

# Texture features of magnetic resonance images

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## RESEARCH ARTICLE

# Texture Features of Magnetic Resonance Images: A Marker of Slight Cognitive Deficits in Parkinson's Disease

Nacim Betrouni, PhD,<sup>1\*</sup>  Renaud Lopes, PhD,<sup>1</sup> Luc Defebvre, MD, PhD,<sup>1,2</sup> Albert F.G. Leentjens, MD, PhD,<sup>3</sup> and Kathy Dujardin, PhD<sup>1,2</sup> 

<sup>1</sup>Université de Lille, Institut National de la Santé et de la Recherche Médicale (INSERM), Centre Hospitalier Universitaire de Lille (CHU Lille), Degenerative & Vascular Cognitive Disorders, Lille, France

<sup>2</sup>Neurology and Movement Disorders Department, CHU Lille, Lille, France

<sup>3</sup>Department of Psychiatry, Maastricht University Medical Center, Maastricht, The Netherlands

**ABSTRACT: Background:** Cognitive impairment is a frequent nonmotor symptom of Parkinson's disease. Depending on severity, patients are considered to have mild cognitive impairment or dementia. However, among the cognitively intact patients, some may have deficits in a less severe range. The early detection of such subtle symptoms may be important for the initiation of care strategies.

**Objective:** To identify imaging markers of early cognitive symptoms, potentially before usual signs, such as atrophy, become manifest.

**Methods:** A total of 102 patients with Parkinson's disease and 17 age-matched cognitively intact healthy controls underwent extensive neuropsychological assessment and T1-weighted magnetic resonance imaging. Parkinson's disease patients were separated into 3 groups according to their cognitive status: intact, with slight slowing, and with mild deficits in executive functions. Texture features as measured by first-order and second-order statistics were computed in the following 6 brain regions: the hippocampus, thalamus, amygdala, putamen, caudate nucleus,

and pallidum. They were tested between the groups, and their correlation with cognition was examined. Volumetric measurements were made for comparison.

**Results:** Texture analysis showed significant between-group differences for 2 features—skewness and entropy in the hippocampus, the thalamus, and the amygdala—and the volume analysis revealed no between-group difference. These features were significantly correlated with cognitive performance.

**Conclusion:** These results support the assumption that signal alterations associated with Parkinson's disease-related cognitive decline can be captured very early by texture analysis. As these changes appear to reflect clinical phenomena, texture analysis may be a promising marker for helping cognitive phenotyping in Parkinson's disease. © 2019 International Parkinson and Movement Disorder Society

**Key Words:** cognitive deficits; magnetic resonance imaging (MRI); Parkinson's disease; texture analysis

Cognitive deficits are frequent nonmotor symptoms of Parkinson's disease (PD). The percentage of patients meeting the criteria for mild cognitive impairment (MCI) ranges from 20.3% to 60.5%.<sup>1-6</sup> The prevalence of cognitive deficits as well as the risk of dementia increases with age, disease duration and motor symptom severity.<sup>7</sup>

\*Correspondence to: Dr. Nacim Betrouni, INSERM U1171, Laboratoire de Pharmacologie, Faculté de Médecine 1, Place de Verdun, 59000 Lille, France; E-mail: nacim.betrouni@inserm.fr

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The usual categorization of PD patients as those without cognitive impairment, those with MCI, and those with dementia does not allow identification of cognitive phenotypes with less severe cognitive deficits that do not meet the criteria of PD-MCI. However, the early detection of such subtle cognitive alterations may be an important step for the initiation of care strategies such as cognitive stimulation. Nevertheless, this will be particularly challenging because cognitive profiles in PD are heterogeneous.<sup>8,9</sup>

Typically, cognitive profiling is based on extensive neuropsychological assessment that is time consuming and not always easily available in routine clinical practice. Moreover, cognitive performance may be influenced by a large number of noncognitive factors such as motor

fluctuations, medication, and other nonmotor symptoms including pain, depression, apathy, and anxiety. The quality of the normative data to which patient performance is compared also plays a role in the detection of cognitive impairment.<sup>10</sup> Hence, additional markers of cognitive deficits may be useful. In clinical practice, magnetic resonance imaging (MRI) is still of marginal interest for predicting the prognosis of cognitive performance in PD patients, even though several structural and functional alterations have been reported in PD patients with cognitive decline when compared with those without cognitive symptoms.<sup>11,12</sup> The severity of cognitive decline in PD is correlated with reduced gray matter volume in several cortical areas<sup>13</sup> as well as with reduced gray matter volume of structures such as the hippocampus and amygdala.<sup>14,15</sup> However, atrophy of these structures is not detectable at the prodromal or early phases of cognitive impairment.

