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

Alexis Nobileau, Rahul Gaurav, Lydia Chougar, Alice Faucher, Romain Valabrègue, Graziella Mangone, Smaranda Leu-Semenescu, François-xavier Lejeune, Jean-christophe Corvol, Isabelle Arnulf, et al.

13. Ashburner J, Friston KJ. Unified segmentation. Neuroimage 2005;26(3):839–851. https://doi.org/10.1016/j.neuroimage.2005.02.018
14. Rajapakse JC, Giedd JN, Rapoport JL. Statistical approach to segmentation of single-channel cerebral MR images. IEEE Trans Med Imaging 1997;16(2):176–186. https://doi.org/10.1109/42.563663
15. Manjón JV, Coupé P, Martí-Bonmatí L, Collins DL, Robles M. Adaptive non-local means denoising of MR images with spatially varying noise levels. J Magn Reson Imaging 2010;31(1):192–203. https://doi.org/10.1002/jmri.22003
16. Lorio S, Fresard S, Adaszewski S, et al. New tissue priors for improved automated classification of subcortical brain structures on MRI. Neuroimage 2016;130:157–166. https://doi.org/10.1016/j.neuroimage.2016.01.062
17. Tohka J, Zijdenbos A, Evans A. Fast and robust parameter estimation for statistical partial volume models in brain MRI. Neuroimage 2004;23(1):84–97. https://doi.org/10.1016/j.neuroimage.2004.05.007
18. Ashburner J. A fast diffeomorphic image registration algorithm. Neuroimage 2007;38(1):95–113. https://doi.org/10.1016/j.neuroimage.2007.07.007
19. Ashburner J, Friston KJ. Diffeomorphic registration using geodesic shooting and Gauss-Newton optimisation. Neuroimage 2011;55(3):954–967. https://doi.org/10.1016/j.neuroimage.2010.12.049
20. Zaborszky L, Hoemke L, Mohlberg H, Schleicher A, Amunts K, Zilles K. Stereotaxic probabilistic maps of the magnocellular cell groups in human basal forebrain. Neuroimage 2008;42(3):1127–1141. https://doi.org/10.1016/j.neuroimage.2008.05.055
21. Eickhoff SB, Stephan KE, Mohlberg H, et al. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage 2005;25(4):1325–1335. https://doi.org/10.1016/j.neuroimage.2004.12.034
22. Gersel Stokholm M, Iranzo A, Østergaard K, et al. Cholinergic denervation in patients with idiopathic rapid eye movement sleep behaviour disorder. Eur J Neurol 2020;27(4):644–652. https://doi.org/10.1111/ene.14127
23. Kotagal V, Albin RL, Müller MLTM, et al. Symptoms of rapid eye movement sleep behavior disorder are associated with cholinergic denervation in Parkinson disease. Ann Neurol 2012;71(4):560–568. https://doi.org/10.1002/ana.22691
24. Hanyu H, Inoue Y, Sakurai H, et al. Voxel-based magnetic resonance imaging study of structural brain changes in patients with idiopathic REM sleep behavior disorder. Parkinsonism Relat Disord 2012;18(2):136–139. https://doi.org/10.1016/j.parkreldis.2011.08.023
25. Pereira JB, Hall S, Jalakas M, et al. Longitudinal degeneration of the basal forebrain predicts subsequent dementia in Parkinson's disease. Neurobiol Dis 2020;139:104831. https://doi.org/10.1016/j.nbd.2020.104831
26. Rémillard-Pelchat D, Rahayel S, Gaubert M, et al. Comprehensive analysis of brain volume in REM sleep behavior disorder with mild cognitive impairment. JPD 2022;12(1):229–241. https://doi.org/10.3233/JPD-212691
27. Massicotte-Marquez J, Décary A, Gagnon JF, et al. Executive dysfunction and memory impairment in idiopathic REM sleep behavior disorder. Neurology 2008;70(15):1250–1257. https://doi.org/10.1212/01.wnl.0000286943.79593.a6
28. Solari N, Hangya B. Cholinergic modulation of spatial learning, memory and navigation. Eur J Neurosci 2018;48(5):2199–2230. https://doi.org/10.1111/ejn.14089
29. Newman EL, Gupta K, Climer JR, Monaghan CK, Hasselmo ME. Cholinergic modulation of cognitive processing: insights drawn from computational models. Front Behav Neurosci 2012;6:24. https://doi.org/10.3389/fnbeh.2012.00024

