for age, gender, and
5 global cognitive functioning using the Montreal Cognitive Assessment (MoCA) score. Patients
6 were diagnosed with Parkinson's disease for at least 1 year in accordance with the Movement
7 Disorder Society criteria.⁴¹ The Movement Disorder Society Revised Unified Parkinson's
8 Disease Rating Scale (MDS-UPDRS) was used to assess Parkinson's disease symptoms,
9 including separate assessments of non-motor symptoms (UPDRS-I), daily activity (UPDRS-II),
10 motor symptoms (UPDRS-III), and motor complications (UPDRS-IV).⁴² In addition, the 39-item
11 Parkinson's Disease Questionnaire (PDQ-39) was used to evaluate quality of life.⁴³ All patients
12 were assessed in the "ON" state with their usual antiparkinsonian medication. Levodopa
13 equivalent daily dose (LEDD) was calculated according to previously published conversion
14 rules.⁴⁴ Most of the patients with PD were in the early and middle stage of their disease with a
15 mean Hoehn & Yahr score of 1.8 and MDS-UPDRS-III score in the "on" state of 17.7 (\pm 12.3).
16 Exclusion criteria were medications that interfere with the noradrenergic system, a diagnosis of
17 other neurological or psychiatric disorders, and the presence of major dyskinesia or tremor in the
18 patients for technical imaging purposes. The study was conducted in accordance with the
19 Declaration of Helsinki and approved by the local Ethical Committee in Biomedical Research
20 (N° CPP 19_01_02/N°EudraCT 2018-003999-13). Written informed consent was obtained from
21 all the subjects before the study.

22 **Magnetic Resonance Imaging**

23 MRI data were acquired on a Biograph mMR (hybrid MRI/PET) including a whole brain high-
24 resolution anatomical 3D T1-weighted MPRAGE sequence in the sagittal plane (matrix size 256
25 \times 256 \times 176, voxel size 1 \times 1 \times 1 mm³), and a 2D axial turbo spin-echo (TSE) sequence (in plane
26 resolution 0.4 \times 0.4 mm², slice thickness 3 mm, matrix size 464 \times 512 \times 15) which provided a
27 neuromelanin-sensitive MRI.

1 **Voxel-based morphometry analysis**

2 To exclude the possibility that structural degeneration affects the results of [¹¹C]yohimbine
3 binding, voxel-based morphometry (VBM) analysis was conducted. Standard VBM
4 preprocessing protocol of the Computational Anatomy Toolbox (CAT12, [http://www.neuro.uni-](http://www.neuro.uni-jena.de/cat/)
5 [jena.de/cat/](http://www.neuro.uni-jena.de/cat/)) running on Statistical Parametric Mapping (SPM12; Welcome Trust Centre for
6 Neuroimaging, University College, London, UK) was employed. Briefly, each 3D T1-weighted
7 image was bias-corrected and segmented into grey matter, white matter and cerebrospinal fluid
8 tissue classes using SPM's unified segmentation function. The grey matter segmentation
9 probability maps were spatially transformed to the Montreal Neurological Institute (MNI)
10 standard space using the ICBM-152 template according to the DARTEL approach with default
11 settings in 1.5 mm cubic resolution, and then smoothed with a Gaussian kernel of 8 mm full-
12 width-at-half-maximum. Lastly, to correct for individual differences in brain size, the Total
13 Intracranial Volume (TIV) was estimated for each subject using CAT12 interface (Statistical
14 Analyses – Estimate TIV), as the sum of the grey matter, white matter, and CSF volumes.

15 **Neuromelanin-sensitive MRI analysis**

16 To calculate signal intensity in the LC, an approach similar to that published by García-Lorenzo
17 and colleagues⁶ was implemented. First, two regions were manually drawn on the T1 MRI high
18 resolution MNI template using FSLeyes (FSL v5.0.11, FMRIB, Oxford, UK). These two regions
19 (one for each side) were defined as large 3D bounding boxes and placed around the hyperintense
20 voxels at the lateral border of the fourth ventricle so that they included the LC, but excluded the
21 substantia nigra which also contains neuromelanin.⁴⁵ In addition, we used the central reference
22 mask freely available to normalize the intensity of the LC.⁴⁶ These three regions were then
23 wrapped and resampled onto the subject's neuromelanin-sensitive T1 image using SPM12. Using
24 FSL functions, the LC was defined as the area of the 10 voxels with the brightest intensity within
25 each bounding box. We considered the intensity of the LC as the average of the intensities of the
26 10 voxel region (Fig. 1). The contrast-to-noise ratio (CNR) was calculated for each LC (right and
27 left) as $CNR_{LC} = (S_{LC} - S_{REF}) / S_{REF}$ where S_{LC} and S_{REF} correspond to the mean signal intensity of
28 the LC and the reference region respectively. Normalization of the LC signal to a central
29 reference region (pons) to calculate the CR by relative difference has been the most commonly
30 used and recommended method in previous studies.⁴⁷

1 **[¹¹C]yohimbine PET**

2 Radiosynthesis of [¹¹C]yohimbine was performed as previously described.³⁷ The radiochemical
3 purities of syntheses used for the study were greater than 95%, with molar activities of 85 ± 30
4 GBq/ μ mol at the end of synthesis. All subjects received an intravenous bolus injection of 370
5 MBq \pm 10% of [¹¹C]yohimbine. List-mode PET data were acquired during the 90 min from the
6 injection of the tracer. MRI data were acquired simultaneously.