If we assume that cognitive decline and the related neuronal changes in specific brain regions may disturb the measured signal in these regions, gray-level distribution in the MRI images would thus be affected. Texture features measured on these images may be able to identify imaging markers of these alterations, potentially even before the atrophy becomes manifest.<sup>16</sup> Indeed, texture analysis allows quantifying the gray levels inside an image by the measurement of spatial relationships through different quantitative values. It is a well-known method of image processing widely used in different fields, specifically in medical imaging. In PD, very few studies have investigated this technique. The concept was studied with dopamine transporter single-photon emission computed tomography imaging<sup>17</sup> and was shown to improve the prediction of clinical, motor, and cognitive outcomes. Recently, Li and colleagues<sup>18</sup> applied the technique on MRI of the substantia nigra and reported that the measured features were able to discriminate PD patients from healthy controls.

The aim of the present study was to investigate if texture analysis is sensitive enough to identify early imaging markers of subtle cognitive alterations in patients with PD.

## Methods

### Participants and Data

Data were collected from PD patients and healthy controls. All patients met the United Kingdom Brain Bank diagnostic criteria for PD.<sup>19</sup> Patients with moderate and severe dementia (defined as a score >1 on the Clinical Dementia Rating scale<sup>20</sup> and meeting the Movement Disorders criteria for PD patients with dementia<sup>21</sup>), patients older than 80 years, and patients with neurodegenerative disorders other than PD were excluded. Patients treated with deep brain stimulation or those meeting contraindications for MRI were excluded. All patients received

stable doses of antiparkinsonian medication and were tested in their *on* drug state.

The PD patient data came from a previous study involving 2 independent centers in Lille, France, and Maastricht, The Netherlands (ClinicalTrials.gov identifier NCT01792843).<sup>22</sup> The study included 156 patients and aimed to confirm cognitive disorders classification in PD using a cluster analysis of the results of neuropsychological tests. The initial classification, proposed by Dujardin and colleagues<sup>23</sup> highlighted a clinically relevant 5-cluster model characterizing the patients. All patients underwent a neurological examination and an extensive neuropsychological test battery. The Movement Disorder Society–Unified Parkinson's Disease Rating Scale (sections I–IV) was used to measure the severity and experiences of nonmotor and motor symptoms, and the Hoehn and Yahr staging scale was used to measure disease stage.<sup>24</sup> The severity of depression, anxiety, and apathy was assessed by the score at the 17-item Hamilton Depression Rating Scale,<sup>25</sup> the Parkinson Anxiety Scale,<sup>26</sup> and the Lille Apathy Rating Scale,<sup>22</sup> respectively.

The neuropsychological test battery included the Mattis Dementia Rating Scale for global cognition and tests assessing 5 cognitive domains (attention and working memory, executive functions, verbal episodic memory, language and visuospatial functions). Details of the procedure are described Dujardin and colleagues.<sup>27</sup> A K-means cluster analysis conducted on 19 variables derived from the neuropsychological tests confirmed the 5-cluster classification obtained previously. For the current study, as the aim was to investigate MRI markers of subtle cognitive alteration, only the 3 first groups were considered: cognitively intact patients (PDCN); cognitively intact patients with slight cognitive slowing (PDCN-S); and patients showing mild cognitive deficits, particularly in executive functioning (PD-EXE). A total of 102 (Lille,  $n = 52$ ; Maastricht,  $n = 50$ ) patients corresponded to this classification.

Lastly, a group of 17 healthy controls (CTRL) matched according to age and education with the patients was included. They had no history of neurological or psychiatric disorders and no contraindication for the MRI. Participants with a score on the Mini-Mental State Examination <26 were excluded. Their demographic data were recorded, and they underwent the same neuropsychological assessments as the patients.

The demographic and clinical characteristics of the patient and control groups are described in Table 1.