Supporting Data

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

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

Alexis Nobileau, MD,[1,2,3†] Rahul Gaurav, MS, PhD,[1,2,4†*] Lydia Chougar, MD,[1,2,3,4] Alice Faucher, MD,[5,6] Romain Valabrègue, PhD,[1,2] Graziella Mangone, MD, PhD,[1,7] Smaranda Leu-Semenescu, MD,[8] François-Xavier Lejeune, PhD,[1] Jean-Christophe Corvol, MD, PhD,[1,7] Isabelle Arnulf, MD, PhD,[1,4,8] Marie Vidailhet, MD,[1,4,9] David Grabli, MD, PhD,[1,9] Bertrand Degos, MD, PhD,[5,6] and Stéphane Lehéricy, MD, PhD[1,2,3,4]

[1]*Paris Brain Institute (ICM), Sorbonne Université, INSERM U1127, CNRS 7225, Pitié-Salpêtrière Hospital, Paris, France* [2]*ICM, Center for NeuroImaging Research, Paris, France* [3]*Department de Neuroradiology, Assistance Publique Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, Paris, France* [4]*ICM, Team "Movement Investigations and Therapeutics" (MOV'IT), Paris, France* [5]*Dynamics and Pathophysiology of Neuronal Networks Team, Center for Interdisciplinary Research in Biology, Collège de France, CNRS UMR7241/INSERM U1050, Université PSL, Paris, France* [6]*Service de Neurologie, Hôpital Avicenne, Hôpitaux Universitaires de Paris-Seine Saint Denis, Sorbonne Paris Nord, Bobigny, France* [7]*Department de Neurology, Centre d'Investigation Clinique Neurosciences, Assistance Publique Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, Paris, France* [8]*Sleep Disorder Unit, Assistance*

*__Correspondence to:__ Dr. Rahul Gaurav, Centre de NeuroImagerie de Recherche, Institut du Cerveau, Hôpital Pitié-Salpêtrière, 47 Boulevard de l'Hôpital, 75013 Paris, France; E-mail: rahul.gaurav@icm-institute.org

†Rahul Gaurav and Alexis Nobileau contributed equally to this article.

Relevant conflicts of interest/financial disclosures: R.G. and S.L. received grant funding from Biogen Inc. USA. A.N., L.C., A.F., R.V., G.M., F.-X.L., M.V., and D.G. have nothing to report. S.L.-S. received funds for travel to conferences by UCB Pharma. J.-C.C. has served in advisory boards for Air Liquide, Biogen Inc., Denali, Ever Pharma, Idorsia, Prevail Therapeutic, Theranexus, and UCB and has received grants from Sanofi and The Michael J. Fox Foundation. I.A. received honoraria from Idorsia Pharma and speaking engagement from UCB Pharma, unrelated to this study. B.D. received honoraria from Ipsen and travel funding from Orkyn, unrelated to this study.
Full financial disclosures and author roles may be found in the online version of this article.

Received: 6 July 2022; **Revised:** 16 November 2022; **Accepted:** 21 November 2022

Published online 2 January 2023 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29309

Publique Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, Paris, France
[9]*Department de Neurology, Assistance Publique Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, Paris, France*

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

Introduction

The locus coeruleus/subcoeruleus complex (LC/LsC) is a small pontine bilateral heterogeneous structure.[1,2] 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.[3,4] 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).[5] Histological studies have shown that the LC/LsC degenerates in parkinsonian syndromes, including Parkinson's disease (PD),[6,7] as well as atypical parkinsonism, including multiple system atrophy (MSA)[8-11] and progressive supranuclear palsy (PSP).[1,12] Because neurons in the LC/LsC are melanized, this structure can be imaged using neuromelanin-sensitive magnetic resonance imaging (MRI).[13,14] Various MRI studies have demonstrated that the LC/LsC signal decreases in isolated RBD (iRBD, a prodromal form of parkinsonism)[5,15] and in PD with RBD.[16] Studies also reported a reduction in neuromelanin signal of the LC/LsC in MSA[17-19] and PSP.[17,19] However, results were discordant with respect to the severity of damage between various parkinsonian syndromes.[17-20] Disagreement may come from insufficient power in studies, including reduced number of participants,[17,18] methodology (quantitative vs. visual analysis),[20] 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.