7 Raw PET data were corrected for motion,⁴⁸ and then rebinned into 24 time frames (variable
8 length frames, 8×15 s, 3×60 s, 5×120 s, 1×300 s, 7×600 s) sinograms for dynamic
9 reconstruction. Sinograms were corrected for scatter, randoms, normalization, and attenuation.⁴⁹
10 Images were reconstructed using 3D ordinary Poisson-ordered subsets expectation maximization
11 (OP-OSEM 3D), incorporating the system point spread function using 3 iterations of 21 subsets.
12 Reconstructions were performed with a zoom of 2 in a matrix of 172×172 voxels, yielding a
13 voxel size of $2.03 \times 2.03 \times 2.08$ mm³, with a 4 mm 3D post-reconstruction Gaussian filtering.
14 Regional time activity curves were extracted based on labelling of structural brain regions
15 obtained with the multi-atlas propagation with enhanced registration methodology (MAPER)⁵⁰
16 and the 83-region Hammers atlas.⁵¹ [¹¹C]yohimbine non-displaceable binding potential (BP_{ND})
17 parametric maps were then generated using the simplified reference tissue model (SRTM), with
18 the corpus callosum as reference region.³⁴ PET parametric images were spatially normalized to
19 the MNI space with parameters derived from the individual T1 MRI.

20 **Statistics**

21 Statistical analyses on demographic data were performed using Rstudio
22 (<https://github.com/rstudio/rstudio>). All data were tested for normal distribution using the
23 Shapiro-Wilk test and the Levene test for homogeneity of variance. Independent samples t-tests
24 or Wilcoxon tests, as appropriate, were used to compare demographics group mean differences.
25 We assessed group differences in the CNR_{LC} with an analysis of covariance accounting for age
26 and sex as covariates. A two-tailed t-test was generated in the SPM12 toolbox to assess between-
27 group differences on grey matter concentration using family-wise error (FWE) correction with p
28 < 0.05 threshold. The extend threshold was set to 100 voxels and total intracranial volume was
29 used as covariate of no interest.

1 SPM12 in Matlab2020a was used for between-group comparisons of [^{11}C]yohimbine BP_{ND} at the
2 voxel level (2-sample t-test) controlling for age and gender. Spatially normalized parametric
3 images were smoothed with an 8-mm Gaussian filter, and an average cortical grey-matter mask
4 was used for explicit masking within the SPM software. The voxel-level analysis threshold was p
5 < 0.001 (uncorrected), and subsequently a FWE cluster-level correction at $p < 0.05$ was applied.

6 We assessed the association of MRI and PET signals and interrogated nonparametric (partial)
7 correlations between CNR_{LC} and [^{11}C]yohimbine BP_{ND} values extracted from the ROIs,
8 employing Spearman correlation test adjusted for age and sex.

9 We assessed the links between both noradrenergic markers and specific clinical characteristics
10 within our group of Parkinson's disease patients by means of partial correlation coefficients
11 adjusted for age and sex. Indeed, it is known that both variables influence the phenotypical
12 expression of Parkinson's disease,⁵² that healthy ageing influences neuromelanin accumulation
13 in the LC,⁵³ and that [^{11}C]yohimbine BP_{ND} might be influenced by gender.³⁶ All correlations
14 were two-sided and significance was set at $p < 0.05$.

15

16 **Results**

17 **Altered LC integrity in patients with Parkinson's disease**

18 Parkinson's disease patients had lower CNR_{LC} than healthy controls (0.29 ± 0.04 vs 0.31 ± 0.04 ,
19 respectively; $F(1, 99) = 5.72$, $p = 0.019$). CNR was higher in the left than the right LC ($0.32 \pm$
20 0.03 versus 0.28 ± 0.04 , respectively; $F(1,99) = 22.02$, $p < 0.001$). No significant effect of
21 gender and no interaction were found ($p > 0.3$). Because of the side effect, all other analyses
22 have been conducted for both sides separately.

23 **Reduced [^{11}C]yohimbine binding in Parkinson's disease patients**

24 Reduced binding of [^{11}C]yohimbine was observed in the Parkinson's disease group compared to
25 healthy controls in four significant clusters including mainly cortical regions across all lobes and
26 the insula, the putamen and the thalamus (Table 2, Fig. 2). VBM was additionally employed to
27 assess grey matter volume loss in Parkinson's disease patients compared to controls as a

1 potential confounding factor within the ROI. No significant effect was found between the two
2 groups using FWE with corrected p value < 0.05 in the t-test.