### Anatomical Structures and Texture Features

For all the participants, MRI images were acquired on a 3T whole-body scanner (Achieva TX; Philips Healthcare, Best, the Netherlands) using an 8-channel sensitivity encoding (SENSE) head coil. High-resolution 3-dimensional (3D) T1-weighted images were acquired in

**TABLE 1.** Demographic and clinical characteristics of the participants included in the study

	CTRL, n = 17	PDCN, n = 30	PDCN-S, n = 29	PD-EXE, n = 43	P value	Post hoc tests
Age, y	62.76 ± 4.19	60.18 ± 8.51	65.23 ± 5.11	66.65 ± 7.91	0.001	PDCN ≠ PD-EXE
Sex, F/M	7/10	10/20	9/20	16/27	–	
Education, y	13.76 ± 1.92	13.26 ± 3.4	13.41 ± 4.17	11.63 ± 3.59	0.02	PDCN ≠ PD-EXE
Disease duration, y	–	7.7 ± 5.20	8.69 ± 7.87	8.81 ± 5.02	0.46	
Hoehn & Yahr stage	–	1.92 ± 0.39	2.19 ± 0.54	2.21 ± 0.59	0.03	
MDS_UPDRS3 score	–	26.02 ± 11.70	29.31 ± 12.39	28.74 ± 11.44	0.38	
LEDD, mg/day	–	702.4 ± 648.7	800.15 ± 635.80	907.57 ± 573.59	0.15	
Hamilton Depression Rating Scale	1.12 ± 1.45	5.20 ± 4.20	5.34 ± 4.98	6.05 ± 4.25	<0.0001	PDCN ≠ CTRLPDCN-S ≠ CTRLPD-EXE ≠ CTRL
Lille Apathy Rating Scale	–28.35 ± 4.47	–26.78 ± 5.56	–26.80 ± 6.22	–22.60 ± 7.15	0.001	PDCN ≠ PD-EXEPDCN-S ≠ PD-EXECTRL ≠ PD-EXE
Parkinson Anxiety Scale (score of persistent anxiety)	1.35 ± 2.06	3.03 ± 3.65	4.50 ± 4.13	5.45 ± 5.08	0.001	PDCN-S ≠ CTRLPD-EXE ≠ CTRL
Mattis DRS (score on 144)	142.06 ± 1.71	140.95 ± 3.01	140.24 ± 2.85	134.30 ± 5.39	<0.0001	PDCN ≠ PD-EXEPDCN-S ≠ CTRLPD-EXE ≠ CTRL
SDMT, N	47.06 ± 5.39	55.37 ± 8.25	43.64 ± 3.5	32.87 ± 6.48	<0.0001	PDCN ≠ PDCN-SPDCN-S ≠ PD-EXEPDCN-S ≠ PD-EXEPD-EXE ≠ CTRL

N refers to the number of items correctly coded in 90 seconds. P value measured using the Kruskal-Wallis test and post hoc tests done using the Dunn test with Bonferroni correction.  
 CTRL, healthy controls; PDCN, cognitively intact; PDCN-S, cognitively intact with slowing; PD-EXE, mild cognitive deficits, particularly in executive functioning; F, female; M, male; MDS\_UPDRS3, Movement Disorders Society–Unified Parkinson’s Disease Rating Scale–part III (severity of motor symptoms); LEDD, levodopa equivalent daily dose; Mattis DRS, Mattis Dementia Rating Scale; SDMT, Symbol digit modalities test.

the sagittal plane with 256 × 256 matrix and 1 mm<sup>3</sup> isotropic voxel size. Visual inspection was done, and images with high movement peaks or large motion artefacts were excluded.

Different deep gray matter structures as well as cortical regions have been reported to show atrophy in PD patients with cognitive impairment.<sup>13-15</sup> Therefore, we considered and investigated changes in the following structures: the thalamus, the hippocampus, the putamen, the pallidum, the caudate nucleus, and the amygdala. The need for a specific parcellation and the complex morphology of the cortex were considered as limits for the texture analysis, and consequently the cortical areas were not included in the study.