Subjects and Methods

Subjects

All subjects were recruited in three prospective research studies at the Paris Brain institute (Iceberg and Nucleipark studies) and the Pitié-Salpêtrière hospital (Parkatypique study) by movement disorders and sleep experts. Participants were diagnosed according to international diagnostic criteria as iRBD,[21] PD,[22] PSP with Richardson's syndrome,[23] or MSA[24] 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.[25] Disease duration was calculated using the date of diagnosis as the starting point. The presence of RBD was defined by international diagnostic criteria[21] after an

TABLE 1 *Demographic and clinical characteristics and LC/LsC signal intensity*

Status	HC	PD			MSA		
		iRBD	PDRBD−	PDRBD+	PSP	Total	MSAp	MSAc
Subjects, n	98	47	142	75	19	19	14	5
Age, y	61.6 ± 8.7	67.2 ± 5.1	61.3 ± 10.0	64.9 ± 8.2	70.9 ± 8.0	61.4 ± 7.9	62.7 ± 8.5	57.6 ± 5.1
Sex (M/F), n	51/47	41/6	85/57	54/21	10/12	12/5	8/6	4/1
Disease duration, y	NA	NA	5.4 ± 2.4	6.6 ± 3.3	4.9 ± 3.1	3.6 ± 1.7	4.0 ± 1.7	2.4 ± 1.5
MDS-UPDRS Part III OFF	5.5 ± 5.1	11.5 ± 6.2	29.4 ± 7.9	30.8 ± 7.9	NA	NA	NA	NA
UPDRS Part III OFF	0.4 ± 0.8	NA	22.5 ± 9.2	30.0 ± 10.8	33.1 ± 16.9	22.2 ± 10.8	27.0 ± 13.1	17.3 ± 7.2
H&Y stage	0.1 ± 0.5	0.7 ± 0.9	2.0 ± 0.3	2.1 ± 0.5	NA	NA	NA	NA
LC/LsC signal intensity	127.5 ± 5.3[a,b,c,d]	124.2 ± 3.9★[d,e]	126.0 ± 4.7[b,c,d]	123.4 ± 4.6★[e,f]	123.0 ± 3.0★[e]	120.6 ± 4.2[a,e,f]	120.9 ± 4.1	119.7 ± 4.7

Demographic and clinical characteristics were compared using Kruskal–Wallis test followed by post hoc Dunn's test for pairwise comparisons, while χ^2 tests with Holm's correction were used to assess differences in sex distribution. Data are represented as mean ± standard deviation.★$P < 0.01$. [a]Significant differences vs. iRBD. [b]Significant differences vs. PDRBD+. [c]Significant differences vs. PSP. [d]Significant differences vs. MSA. [e]Significant differences vs. HC. [f]Significant differences vs. PDRBD−.

Abbreviations: LC/LsC, locus coeruleus/subcoeruleus complex; HC, healthy control subject; iRBD, isolated rapid eye movement sleep behavior disorder; PD, Parkinson's disease; PDRBD−, Parkinson's disease without rapid eye movement sleep behavior disorder; PDRBD+, 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 stage, Hoehn and Yahr stage.

interview of participants or their bed partners conducted by neurologists (for all groups) and after video-polysomnography (for all groups, except PSP patients and seven patients with MSA). The percentage of REM sleep without atonia was calculated from the polysomnographic recordings for PD and iRBD in the Iceberg cohort.[5]

MRI Data Acquisition

All subjects were scanned at 3 T using whole-brain three-dimensional T1-weighted imaging and axial turbo spin-echo two-dimensional T1-weighted neuromelanin-sensitive imaging with a field of view restricted to midbrain (Nucleipark: 3-T Siemens TRIO 32-channel TIM system, 12-channel head coil; Iceberg: 3-T Siemens PRISMA scanner, 64-channel head coil; Parkatypique: 3-T Siemens SKYRA, 64-channel head coil) (Supporting Information Table S1).

