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Neuromelanin-Sensitive Magnetic Resonance Imaging Changes in the Locus Coeruleus/Subcoeruleus Complex in Patients with Typical and Atypical Parkinsonism

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.
ABSTRACT: Background: The locus coeruleus/subcoeruleus complex (LC/LsC) is a structure comprising melanized noradrenergic neurons.

Objective: To study the LC/LsC damage across Parkinson’s disease (PD) and atypical parkinsonism in a large group of subjects.

Methods: We studied 98 healthy control subjects, 47 patients with isolated rapid eye movement sleep behavior disorder (RBD), 75 patients with PD plus RBD, 142 patients with PD without RBD, 19 patients with progressive supranuclear palsy (PSP), and 19 patients with multiple system atrophy (MSA). Twelve patients with MSA had proven RBD. LC/LsC signal intensity was derived from neuromelanin magnetic resonance imaging using automated software.

Results: The signal intensity was reduced in all parkinsonian syndromes compared with healthy control subjects, except in PD without RBD. The signal intensity decreased as age increased. Moreover, the signal intensity was lower in MSA than in isolated RBD and PD without RBD groups. In PD, the signal intensity correlated negatively with the percentage of REM sleep without atonia. There were no differences in signal intensity between PD plus RBD, PSP, and MSA.

Conclusions: Neuromelanin signal intensity was reduced in all parkinsonian disorders, except in PD without RBD. The presence of RBD in parkinsonian disorders appears to be associated with lower neuromelanin signal intensity. Furthermore, lower LC/LsC signal changes in PSP could be partly caused by the effect of age. © 2023 The Authors. Movement Disorders published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: locus coeruleus/subcoeruleus; neuromelanin; rapid eye movement sleep behavior disorder; Parkinson’s disease; progressive supranuclear palsy; multiple system atrophy

Subjects and Methods

Subjects

All subjects were recruited in three prospective research studies at the Paris Brain Institute (Iceberg and Nucleipark studies) and the Pitie-Salpetriere hospital (Parkatypique study) by movement disorders and sleep experts. Participants were diagnosed according to international diagnostic criteria as iRBD, PD, PSP with Richardson’s syndrome, or MSA or were age-matched healthy control subjects (HCs). Exclusion criteria comprised contraindications to MRI and presence of stroke or brain tumor on MRI examinations. The characteristics of the populations are presented in Figure 1 and Table 1. Local ethics committees approved all studies, and all subjects provided written informed consent (Nucleipark: RCB: 2009-A00922-55, Iceberg: RCB 2014-A00725-42, Parkatypique: Institutional Review Board—CPP Ile-de-France VI, 08012015).

Neurological Examination

Clinical examination included the Unified Parkinson’s Disease Rating Scale Part III (UPDRS Part III) scores for the Nucleipark and Parkatypique cohorts and the Movement Disorder Society (MDS)-UPDRS Part III for the Iceberg cohort. Hoehn and Yahr scores were obtained in HCs, patients with iRBD, and patients with PD. Disease duration was calculated using the date of diagnosis as the starting point. The presence of RBD was defined by international diagnostic criteria after an

Introduction

The locus coeruleus/subcoeruleus complex (LC/LsC) is a small pontine bilateral heterogeneous structure. The LC contains melanized noradrenergic neurons, the major source of noradrenaline to the rostral brain. It contributes to arousal, memory, and attention, as well as autonomic control. The LsC, located right below the LC, contains neurons driving muscle atonia during rapid eye movement (REM) sleep. Its damage causes REM sleep behavior disorder (RBD). Histological studies have shown that the LC/LsC degenerates in parkinsonian syndromes, including Parkinson’s disease (PD), as well as atypical parkinsonism, including multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). Because neurons in the LC/LsC are melanized, this structure can be imaged using neuromelanin-sensitive magnetic resonance imaging (MRI). Various MRI studies have demonstrated that the LC/LsC signal decreases in isolated RBD (iRBD, a prodromal form of parkinsonism) and in PD with RBD. Studies also reported a reduction in neuromelanin signal of the LC/LsC in MSA and PSP. However, results were discordant with respect to the severity of damage between various parkinsonian syndromes. Disagreement may come from insufficient power in studies, including reduced number of participants, methodology (quantitative vs. visual analysis), or the absence of evaluation of REM sleep without atonia in patients with PD.