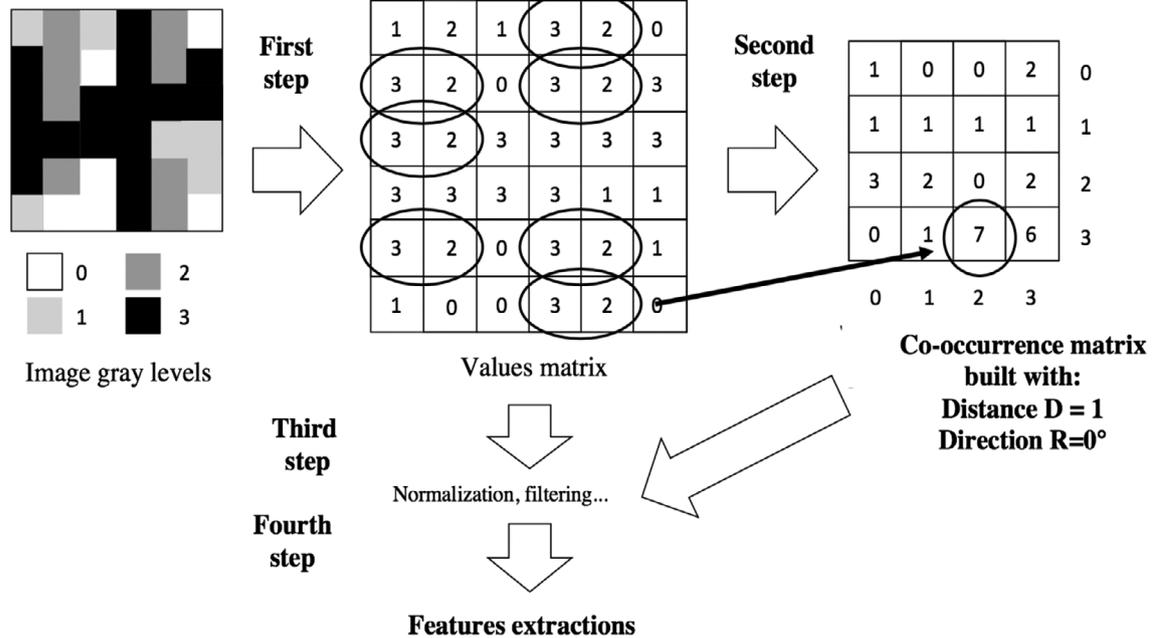
After segmentation using the automatic Freesurfer pipeline<sup>28</sup> with visual checking and manual correction if appropriate, the images were corrected for field bias and inhomogeneities using the nonparametric, nonuniform intensity normalization algorithm (N3) and interpolated to a spatial resolution of 256 × 256 × 256 voxels. Thereafter, texture features were estimated for each structure by considering the left and right parts as regions of interest (ROI). Four parameters from the first-order statistics and 7 second-order statistic parameters were estimated in each ROI. First-order statistics were means and standard deviations of gray levels or intensity values in the ROI as well as skewness and kurtosis that quantify the asymmetry of the values relative to a normal distribution. Second-order statistics were derived from the gray-level co-occurrence matrix, a method of image texture quantification widely applied in pattern recognition tasks. The

basis of the approach is to build a second-order joint conditional probability density function as a square matrix whose size depends on the intensity levels within the 3D ROI. The (i, j) elements of the matrix represents the number of times, that intensity levels i and j occur in 2 voxels separated by a defined distance D in the direction R. Consequently, from this matrix quantitative features can be extracted (Fig. 1).

In the present study, co-occurrence matrices were built using 26 connected directions of neighboring voxels in a 3D space and a distance D set to 1 voxel. The following 7 features were then computed: homogeneity that represents the uniformity of the texture intensity, contrast that represents the degree to which the texture intensity levels differ between voxels or local intensity variation, entropy that represents the degree of uncertainty (measure of randomness), correlation that represents the degree of mutual dependency between voxels, variance that gives high weights for the elements different from the average value, sum-average that measures the relationship between occurrences of pairs with lower intensity values, and occurrences of pairs with higher intensity values and inverse difference moments (InvDiff) that measure the difference between the highest and the lowest values of a contiguous set of voxels.

### Volumetry

To compare group differentiation abilities between texture analysis and more classical MRI approaches based on brain atrophy measurement, we examined



**FIG. 1.** Gray levels co-occurrence matrix building illustration. The matrix is built with neighboring set to 1 voxel and direction 0°. For example, the gray level 3 is directly followed (distance D = 1 voxel) by gray level 2 at the right 7 times, the gray level 2 is directly followed by the gray level 1 at the right side twice, and so on.

whether there were variations in volumes between groups, particularly between patient groups because our main concern was to identify markers of subtle cognitive weakness in PD. Two methods were used, ROI volume measurement and voxel-based morphometry (VBM). For the first, bilateral parts of each selected brain structure were measured and normalized to the total intracranial volume (TIV) using the ratio approach where the corrected volume is measured as the ratio of the regional brain region to the TIV.