3 **Correlation between $\alpha 2$ -ARs availability and LC MRI data**

4 No significant correlation was found between regional [^{11}C]yohimbine BP_{ND} values and CNR_{LC}
5 (all $p > 0.1$).

6 **Correlation of neuromelanin MRI data with clinical scores in Parkinson's** 7 **disease**

8 **Clinical characteristics**

9 CNR_{LC} correlated negatively with LEDD (right: $r = -0.52$, $p = 0.011$ and left: $r = -0.49$, $p =$
10 0.017).

11 **Non-motor scores**

12 CNR_{LC} correlated negatively with UPDRS-I total score (right: $r = -0.43$, $p = 0.035$ and left: $r = -$
13 0.47 , $p = 0.02$). We explored within this scale which items mostly driven this effect and found
14 that apathy sub-score was negatively correlated with the right and left CNR_{LC} ($r = -0.48$, $p =$
15 0.018 and $r = -0.46$, $p = 0.025$ respectively), constipation and light headedness on standing sub-
16 scores correlated negatively with the left CNR_{LC} ($r = -0.52$, $p = 0.008$ and $r = -0.47$, $p = 0.02$
17 respectively), while the fatigue sub-score showed significant negative correlation with the right
18 CNR_{LC} ($r = -0.48$, $p = 0.017$).

19 **Motor scores**

20 Although we did not observe any significant correlation between CNR_{LC} and UPDRS-II and -III
21 total scores (all $p > 0.1$), we also specifically explored the relationship between CNR_{LC} and rest
22 tremor, rigidity and bradykinesia. Those were calculated using the following items for MDS-
23 UPDRS-III: rest tremor - 3.17, rigidity - 3.3, bradykinesia - 3.4-3.8. Interestingly, the left CNR_{LC}
24 correlated negatively with the bradykinesia sub-score ($r = -0.42$, $p = 0.043$) while a trend in the
25 right side was also observed ($r = -0.39$, $p = 0.056$), and the right CNR_{LC} correlated positively
26 with the tremor sub-score ($r = 0.45$, $p = 0.026$). Finally, we also found that the left CNR_{LC}
27 correlated negatively with the UPDRS-IV score ($r = -0.44$, $p = 0.03$) with a trend in the right side
28 ($r = -0.38$, $p = 0.069$). Interestingly, this effect was mostly driven by the motor fluctuation sub-

1 score (sum of items 4.3 and 4.4) which showed significant negative correlation with the left and
2 right CNR_{LC} ($r = -0.43$, $p = 0.035$ and $r = -0.41$, $p = 0.044$ respectively) while such correlations
3 were not observed for the dyskinesia sub-score (sum of items 4.1 and 4.2) (all $p > 0.1$).

4 **Correlation of $\alpha 2$ -ARs PET data with clinical scores in Parkinson's disease**

5 We found no correlation between [¹¹C]yohimbine BP_{ND} values in the ROI derived from the
6 between-group SPM contrast and the total scores of the MDS-UPDRS scales. However,
7 significant correlations were found with sub-scores within the different sections of the scale.

8 **Non-motor scores**

9 The item assessing anxiety in the UPDRS-I part correlated negatively with [¹¹C]yohimbine BP_{ND}
10 values in three regions within the right hemisphere : the putamen ($r = -0.50$, $p = 0.008$), the
11 insula ($r = -0.44$, $p = 0.02$) and the superior temporal gyrus ($r = -0.41$, $p = 0.034$).

12 **Motor scores**

13 The item assessing rest tremor in the UPDRS-III part correlated negatively with [¹¹C]yohimbine
14 BP_{ND} values in the right thalamus ($r = -0.46$, $p = 0.015$). In other words, the lower the binding in
15 the thalamus, the more the patients suffered from tremor.

16 **Discussion**

17 In the present study, we investigated two aspects of the noradrenergic system using multimodal
18 *in vivo* imaging in Parkinson's disease patients and healthy controls with hybrid MRI/PET: the
19 density of pigmented cell bodies of the LC with neuromelanin sensitive MRI and the availability
20 of the $\alpha 2$ -ARs with [¹¹C]yohimbine PET. Both show marked reductions in signal intensity in
21 patients, confirming that noradrenergic damage is profound and widespread in Parkinson's
22 disease. Clinical, behavioral and anatomical data suggest, however, that noradrenergic
23 dysfunction is multifaceted and may involve different circuits underlying specific motor and
24 non-motor symptoms.

25 **Noradrenergic system integrity in Parkinson's disease**

26 The reduction in signal intensity within the LC in Parkinson's disease patients confirms previous
27 MRI studies^{2,40,54-57} and provides a robust and replicable *in vivo* indication of the loss of