Image Analysis

Image analysis was performed blindly to the clinical status of the participants using our in-house automated software as described previously.[16] In brief, data analysis included several steps: (1) a priori definition of three anatomical regions of interest in the International Consortium for Brain Mapping templates (two bilateral regions of 700 mm^3 in the pons containing the LC/LsC and one reference region of 6200 mm^3 in the rostral pontomesencephalic area for standardization of the signal intensity); (2) resampling these regions onto the neuromelanin-sensitive T1-weighted images with rigid and nonlinear transformations; (3) automated extraction of the 10 connected voxels with the brightest intensities in each of the two locus regions as representative of the LC/LsC; (4) calculation of the ratio between the average signal intensity of these 10 voxels and the average signal intensity in the reference region using the following formula:

$$\text{LC/LsC signal intensity} = \text{mean\_over\_slices}[\text{Sig}_{\text{LC}}/\text{Sig}_{\text{ref}}] \times 100$$

where Sig_{LC} is the mean signal intensity in the LC/LsC region, and Sig_{ref} is the mean signal intensity in the reference region; and (5) averaging ratios of both sides to obtain the final signal intensity value of the LC/LsC.

Thereafter, quality control was performed by visual inspection after processing. The images with significant motion artifacts or image distortions 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

clinical and demographic data was performed using Kruskal–Wallis test followed by post hoc Dunn's test for pairwise comparisons, while χ^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 PD with than without RBD ($P = 0.02$). In the PD group, LC/LsC signal decreased as REM sleep without atonia increased ($R = -0.176$, $P = 0.04$). There was no difference between MSAp and MSAc or between the other groups (Figure 1).

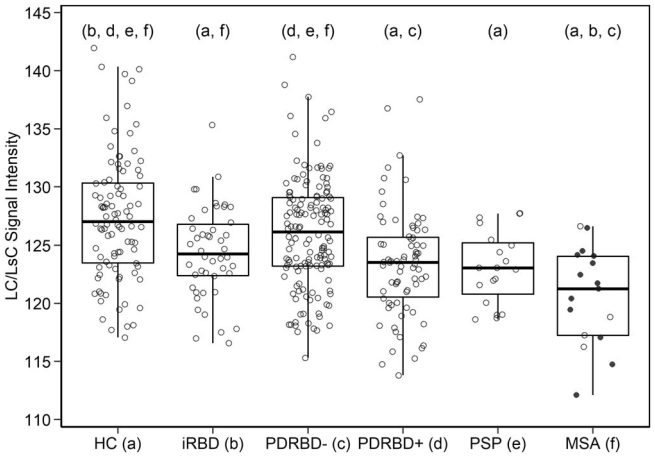

FIG. 1. Box plots of locus coeruleus/subcoeruleus complex (LC/LsC) signal intensity. HC, healthy control subject; iRBD, isolated rapid eye movement sleep behavior disorder; MSA, multiple system atrophy; PDRBD−, Parkinson's disease without rapid eye movement sleep behavior disorder; PDRBD+, Parkinson's disease with rapid eye movement sleep behavior disorder; PSP, progressive supranuclear palsy.

Overall, there was no scanner effect detected with no significant difference in imaging measurements between HC cohort groups ($P = 0.66$).

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,[18] 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.[27-29] 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.[18,19] 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.[1,12] 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.[1] In contrast with a diffusion-based MRI study[30] and histological studies,[1,12] two previous studies using neuromelanin-sensitive MRI did not find signal changes in PSP compared with HC.[17,19] 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 decrease in REM sleep time (because REM sleep executive systems are also located in the LsC).[31,32]

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 Vidailhet, David Grabli, and Bertrand Degos. Conceived and designed the study and wrote the manuscript: Stéphane Lehéricy.

Acknowledgments: This work was supported by grants from ERA PerMed EU-wide project DIGIPD (01KU2110), DHOS-Inserm, France Parkinson, Ecole des NeuroSciences de Paris (ENP), Fondation pour la Recherche Médicale (FRM), and BIOGEN Inc. This work was also supported by grants from the Investissements d'Avenir, IAIHU-06 (Paris Institute of Neurosciences—IHU), ANR-11-INBS-0006, Fondation d'Entreprise EDF, the Fondation Thérèse and René Planiol pour l'étude du Cerveau, Fondation Saint-Michel, and Biogen Inc. USA. We thank Energipole (M. Mallart), M. Villain, and Société Française de Médecine Esthétique (M. Legrand) for unrestricted support for Research on Parkinson's disease. We also thank all of the participants involved in the study, who have helped to make this research possible.

Data Availability Statement

Data available on reasonable request from the corresponding author.