For the VBM method, images were processed using the SPM12 DARTeL toolbox (Wellcome Trust Centre for NeuroImaging, London, UK; <https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) with the default settings.<sup>29</sup>

## Analyses

### Texture Features

Given the large number of variables (6 brain structures, left and right ROIs, and 11 texture features by ROI), a features selection strategy, using a correlation-based method, was first used to reduce the dimensionality. This selection approach belongs to the so-called filter methods that allow defining the optimal features regardless of the type of predictive model to be used later. It consists of ranking the features according to their relevance and significance.<sup>30</sup> The participant groups were organized as a qualitative variable: 0 for the CTRL group, 1 for PDCN, 2 for PD-S, and 3 for PD-EXE. For each ROI, a Spearman's correlation coefficient was used to measure the association between the texture features and the group. Significance was fixed originally to

$P < 0.05$  and corrected using false discovery rate (FDR) correction.

Between-group differences for the selected features were tested with analyses of covariance, with gender, age, TIV, and education duration as well as depression, apathy, and anxiety scores as covariates. Pairwise comparisons were done using *t* tests with significance fixed to  $P < 0.05$  and corrected using FDR correction.

Furthermore, receiver operating characteristic curves were used for assessing the ability of the statistically significant texture features to individually classify the PD patients in 1 of the 3 groups. The predictive capability was assessed using the area under the curve (AUC) by considering 1 patient group versus the 2 others.

### Texture and Cognition

The association between the selected texture features and cognition was examined using multiple regression analyses of these features with the scores of 2 tests of the neuropsychological battery, the Mattis Dementia Rating Scale for global cognition, and the Symbol Digit Modalities Test (SDMT) for cognitive slowing, with gender, age, and education as covariates. We had a particular interest for the SDMT because we previously found that it was particularly discriminant and allowed to detect a specific cluster of patients according to their cognitive profiles.<sup>27</sup>

### Volumetry

For the ROI-based approach, the variations between the groups were analyzed using an analysis of variance test with significance fixed to  $P < 0.05$ .

All of the analyses were run using XLStat (Addinsoft, XLSTAT 2016, Paris, France).

For the VBM method, *t* tests were performed to identify differences in whole brain gray matter volumes. Clusters were considered significant with a threshold in term of size fixed to 10 voxels and after controlling of family-wise error rates using FDR. Age, gender, TIV, and education were entered as covariates into the design matrix.