1 pigmented LC neurons previously suggested in post-mortem histological studies.^{58–60} On the
2 contrary, there was only very sparse evidence about the loss of $\alpha 2$ -ARs in Parkinson's disease
3 patients, including only one *in vitro* autoradiography study reporting a decrease of density in the
4 prefrontal cortex³³ and one preliminary *in vivo* study using [¹¹C]yohimbine in a small group of
5 PD patients reporting a global reduction in [¹¹C]yohimbine distribution volume in the temporal,
6 parietal and occipital cortices, the insula and the cingulate gyrus.⁶¹ Our data provide a precise
7 mapping of [¹¹C]yohimbine binding reduction in Parkinson's disease patients (Fig. 2). Within the
8 parietal lobe, the angular gyrus, the superior parietal lobule and the postcentral gyrus are
9 especially affected. The occipital cortex also shows multiple sources of binding differences both
10 in the primary and associative visual cortices. In the frontal lobe, only motor structures (primary
11 motor cortex, supplementary motor area and premotor cortex) and the inferior frontal gyrus
12 reveal binding reduction in patients. The temporal lobe seems also relatively preserved since
13 only one region in the superior temporal gyrus shows group differences. Medially, the posterior
14 cingulate/precuneus region is particularly affected. Finally, binding reduction in Parkinson's
15 disease also concerns the insula, the putamen and the thalamus (Fig. 2). This latter observation is
16 in good agreement with previous post-mortem and animal studies showing severe reductions of
17 noradrenaline levels in almost all subregions of the thalamus.^{30,62}

18 Interpreting [¹¹C]yohimbine binding reduction is not straightforward. Indeed, as $\alpha 2$ -ARs are
19 located both pre- and post-synaptically,^{63,64} the decrease in [¹¹C]yohimbine binding could reflect
20 both a reduction of presynaptic $\alpha 2$ -ARs due to the diminished innervation caused by the
21 degeneration of noradrenergic neurons, and/or a reduction in the availability of postsynaptic $\alpha 2$ -
22 ARs which can be relatively independent of the degeneration of noradrenergic neurons (as
23 observed for the dopaminergic system).⁶⁵ The former hypothesis predicts strong correlations
24 between neuromelanin MRI and [¹¹C]yohimbine PET signals. Our results are not consistent with
25 this prediction. They are rather reminiscent of the conclusion obtained from [¹¹C]MeNER -a
26 marker of noradrenaline transporter availability- PET studies that deficits in noradrenergic
27 terminals and LC cell bodies are partly uncoupled.^{2,40} It seems that the number of noradrenergic
28 cells in the LC would be a major determinant of $\alpha 2$ -AR density only in the LC itself.⁶⁶ Our data
29 are in line with the overall hypothesis according to which monoaminergic receptors undergo
30 adaptive changes in Parkinson's disease that make the availability of their receptors non
31 proportional to the extent of neuronal death of the corresponding cell bodies.^{65,67} It is therefore

1 essential to disentangle, within the global clinical picture, the symptoms that might be more
2 related to the loss of $\alpha 2$ -ARs and/or to the loss of noradrenergic cells in the LC.

3 **Non-motor symptoms**

4 **Fatigue**

5 Fatigue was found to be associated with LC neuronal loss. This is in line with the idea that
6 fatigue results from disruption of nondopaminergic pathways, including the noradrenergic
7 system.⁶⁸⁻⁷⁰ This is not incompatible with the hypothesis that fatigue in Parkinson's disease is
8 also associated with serotonergic dysfunction in prefrontal-basal ganglia and limbic circuits.⁷¹
9 Indeed, it is well known that there are strong interactions between the noradrenergic and
10 serotonergic systems (mainly through the LC-dorsal raphe nucleus connection)⁷²⁻⁷⁴ suggesting
11 that both are likely to contribute to the appearance of the symptom. However, the argument that
12 fatigue characterizes a specific serotonergic phenotype of Parkinson's disease is based on
13 associations between fatigue and other non-motor symptoms related to the degeneration of
14 serotonergic pathways (apathy, anxiety, sleep problems and daytime sleepiness)⁷⁵ that are most
15 often moderate⁶⁹ and that are not all reported in the present study as only apathy was also found
16 to be associated with LC neuronal loss. Anxiety was just associated with a reduction of $\alpha 2$ -ARs
17 availability in the putamen, the insula and the superior temporal gyrus, but not with a reduction
18 in signal intensity within the LC. Yet, neither LC neuronal loss nor $\alpha 2$ -ARs availability were
19 found to account for sleep disorders. This observation is in line with several pharmacological
20 studies of physical exercise in healthy humans suggesting that the role of the serotonergic
21 system in central fatigue might be overestimated⁷⁶ while the role of the noradrenergic system
22 might conversely be underestimated.⁷⁷ In addition, given that fatigue is a non-dopaminergic
23 symptom, the fact that Methylphenidate -a reuptake inhibitor of dopamine and noradrenaline- is
24 proposed as a treatment against fatigue in Parkinson's disease^{78,79} is also consistent with the idea
25 that the pathophysiological mechanism leading to fatigue involves the degeneration of the
26 noradrenergic system. Beyond Parkinson's disease, the association of fatigue with a loss of
27 noradrenergic cells in the LC but not with a loss of $\alpha 2$ -ARs in other specific brain regions is not
28 trivial. It relates the global perception of an internal state of energy to the general function of the
29 noradrenergic system which is to mobilize the whole brain and body for action from a unique but

1 widely distributed source. This association is not put forward in current biological theories of
2 fatigue.⁶⁹