We tested the hypothesis that the LC/LsC damage is present in all three neurodegenerative parkinsonian disorders in a large group of subjects. Furthermore, we also studied its relationship with the presence of REM sleep without atonia.
TABLE 1  Demographic and clinical characteristics and LC/LsC signal intensity

<table>
<thead>
<tr>
<th>Status</th>
<th>HC</th>
<th>iRBD</th>
<th>PD</th>
<th>PDRBBD+</th>
<th>PSP</th>
<th>Total</th>
<th>MSA</th>
<th>MSAp</th>
<th>MSAc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n</td>
<td>98</td>
<td>47</td>
<td>142</td>
<td>75</td>
<td>19</td>
<td>19</td>
<td>14</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>61.6 ± 8.7</td>
<td>67.2 ± 5.1</td>
<td>61.3 ± 10.0</td>
<td>64.9 ± 8.2</td>
<td>70.9 ± 8.0</td>
<td>61.4 ± 7.9</td>
<td>62.7 ± 8.5</td>
<td>57.6 ± 5.1</td>
<td></td>
</tr>
<tr>
<td>Sex (M/F), n</td>
<td>51/47</td>
<td>41/6</td>
<td>85/57</td>
<td>54/21</td>
<td>10/12</td>
<td>12/5</td>
<td>8/6</td>
<td>4/1</td>
<td></td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>NA</td>
<td>NA</td>
<td>5.1</td>
<td>61.4</td>
<td>8.0</td>
<td>62.7</td>
<td>8.5</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>MDS-UPDRS Part III OFF</td>
<td>7.9</td>
<td>22.5</td>
<td>13.1</td>
<td>17.3</td>
<td>11.1</td>
<td>15.6</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>UPDRS Part III OFF</td>
<td>0.4</td>
<td>0.8</td>
<td>0.3</td>
<td>2.1</td>
<td>0.5</td>
<td>0.3</td>
<td>0.5</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>H&amp;Y stage</td>
<td>0.1</td>
<td>0.5</td>
<td>0.7</td>
<td>10.9</td>
<td>2.1</td>
<td>0.5</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>LC/LsC signal intensity</td>
<td>127.5 ± 5.3</td>
<td>124.2 ± 3.9</td>
<td>126.0 ± 4.6</td>
<td>123.4 ± 4.6</td>
<td>123.0 ± 3.0</td>
<td>120.6 ± 4.2</td>
<td>120.9 ± 4.1</td>
<td>119.7 ± 4.7</td>
<td></td>
</tr>
</tbody>
</table>

Demographic and clinical characteristics were compared using Kruskal-Wallis test followed by post hoc Dunn's test for pairwise comparisons, while \( \chi^2 \) tests with Holm's correction were used to assess differences in sex distribution. Data are represented as mean ± standard deviation. *\( P < 0.01 \) Significant differences vs. iRBD. Significant differences vs. PD. Significant differences vs. PD RBD+. Significant differences vs. PSP. Significant differences vs. MSA. Significant differences vs. iRBD. Abbreviations: LC/LC, locus coeruleus/subcoeruleus complex; HC, healthy control subject; iRBD, isolated rapid eye movement sleep behavior disorder; PD, Parkinson's disease; PD RBD−, Parkinson's disease without rapid eye movement sleep behavior disorder; PD RBD+, Parkinson's disease with rapid eye movement sleep behavior disorder; PSP, progressive supranuclear palsy; MSA, multiple system atrophy; MSAc, multiple system atrophy of the cerebellar type, MSAp, multiple system atrophy of the parkinsonian type; M, male; F, female; NA, not available; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr stage.

Image analysis was performed blindly by the clinical status of the participants using the same automated software as described previously. In brief, data analysis included several steps: (1) A Priori definition of three anatomical regions of interest in the bilateral mesencephalic areas; (2) Image acquisition of 700 mm slices containing the LC/LsC and one reference region of 6200 mm³ in the rostral pontomesencephalic region; (3) Automated image analysis using the following formula:

\[
\text{SigLC} = \frac{\text{mean over slices[SigLC]} \times 100}{\text{Sigref}}
\]

where SigLC is the mean signal intensity in the LC/LsC region, and Sigref is the mean signal intensity in the reference region. Thereafter, quality control was performed by visual inspection of the images. Images with significant artifacts were excluded from the analyses (Supporting Information Table S1). Thereafter, quality control was performed by visual inspection of the images. Images with significant artifacts were excluded from the analyses (Supporting Information Table S1).