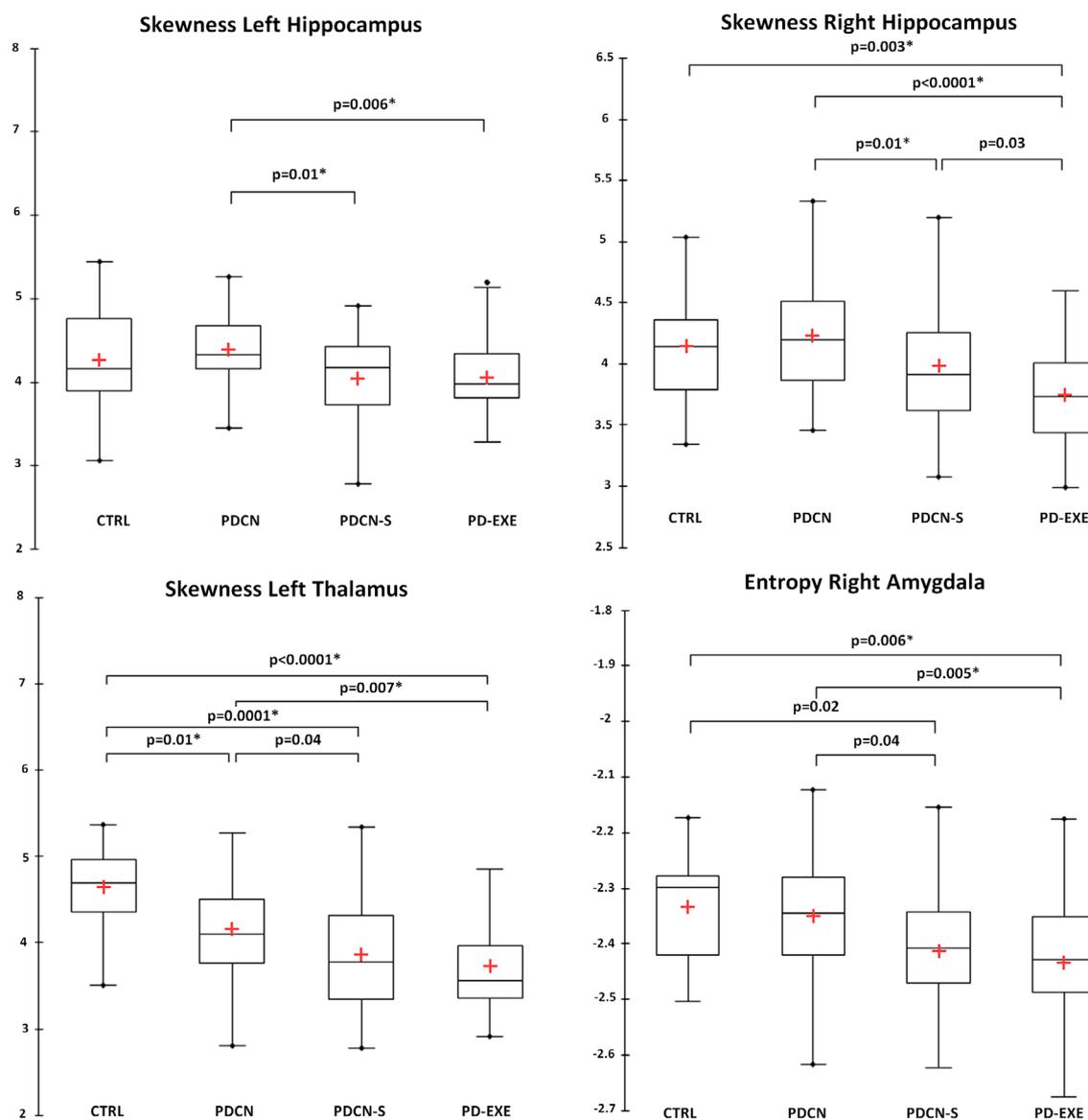
## Results

### Texture Features

After FDR correction, significance was set at  $P < 0.009$ , and the feature-selection strategy revealed the

skewness and the entropy as the most discriminant. The skewness significantly correlated with group in the left ( $r = -0.27, P = 0.002$ ) and right ( $r = -0.30, P = 0.001$ ) hippocampus as well as in the left thalamus ( $r = -0.33, P = .001$ ), whereas the entropy exhibited significant correlations in the left hippocampus ( $r = -0.33, P < 0.0001$ ), the left ( $r = -0.27, P = 0.003$ ) and right ( $r = -0.24, P = .001$ ) thalamus, and the left ( $r = -0.28, P = 0.002$ ) and right ( $r = -0.33, P < 0.0001$ ) amygdala. No other significant correlations were found for the other texture features or for the other considered structures: putamen, pallidum, and caudate nucleus.

The analyses of covariance of skewness in the previously indicated regions showed significant group differences for the left hippocampus ( $F = 8.65, P = 0.018$ ),



**FIG. 2.** Box plots with *t* tests results for pairwise comparisons of the texture feature skewness and entropy. False discovery rate corrected *P* value = 0.018. CTRL, healthy controls; PDCN, cognitively intact; PDCN-S, with slowing; PD-EXE, mild cognitive deficits, particularly in executive functioning. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

**TABLE 2.** Results of the receiver operating characteristic curves analyses of skewness and entropy texture features between the following 3 PD patient groups: PDCN, PDCN-S, and PD-EXE

Texture Feature	AUC	Sensitivity	Specificity
PDCN against PDCN-S and PD-EXE			
Skewness, left hippocampus	0.70	0.75	0.64
Skewness, right hippocampus	0.73	0.78	0.65
Skewness, left thalamus	0.68	0.74	0.64
Entropy, right amygdala	0.67	0.72	0.65
PDCN-S against PDCN and PD-EXE			
Skewness, left hippocampus	0.69	0.74	0.66
Skewness, right hippocampus	0.74	0.79	0.69
Skewness, left thalamus	0.70	0.70	0.68
Entropy, right amygdala	0.65	0.70	0.65
PD-EXE against PDCN and PDCN-S			
Skewness, left hippocampus	0.69	0.74	0.73
Skewness, right hippocampus	0.80	0.80	0.78
Skewness, left thalamus	0.73	0.76	0.74
Entropy, right amygdala	0.69	0.75	0.72

PDCN, cognitively intact; PDCN-S, cognitively intact with slowing; PD-EXE, mild cognitive deficits, particularly in executive functioning; AUC, area under curve.

right hippocampus ( $F = 10.34, P = 0.002$ ), and left thalamus ( $F = 13.62, P < 0.0001$ ). For the entropy, differences were only significant for the right amygdala ( $F = 10.02, P = 0.002$ ). No significant difference was observed for the other structures (left hippocampus [ $F = 5.59, P = 0.19$ ], left thalamus [ $F = 5.64, P = 0.18$ ], right thalamus [ $F = 4.72, P = 0.7$ ], and left amygdala [ $F = 4.74, P = 0.6$ ]). Post hoc analyses for pairwise comparisons highlighted significant differences between the participant groups and especially for the PDCN and PDCN-S groups for skewness in the hippocampus and the thalamus and for the entropy in the amygdala. Detailed results of these comparisons are shown in Figure 2.