References

1. Kaalund SS, Passamonti L, Allinson KSJ, et al. Locus coeruleus pathology in progressive supranuclear palsy, and its relation to disease severity. Acta Neuropathol Commun 2020;8(1):1–11. https://doi.org/10.1186/s40478-020-0886-0
2. Baker KG, Törk I, Hornung JP, Halasz P. The human locus coeruleus complex: an immunohistochemical and three dimensional reconstruction study. Exp Brain Res 1989;77(2):257–270. https://doi.org/10.1007/BF00274983
3. Benarroch EE. The locus ceruleus norepinephrine system. Neurology 2009;73(20):1699–1704. https://doi.org/10.1212/WNL.0b013e3181c2937c
4. Betts MJ, Kirilina E, Otaduy MCG, et al. Locus coeruleus imaging as a biomarker for noradrenergic dysfunction in neurodegenerative diseases. Brain 2019;142(9):2558–2571. https://doi.org/10.1093/brain/awz193
5. Ehrminger M, Latimier A, Pyatigorskaya N, et al. The coeruleus/subcoeruleus complex in idiopathic rapid eye movement sleep behaviour disorder. Brain 2016;139(4):1180–1188. https://doi.org/10.1093/brain/aww006
6. German DC, Manaye KF, White CL, et al. Disease-specific patterns of locus coeruleus cell loss. Ann Neurol 1992;32(5):667–676. https://doi.org/10.1002/ana.410320510
7. Braak H, Del Tredici K, Rüb U, De Vos RAI, Jansen Steur ENH, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003;24(2):197–211. https://doi.org/10.1016/S0197-4580(02)00065-9
8. Rajput AH, Kazi KH, Rozdilsky B. Striatonigral degeneration response to levodopa therapy. Lancet 1972;300(7779):707. https://doi.org/10.1016/S0140-6736(72)92109-5
9. Bannister R, Gibson W, Michaels L, Oppenheimer DR. Laryngeal abductor paralysis in multiple system atrophy: a report on three necropsied cases, with observations on the laryngeal muscles and the nuclei ambigui. Brain 1981;104(2):351–368. https://doi.org/10.1093/brain/104.2.351
10. Jellinger K, Danielczyk W. Striato-nigrale Degeneration. Acta Neuropathol 1968;257:242–257.
11. Jellinger KA. Recent developments in the pathology of Parkinson's disease. J Neural Transm Suppl 2002;62:347–376. https://doi.org/10.1007/978-3-7091-6139-5_33
12. Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy: a heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia. Semin Neurol 2014;34(2):129–150. https://doi.org/10.1055/s-0034-1377058
13. Sasaki M, Shibata E, Tohyama K, et al. Neuromelanin magnetic resonance imaging of locus ceruleus and substantia nigra in Parkinson's disease. Neuroreport 2006;17(11):1215–1218. https://doi.org/10.1097/01.wnr.0000227984.84927.a7
14. Sulzer D, Cassidy C, Horga G, et al. Neuromelanin detection by magnetic resonance imaging (MRI) and its promise as a biomarker for Parkinson's disease. npj Park Dis 2018;4(1):11. https://doi.org/10.1038/s41531-018-0047-3
15. Knudsen K, Fedorova TD, Hansen AK, et al. In-vivo staging of pathology in REM sleep behaviour disorder: a multimodality imaging case-control study. Lancet Neurol 2018;17(7):618–628. https://doi.org/10.1016/S1474-4422(18)30162-5

16. García-Lorenzo D, Longo-Dos Santos C, Ewenczyk C, et al. The coeruleus/subcoeruleus complex in rapid eye movement sleep behaviour disorders in Parkinson's disease. Brain 2013;136(7):2120–2129. https://doi.org/10.1093/brain/awt152

17. Ohtsuka C, Sasaki M, Konno K, et al. Differentiation of early-stage parkinsonisms using neuromelanin-sensitive magnetic resonance imaging. Park Relat Disord 2014;20(7):755–760. https://doi.org/10.1016/j.parkreldis.2014.04.005

18. Matsuura K, Maeda M, Yata K, et al. Neuromelanin magnetic resonance imaging in Parkinson's disease and multiple system atrophy. Eur Neurol 2013;70(1–2):70–77. https://doi.org/10.1159/000350291

19. Matsuura K, Ii Y, Maeda M, et al. Neuromelanin-sensitive magnetic resonance imaging in disease differentiation for parkinsonism or neurodegenerative disease affecting the basal ganglia. Park Relat Disord. 2021;87(4):75–81. https://doi.org/10.1016/j.parkreldis.2021.05.002

20. Simões RM, Castro Caldas A, Grilo J, et al. A distinct neuromelanin magnetic resonance imaging pattern in parkinsonian multiple system atrophy. BMC Neurol 2020;20(1):1–12. https://doi.org/10.1186/s12883-020-02007-5

21. American Academy of Sleep Medicine. The International Classification of Sleep Disorders:(ICSD-3). Darien: American Academy of Sleep Medicine; 2014.

22. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015;30(12):1591–1601. https://doi.org/10.1002/mds.26424

23. Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology 1996;47(1):1–9. https://doi.org/10.1212/wnl.47.1.1

24. Wenning SGGK, Low PA, Brooks DJ, et al. Second consensus statement on the diagnosis of multiple system atrophy. J Auton Nerv Syst 2008;74(2–3):189–192. https://doi.org/10.1055/s-0028-1086654

25. Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. Neurology 1967;17(5):427–442.

26. Horsager J, Andersen KB, Knudsen K, et al. Brain-first vs. body-first Parkinson's disease – a multi-modal imaging case-control study. Brain 2020;143(10):1–25.

27. Rekik S, Martin F, Dodet P, et al. Stridor combined with other sleep breathing disorders in multiple system atrophy: a tailored treatment? Sleep Med 2018;42:53–60. https://doi.org/10.1016/J.SLEEP.2017.12.008

28. Plazzi G, Corsini R, Provini F, et al. REM sleep behavior disorders in multiple system atrophy. Neurology 1997;48(4):1094–1097. https://doi.org/10.1212/wnl.48.4.1094

29. Wu D, Su W, Li S, et al. A questionnaire-based study on clinical REM sleep behavior disorder and subtypes in multiple system atrophy. Eur Neurol 2021;84(5):368–374. https://doi.org/10.1159/000517149

30. Pyatigorskaya N, Yahia-Cherif L, Gaurav R, et al. Multimodal magnetic resonance imaging quantification of brain changes in progressive supranuclear palsy. Mov Disord 2020;35(1):161–170. https://doi.org/10.1002/mds.27877

31. Luppi PH, Clément O, Valencia Garcia S, Brischoux F, Fort P. New aspects in the pathophysiology of rapid eye movement sleep behavior disorder: the potential role of glutamate, gamma-aminobutyric acid, and glycine. Sleep Med 2013;14(8):714–718. https://doi.org/10.1016/j.sleep.2013.02.004

32. Arnulf I, Merino-Andreu M, et al. REM sleep behavior disorder and REM sleep without atonia in patients with progressive supranuclear palsy. Sleep 2005;28(3):349–354. http://www.ncbi.nlm.nih.gov/pubmed/16173657

Supporting Data

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

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

Caroline Weill, MD,[1,2*] Akiva Gallant, BMedSc,[1,2] Halen Baker Erdman, MSc,[3] Muneer Abu Snineh, MD,[1,2] Eduard Linetsky, MD,[1,2] Hagai Bergman, MD, PhD,[3,4,5] Zvi Israel, BSc MBBS,[2,5] and David Arkadir, MD, PhD[1,2]

[1]*Department of Neurology, Hadassah Medical Center, Jerusalem, Israel* [2]*Faculty of Medicine, The Hebrew University, Jerusalem, Israel* [3]*The Edmond and Lily Safra Center for Brain Sciences, The Hebrew University, Jerusalem, Israel* [4]*Department of Medical Neurobiology, Institute of Medical Research Israel-Canada, The Hebrew University-Hadassah Medical School, Jerusalem, Israel* [5]*Department of Neurosurgery, Hadassah Medical Center, Jerusalem, Israel*

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

***Correspondence to:** Dr. Caroline Weill, Department of Neurology, Hadassah Medical Center, POB 12000, Jerusalem 91120, Israel; E-mail: caroline@hadassah.org.il

Caroline Weill, Akiva Gallant, and Halen Baker Erdman contributed equally to this work.

Relevant conflicts of interest/financial disclosures: Nothing to report.

Received: 4 September 2022; **Revised:** 13 November 2022; **Accepted:** 5 December 2022

Published online 9 January 2023 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29310