**Statistical Analyses**

All analyses were performed using R (R Core Team 2019, v3.6.1). Comparison of the groups with the 2018, 3.6.1. Comparison of the groups with the 2019, v3.6.1. Comparison of the groups with the 2021, v3.6.1. Comparison of the groups with the 2023, v3.6.1. Comparison of the groups with the 2023, v3.6.1. Compari

**Image Analysis**

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\[
\text{SigLC} = \frac{\text{mean over slices[SigLC]} \times 100}{\text{Sigref}}
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where SigLC is the mean signal intensity in the LC/LsC region, and Sigref is the mean signal intensity in the reference region. Thereafter, quality control was performed by visual inspection of the images. Images with significant artifacts were excluded from the analyses (Supporting Information Table S1). Thereafter, quality control was performed by visual inspection of the images. Images with significant artifacts were excluded from the analyses (Supporting Information Table S1).
clinical and demographic data was performed using Kruskal–Wallis test followed by post hoc Dunn’s test for pairwise comparisons, while \(\chi^2\) tests with Holm correction were used to assess differences in sex distribution. Multivariate linear regression was used to explore the association between the LC/LsC signal intensity of the HC and patient groups, while controlling for age and sex as covariates. The group effect was assessed using F test, and all pairwise comparisons among groups were conducted with post hoc Tukey’s tests from the emmeans R package (v1.4.5). Differences were considered significant at \(p < 0.05\).

Results

We analyzed HCs (\(n = 98\)) and patients (\(n = 305\)), including patients with iRBD (\(n = 47\)), PD with (\(n = 75\)) and without RBD (\(n = 142\)), PSP (\(n = 19\)), and MSA (\(n = 19, 14\) with the parkinsonian form [MSAp] and 5 with the cerebellar form [MSAc]) (Table 1). The participants showing both concomitant parkinsonian and cerebellar signs were included in the MSAp group. Twelve patients with MSA had RBD (63%) confirmed by video-polysomnography, and the RBD status of the remaining seven patients was unknown. Patients with PSP had no sign of RBD during interview.

Overall, age was different between groups (\(H = 30.40, 5\) degrees of freedom, \(P < 0.001\); Table 1). HCs were younger than patients with iRBD (\(P = 0.005\)) and PSP (\(P = 0.003\)). Participants with iRBD (\(P = 0.002\)) and PSP (\(P = 0.002\)) were older than patients with PD without RBD. The sex ratio differed between groups (\(\chi^2 = 21.63, P < 0.0001\)) because there were more men in iRBD compared with HC (\(P = 0.002\)), PSP (\(P = 0.01\)), and PD without RBD (\(P = 0.009\) groups).

Although when using a paired \(t\) test the LC/LsC signal intensity was significantly higher in the left side than in the right side (\(P < 0.001\)), we observed a strong linear correlation between the left and right sides (\(R^2 = 0.36, P < 0.001\)). Hence we used the average of left and right LC/LsC values. For MRI measurements, there was an overall group effect in LC/LsC signal intensity (\(F = 8.90, P < 0.001\); Table 1, Supporting Information Table S1). The LC/LsC signal intensity decreased linearly with age in all groups (no interaction effect between the groups and age).

Pairwise comparisons demonstrated that LC/LsC signal intensity was higher in HCs than in iRBD (\(P = 0.03\)), PSP (\(P = 0.04\)), MSA (\(P < 0.0001\)), and PD with RBD (\(P < 0.0001\) groups, but not PD without RBD group. The HCs had the highest and patients with MSA the lowest signal intensity. LC/LsC signal intensity was lower in MSA than iRBD (\(P = 0.02\)) and PD without RBD (\(P < 0.001\)). LC/LsC signal intensity was lower in MSA than iRBD (\(P < 0.001\)).