3 **Apathy**

4 Apathy is a complex and multifactorial alteration of the internal and external drives of goal-
5 directed behavior.⁸⁰ It has been associated with dysfunctions of different neural networks
6 supporting emotional/affective, cognitive and auto-activation circuits,^{3,81,82} for which meso-
7 cortico-limbic dopaminergic and serotonergic lesions are thought to play a major role. The
8 present study provides new insight into apathy pathophysiology and suggests that there is a role
9 of noradrenergic alteration since we found a correlation between apathy and LC neuronal loss.
10 This observation is reminiscent of a former recent study using pharmacological MRI and testing
11 more specifically predictive processing (i.e., executive functions) of goal-directed behavior.⁸³
12 Although we cannot disentangle cognitive from motivational apathy in the present study, it is
13 tempting to speculate that the noradrenergic dysfunction identified in our empirical observations
14 may be more closely associated with cognitive apathy (which includes dysfunction of a set of
15 executive mechanisms required for achieving a goal) than with motivational apathy.⁸⁴ Our results
16 also strengthen the idea that fatigue is associated with apathy (both relying on the general
17 activation function of the LC-NA system, not on specific losses of $\alpha 2$ -ARs) but not with
18 anxiety⁸⁵ (which does not involve LC neuronal loss in the present study).

19 **Anxiety**

20 Anxiety is commonly associated with apathy and depression to constitute a behavioral « non-
21 motor triad » in Parkinson's disease governed by serotonergic and dopaminergic
22 degeneration.^{3,86} However, while anxiety symptoms are clearly linked to alterations of limbic
23 cortico-striato-thalamo-cortical circuits, several studies have proposed that basal ganglia and
24 brainstem nuclei could be at the root of such disorders,^{87,88} including a loss of noradrenaline
25 innervation in the locus coeruleus and the limbic system.^{87,89} Our data are consistent with the
26 involvement of noradrenergic dysfunction in anxiety as its severity is associated with a reduction
27 of $\alpha 2$ -ARs availability in a brain network including the putamen, the insula and the superior
28 temporal gyrus (but not with a loss of noradrenergic cells in the LC). However, we found no
29 evidence for a common noradrenergic dysfunction of the “non-motor triad” as they all seem to

1 have different origins: anxiety was associated with alteration of noradrenergic terminals, apathy
2 with alteration of LC cell bodies, while depression was not linked to any of these dysfunctions.

3 **Constipation**

4 Constipation is one of the most common nonmotor symptoms that emerge from the very early
5 phase.^{90,91} The underlying mechanisms of constipation in Parkinson's disease are still unknown,
6 but neurodegeneration of autonomic centers of both the enteric and central nervous systems are
7 likely.⁹² Our observation that constipation is associated with a reduction of signal intensity in the
8 LC fits with the general idea that dysfunction of the noradrenergic system is closely linked to
9 numerous premotor symptoms of Parkinson's disease.⁹³⁻⁹⁶ But most importantly, it is also
10 consistent with rodent studies providing specific evidence that: 1) the LC participates in the
11 regulation of colorectal motility (via activation of α 1-ARs in the lumbosacral defecation
12 center),⁹⁷ 2) noradrenaline plays a major role in regulating colon immune homeostasis,⁹⁸ and 3)
13 the reduction of noradrenaline level in the intestine causes colon inflammation, α -synuclein
14 pathology, neuronal loss and, in fine, constipation.^{98,99}

15 **Motor symptoms**

16 LC neuronal loss in Parkinson's disease has been associated with the disease, but not directly
17 with motor symptoms.^{6,100} Here, we provide evidence for a direct link with bradykinesia, rest
18 tremor, and motor fluctuations. By contrast, while noradrenergic denervation of the motor
19 areas¹⁰¹ and noradrenergic transporters density decrease in the motor cortex¹⁰² have been
20 associated with motor cortical dysfunction in Parkinson's disease,^{103,104} the substantial reduction
21 of α 2-ARs availability in the motor cortices of Parkinson's disease patients found in the present
22 study revealed no direct relationship with a global motor dysfunction (i.e, neither with the
23 UPDRS-II nor with the UPDRS-III scores). However, it is possible that the potential
24 consequences of cortical α 2-ARs loss are more indirect and more specific. Indeed, as α 2-ARs
25 would be located on inhibitory interneurons, a reduced availability could contribute to the broad
26 reduction of intracortical inhibition at rest and to the increase in cortical excitation frequently
27 observed in PD.¹⁰⁵⁻¹⁰⁷ Future studies are needed to clarify this possible masked relationship.