The results of the receiver operating characteristic curve analyses of the skewness and entropy are summarized in Table 2. In all cases, the AUC was greater than 0.5 with the best performances obtained by the skewness measured in the right hippocampus with an AUC = 0.73, sensitivity = 78%, and specificity = 65% for the PDCN group against the 2 other PD patient groups; AUC = 0.74, sensitivity = 79%, and specificity = 69% when PDCN-S is considered against PDCN and PD-EXE; and AUC = 0.80, sensitivity = 80%, and specificity = 78% for the last case.

### Texture and Cognition

When correlating skewness and entropy with cognition scores and after adjustment by gender, age, and education, significance was found for the SDMT score with skewness measured in the left and right hippocampus ( $R^2 = 0.25, P = 0.002$  and  $R^2 = 0.28, P = 0.001$ , respectively) as well as in the left thalamus ( $R^2 = 0.27, P = 0.006$ ). Entropy measured in the right amygdala showed significance with the SDMT score ( $R^2 = 0.24, P = 0.001$ ). No significant correlation was found for the Mattis Dementia Rating Scale.

### Volumetry

Volume measurement using the ROI-based method revealed no significant between-group differences. Detailed measures and statistical comparisons are shown in Table 3. For the VBM, none of the pairwise comparisons for PDCN versus PDCN-S, PDCN-S versus PD-EXE, or PDCN-S versus PD-EXE highlighted regions with significant differences.

**TABLE 3.** Regions of interest–based volumes expressed in milliliters (mL) and results of the analysis of variance test for the group comparisons after TIV normalization using the ratio method

	CTRL	PDCN	PDCN-S	PD-EXE	P Value
TIV	1108.52 ± 109.92	1174.02 ± 103.73	1165.01 ± 120.14	1117.20 ± 120.77	
Hippocampus R	4.33 ± 0.40	4.56 ± 0.48	4.28 ± 0.55	4.02 ± 0.49	0.18
Hippocampus L	4.28 ± 0.40	4.48 ± 0.48	4.32 ± 0.54	4.02 ± 0.52	0.38
Thalamus R	6.82 ± 0.76	7.33 ± 0.81	7.15 ± 0.84	6.76 ± 0.67	0.90
Thalamus L	7.80 ± 0.94	8.18 ± 1.00	7.96 ± 0.98	7.44 ± 0.76	0.60
Amygdala R	1.75 ± 0.28	1.75 ± 0.22	1.64 ± 0.26	1.54 ± 0.23	0.07
Amygdala L	1.54 ± 0.22	1.66 ± 0.24	1.57 ± 0.27	1.43 ± 0.23	0.13
Pallidum R	1.43 ± 0.24	1.54 ± 0.21	1.55 ± 0.23	1.54 ± 0.16	0.36
Pallidum L	1.40 ± 0.28	1.54 ± 0.20	1.55 ± 0.25	1.53 ± 0.22	0.40
Putamen R	4.82 ± 0.62	5.01 ± 0.69	4.92 ± 0.70	4.84 ± 0.53	0.70
Putamen L	4.56 ± 0.50	5.15 ± 0.72	4.92 ± 0.64	4.81 ± 0.57	0.58
Caudate R	3.68 ± 0.60	3.90 ± 0.63	3.78 ± 0.78	3.75 ± 0.66	0.80
Caudate L	3.37 ± 0.46	3.77 ± 0.61	3.68 ± 0.60	3.55 ± 0.608	0.62

CTRL, healthy controls; PDCN, cognitively intact; PDCN-S, cognitively intact with slowing; PD-EXE, mild cognitive deficits, particularly in executive functioning; TIV, total intracranial volume; L, left; R, right.