Discussion

Neuromelanin signal intensity in the LC/LsC was reduced in iRBD and in parkinsonian disorders as compared with HCs, except in patients with PD without RBD. In PD, our study confirmed that the LC/LsC neuromelanin signal is reduced in PD with RBD and not in PD without RBD.\(^{16}\) Histological studies have consistently reported loss of melanized neurons in this complex in PD.\(^{6}\) The signal intensity was also decreased in participants with iRBD.\(^{5,15,26}\)

Patients with MSA showed the largest neuromelanin signal reduction in the LC/LsC, greater than in PD with RBD and iRBD. Histological studies reported cell loss in the LC in most patients with MSA,\(^8\) whereas others did not show changes in this structure.\(^9,11\) Our results are in agreement with one previous MRI study,\(^16\) but not others that reported greater damage in PD than PSP and MSAp;\(^17\) equal damage in MSAp, MSAc, and PD;\(^19\); or even no difference between MSAp and HC.\(^20\) Differences between studies may be explained by differences in patient characteristics, particularly because the
presence of RBD in patients with PD was not recorded in these studies. In our study, at least 63% of patients with MSA had RBD (the RBD status was unknown in the remaining patients), which was in line with the frequent (70%–90%) occurrence of RBD reported in MSA. 

This suggests that the LsC was also affected in patients with MSA as in patients with PD with RBD. A previous study compared MSAc and MSAp and reported lower neuromelanin signal in the LC of MSAc patients, although the difference was not significant. Nonetheless, this point requires further investigation in larger groups of patients.

Neuromelanin signal in the LC/LsC was also reduced in PSP, in line with histological studies that reported severe changes in this area. The total number of noradrenergic and neuromelanin-containing cells in PSP correlated negatively with disease severity, with fewer cells in patients with more severe disease. In contrast with a diffusion-based MRI study, and histological studies, two previous studies using neuromelanin-sensitive MRI did not find signal changes in PSP compared with HC. Such disagreement may also come from differences in patient characteristics or methodology. Notably, patients with PSP rarely suffer from RBD (although they may present some degree of REM sleep without atonia) but have a major characteristic or methodology. Notably, patients with PSP rarely suffer from RBD (although they may present some degree of REM sleep without atonia) but have a major characteristic or methodology.

In summary, we found reduced neuromelanin signal intensity in the LC/LsC of patients with PD, MSA, and PSP. We confirmed that the signal changes in PD were associated with the presence of RBD. Our results suggested that the signal changes in MSA may also be associated with the presence of RBD.

**Author Contributions**

Conceived and designed the study, contributed analysis tools, performed the analyses, and wrote the manuscript: Rahul Gaurav. Performed the analyses and reviewed the manuscript: Alexis Nobileau, Romain Valabrègue, and François-Xavier Lejeune. Collected the data and reviewed the manuscript: Lydia Chougar, Alice Faucher, Graziella Mangone, Smaranda Leu-Semenescu, Jean-Christophe Corvol, Isabelle Arnulf, Marie Vidalhiet, David Grabi, and Bertrand Degos. Conceived and designed the study and wrote the manuscript: Stéphane Lehéricy.

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**Data Availability Statement**

Data available on reasonable request from the corresponding author.

**References**


The Genetic Etiology of Parkinson’s Disease Does Not Robustly Affect Subthalamic Physiology

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ABSTRACT: Background: It is unknown whether Parkinson’s disease (PD) genetic heterogeneity, leading to phenotypic and pathological variability, is also associated with variability in the unique PD electrophysiological signature. Such variability might have practical implications for adaptive deep brain stimulation (DBS).

Objective: The aim of our work was to study the electrophysiological activity in the subthalamic nucleus (STN) of patients with PD with pathogenic variants in different disease-causing genes.

Methods: Electrophysiological data from participants with negative genetic tests were compared with those from GBA, LRRK2, and PRKN-PD.

Results: We analyzed data from 93 STN trajectories (GBA-PD: 28, LRRK2-PD: 22, PARK-PD: 10, idiopathic PD: 33) of 52 individuals who underwent DBS surgery. Characteristics of β oscillatory activity in the dorsolateral motor part of the STN were similar for patients with negative genetic tests and those from different disease-causing genes.

Supporting Data

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