1 **Bradykinesia**

2 Bradykinesia is a multifaceted concept including potentially distinct motor abnormalities with
3 distinct pathophysiological backgrounds that are all mixed in one single clinical term.¹⁰⁸ Here,
4 we did not find specific correlates of bradykinesia as assessed by means of UPDRS-III in
5 [¹¹C]yohimbine binding data, but report a significant association with a global alteration of LC
6 integrity. Although this observation does not address the problem of the “bradykinesia complex”
7 (ibid), it contributes to the debate about its incomplete response to dopaminergic drugs. Indeed,
8 levodopa only improves overall bradykinesia but does not normalize all other abnormal
9 movement parameters.¹⁰⁹ Our data support the suggestions of several studies promoting the role
10 of noradrenaline in the control of motor behavior¹¹ and the fact that its depletion results in motor
11 deterioration in Parkinson’s disease.^{16,19,30,102} It can be assumed that the role of noradrenaline is
12 indirect. First because it would facilitate nigro-striatal dopamine transmission.¹¹⁰ Second because
13 the noradrenergic system would play a major role in executive functions like response inhibition
14 whose alteration might lead to movement control disorders.^{111–114} Future work on the
15 noradrenergic bases of movement disorders in Parkinson’s disease should include a more
16 detailed clinical evaluation of bradykinesia and its related features.¹⁰⁸

17 **Motor fluctuations**

18 The present study pinpoints a correlation between the decrease in LC signal intensity and the
19 severity of levodopa-induced motor complications (UPDRS-IV total score). However we did not
20 find any relationship with $\alpha 2$ -ARs availability change despite previous studies having reported a
21 potent effect of $\alpha 2$ -ARs antagonists on dyskinesia in a monkey model of Parkinson’s disease^{115–}
22 ¹¹⁸ as well as in patients with Parkinson’s disease when given in combination with levodopa.¹¹⁹
23 In addition, although there are very few investigations of the role of the LC in motor fluctuations,
24 LC denervation in rodents was not found to potentiate levodopa-induced motor complications.¹²⁰
25 These contradictions clearly require further investigations comparing notably Parkinson’s
26 disease patients with and without motor fluctuations and dyskinesias. Nevertheless, the present
27 data bring back to the forefront the issue of the links between motor and non-motor
28 fluctuations,¹²¹ and suggest that alteration of LC integrity might be a common denominator.

1 **Rest tremor**

2 Tremor in Parkinson's disease does not closely correlate with nigrostriatal dopaminergic
3 deficits¹²² and is not fully restored by dopaminergic medication.¹²³ Increasing evidence also
4 involves the noradrenergic system in the network dynamics of parkinsonian tremor.^{27,122,124} Our
5 data are consistent with this view. Both the amount of neuronal loss in the LC inferred from
6 neuromelanin MRI and α 2-ARs availability in the thalamus inferred from [¹¹C]yohimbine
7 binding have been associated with tremor level in the present dataset. The direction of the
8 relationship between neuromelanin MRI and clinical data indicates that tremor is higher in
9 patients for whom LC integrity is better preserved, as previously observed in post-mortem
10 analyses comparing tremor-dominant to akinetic-rigid patients^{125,126} or in *in vivo* investigations
11 using [¹¹C]MeNER PET.¹²⁴ This relationship was also predicted by former observations linking
12 the presence of tremor to a more benign course of disease¹²⁷ or to a relatively preserved LC-NA
13 system.^{27,124} Our data are in line with a group of studies implicating a cerebello-thalamo-cortical
14 circuit in the genesis of tremor^{128–132} as they provide evidence that α 2-ARs availability in the
15 thalamus decreases with the severity of rest tremor. This is particularly consistent with the recent
16 observation that distribution volume ratio of noradrenaline transporters in the thalamus correlates
17 with resting tremor amplitude in patients with Parkinson's disease, suggesting that noradrenaline
18 transporters density is relatively preserved in this region for patients with tremor-dominant
19 Parkinson's disease.¹²⁴

20 **Limitations**

21 There are some limitations to this study that should be acknowledged. First, due to ethical
22 reasons and to the need to reduce movements within the scanner for imaging small brainstem
23 structures like the LC, patients with Parkinson's disease were scanned in the ON medication
24 state. There is evidence from animal studies that administration of levodopa might foster the
25 accumulation of neuromelanin.¹³³ However, these effects are expected to be relatively long-
26 lasting rather than fluctuating between medication states. In the present study, LEDD in patients
27 did correlate with CNRLC indicating that PD patients with higher dose of dopaminergic treatment
28 were those with lower signal in the LC. This was observed for both sides of the LC. A second
29 possible effect of the ON medication state is that postsynaptic α 2-ARs may be

1 downregulated.^{134,135} However, we did not find any correlation between LEDD and
2 [¹¹C]yohimbine BP_{ND}, at least in the regions that have been sampled.

3 Second, it is not possible to distinguish the pre- and post-synaptic locations of the α 2-ARs with
4 [¹¹C]yohimbine. Future studies should consider multitracer approaches with specific presynaptic
5 tracer (such as [¹¹C]MeNER) in order to assess whether changes in α 2-ARs with Parkinson's
6 disease mainly occur at the pre- or at the post-synaptic level (or both). Furthermore, it is also
7 worth mentioning that [¹¹C]yohimbine does not differentiate either between the different
8 subtypes of α 2-ARs that have been characterized pharmacology (α 2A, α 2B, α 2C).¹³⁶ Therefore,
9 there is still a strong need in the future to pursue the effort in developing specific radiotracers to
10 further investigate this noradrenergic system *in vivo*.

11 **Conclusions**

12 In conclusion, the present work is the first multimodal comparative *in vivo* imaging study to
13 assess the association between Parkinson's disease symptoms and the integrity of two aspects of
14 the noradrenergic system: the distribution of α 2-ARs in the brain and the density of cell bodies in
15 the LC. Our results highlight the substantial and multimodal alteration of the noradrenergic
16 system in humans and its possible role in the pathophysiology of Parkinson's disease, not only in
17 terms of non-motor impairments (supporting the noradrenergic phenotype recently proposed by
18 Chaudhuri and colleagues)⁷ but also with regard to some motor aspects of the disease
19 (bradykinesia, motor fluctuations and rest tremor). Overall, our findings may encourage the
20 search for new drugs targeting the α 2-ARs system for the treatment of Parkinson's disease.
21 However, future studies are warranted to shed more light on the specific role of the α 2-ARs and
22 their different subtypes in the pathophysiology of the disease. In particular, further research is
23 needed to sharpen the clinical picture and better characterize the different phenotypes of this
24 heterogeneous and multisystem disease.

25 **Data availability**

26 Data are available upon reasonable request.

27

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7 **Competing interests**

8 The authors report no competing interests.

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18 **Figure legends**

19 **Figure 1 Data pipeline.** [¹¹C]yohimbine and LC Neuromelanin data were acquired
20 simultaneously from hybrid PET/MRI. *Left side:* [¹¹C]yohimbine BP_{ND} parametric maps were
21 used for contrasting the healthy control and the Parkinson's disease groups. The outcome of the
22 voxel-based analysis allowed identification of four significant clusters that provided the ROI for
23 the analysis of the links between [¹¹C]yohimbine BP_{ND} and clinical scores in patients. *Right side:*
24 LC identification was performed for each individual from neuromelanin sensitive T1 images
25 with a three-steps procedure. First, the regions of interest were manually drawn as large 3D
26 bounding boxes in the MNI space, then wrapped and resampled onto the subject's native space.
27 Finally, the clusters of connected voxels with the highest signal intensity were selected to define
28 LC areas. The CNR between the LC and the reference region was calculated to estimate LC

1 signal intensity and these values were referred to the clinical scores of the Parkinson's disease
 2 patients.

3
 4 **Figure 2 Statistical parametric maps comparing Parkinson's disease patients to control**
 5 **subjects.** Decrease in [¹¹C]yohimbine binding is observed in patients with Parkinson's disease
 6 with regard to healthy control subjects.

7
 8
 9 **Table I Demographics and clinical characteristics of participants**

	Healthy Controls	Parkinsonian patients	Statistics
N	30	30	
Sex (female/male)	12/18	12/18	
Age (years)	60.3 ± 8	60.1 ± 7.5	ns ^a
MoCA	27.9 ± 1.5	27.9 ± 2	ns ^b
Parkinson's disease characteristics			
Disease duration (years)		6.5 ± 4	
LEDD (mg/day)		1006 ± 703	
Hoehn & 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	

10 Data are presented as mean ± standard deviation.

11 ^aParametric test (Student's t-test).

12 ^bNon-parametric test (Wilcoxon test).

13

1 **Table 2 SPM results of the two samples t test on [¹¹C]yohimbine binding**

Areas	BA	Side	MNI coordinates			T value	P corr cluster	Cluster size
			x	y	z			
Reduced [¹¹C]yohimbine binding in Parkinson's disease versus healthy controls								
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		

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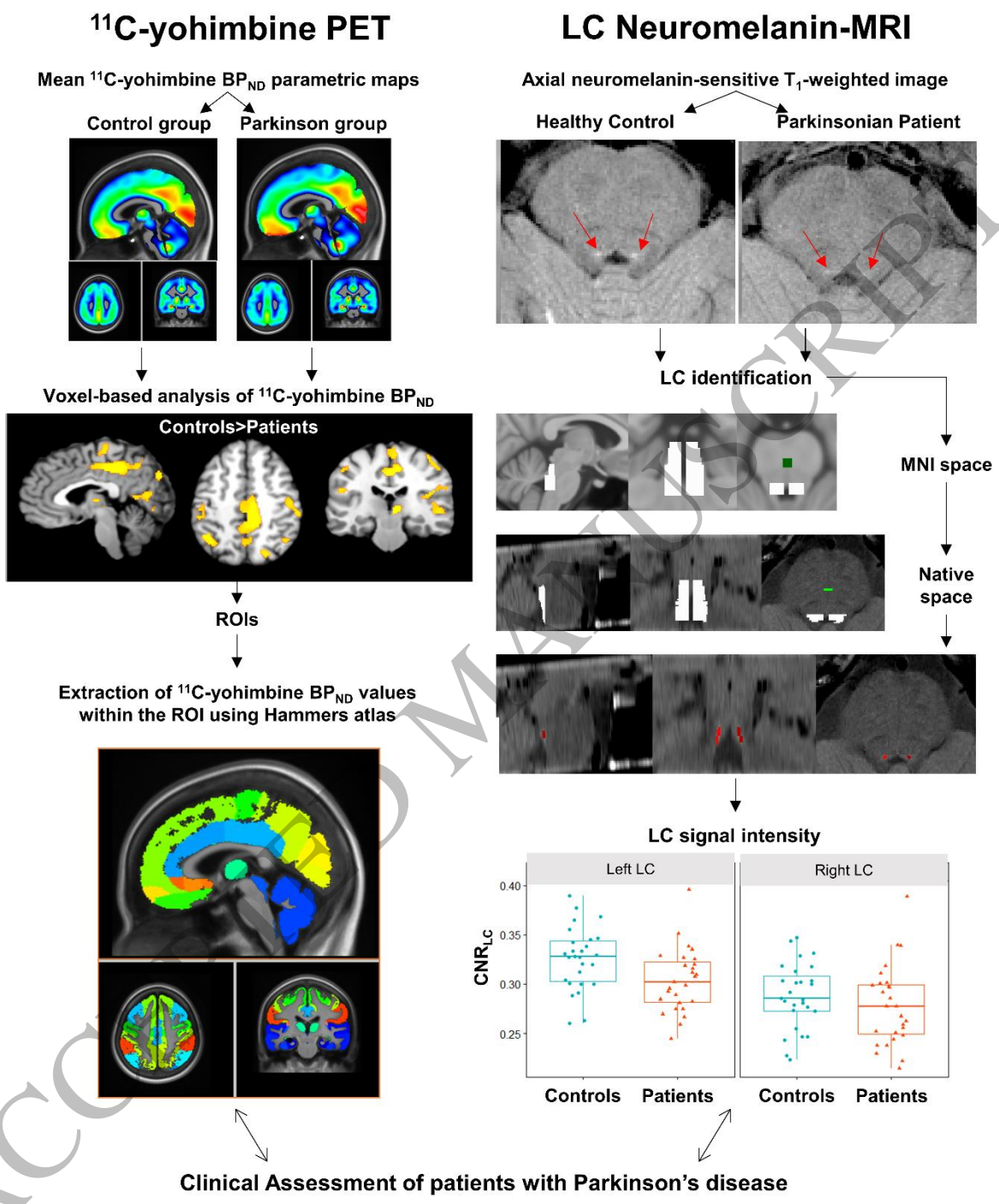


Figure 1
159x188 mm (x DPI)

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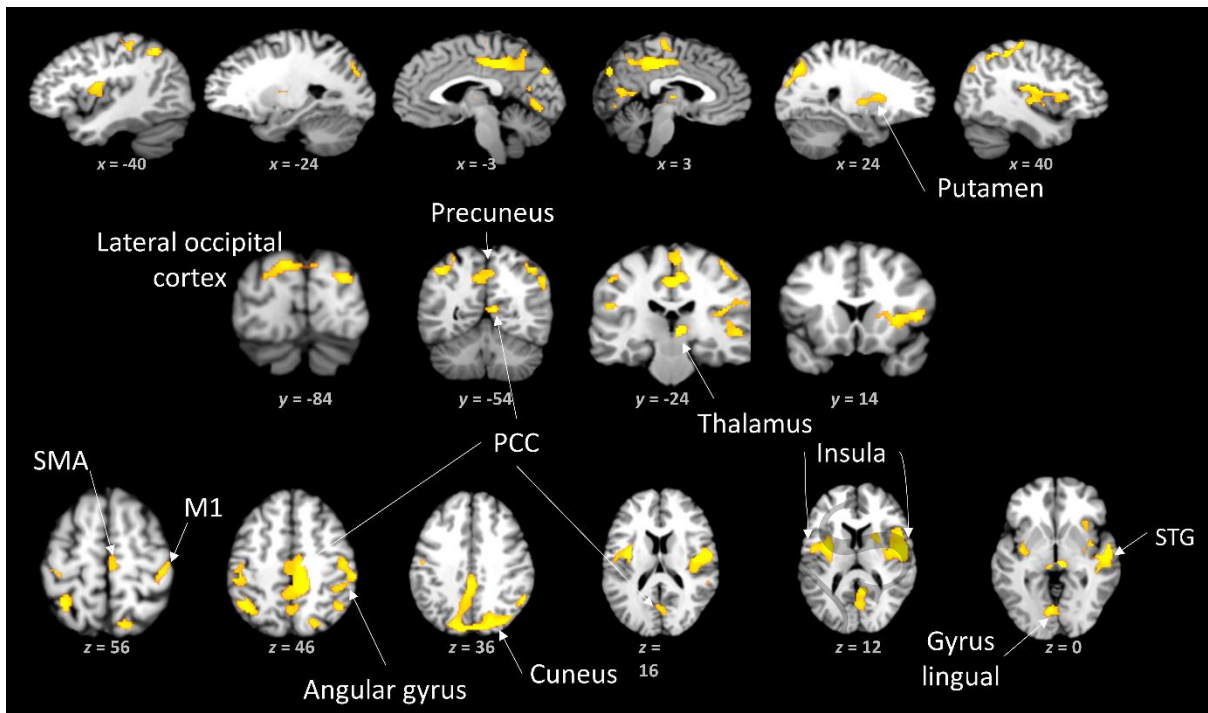


Figure 2
159x93 mm (x DPI)

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