## Discussion

In this study, image texture analysis was investigated as a potential marker for discriminating subtle cognitive impairment in PD, namely, cognitive slowing. The method was applied on a population composed of PD patients and healthy controls, both cognitively characterized by an extensive neuropsychological assessment. The analysis framework extracted different quantitative features that measure statistical and spatial dependencies of the signal values on a T1-weighted MRI image. Texture features were measured in 6 gray matter brain nuclei previously identified as altered with cognitive decline in PD patients.<sup>31</sup> At the first step of the analysis, a stringent selection strategy was applied to define the most appropriate features. Two features—skewness and entropy—emerged as the most discriminant. These results were observed in the hippocampus, the thalamus, and the amygdala. Further group comparisons revealed a gradual decrease of these features with cognitive worsening and significant differences between the PD patient groups, mainly between the PDCN and PDCNS groups, which was the main concern of this study (Fig. 2). These results suggest that neuronal loss related to cognitive decline induces a gradual signal alteration on the images. It was of interest to note that skewness in the hippocampus was a significant marker of slight cognitive slowing because it significantly discriminated the PDCN and PDCN-S groups. Moreover, in agreement with performance at the neuropsychological tests, there was no texture difference between the CTRL and PDCN groups, suggesting that the observed differences are not markers of PD but of cognitive decline in PD. This was confirmed by the significant correlations between the 2 texture features and performance at the SDMT.

To support these results, receiver operating characteristic curve analyses were performed to measure the classification power of each texture feature considered individually. As shown in Table 2, the AUCs were in the range of 0.61–0.80, with sensitivities and specificities in the ranges of 0.67–0.80 and 0.64–0.78, respectively. These are thus promising results for simple imaging features computed from a basic MRI sequence and suggest that their combination using machine-learning methods could enhance their classification performance.

Our main assumption that signal texture alterations associated with cognitive decline can be observed earlier than volume changes was confirmed. Volumetric analyses with 2 classical methods, ROI based and VBM, showed no significant volume differences between the PD groups (Table 3). This better sensitivity of the texture features regarding volumetric methods was already reported in Alzheimer's disease. Hippocampal texture was shown to be a better predictor of MCI to Alzheimer's disease conversion than volume reduction.<sup>16</sup>

Texture analysis allowed detecting early cognition-related signal changes in 3 specific brain structures: the hippocampus, the thalamus, and amygdala. Although atrophy of the hippocampus is traditionally associated with a decline in episodic memory,<sup>32</sup> a relationship with processing speed in nondemented elderly individuals was also described.<sup>33</sup> Up to now, such a relationship has not been reported in patients with PD. Regular MRI analyses have reported hippocampal atrophy mainly in PD patients with dementia.<sup>31</sup> Our results suggest that hippocampal neurons could be affected very early in PD patients, even before atrophy can be detected with commonly used methods, and this could cause a general slowing of information processing.

The thalamus is considered a “critical node of interconnected cortical, subcortical, and cerebellar circuits.”<sup>34</sup> It has been shown to support various cognitive functions, including processing speed. A link between the volume of the thalamus and cognitive slowing was reported in healthy aging,<sup>35</sup> but most of these studies concern patients with multiple sclerosis.<sup>36–38</sup> In PD, the thalamus has mainly been involved in cognition as part of the associative striato-frontal circuit.<sup>39</sup> Atrophy of the thalamus was shown as predictive of conversion from normal cognition to MCI.<sup>40</sup> Our results suggest that texture analysis could detect such an atrophy very early and before patients meet criteria for MCI.

We are aware of the limits of the present study. It was a first approach to test whether texture analysis may be a marker contributing to PD patient cognitive profiling using single T1-weighted MRI images. As a result, it was difficult to make links with the literature because texture analysis is still not widely used as a marker in neuroimaging, particularly in PD where it was never investigated in relation with cognitive decline. In the work by Li and colleagues,<sup>18</sup> different texture features computed in the substantia nigra on Quantitative Susceptibility Mapping (QSM) and R2\* maps were able to differentiate PD patients from healthy volunteers. The AUC values were in the range of 0.68–0.89 in QSM and 0.73–0.77 in R2\*, respectively. The authors identified entropy as the most discriminating feature, with significantly lower values in the PD patient group. In our results, entropy, which is a measure of randomness of information content, and skewness, which can be regarded as a measure of the asymmetry of the signal, were the selected features. Without an anatomo-histological validation study associating a biological signature to each feature, it will remain difficult to have a complete understanding of these texture features. To the best of our knowledge, such a validation is not available for PD. This issue was only addressed in mouse model of Alzheimer's disease by Colgan and colleagues.<sup>41</sup> The authors reported that the kurtosis, a first-order statistics as the skewness,

measured on T2-weighted MRI images, mainly in the hippocampus and the thalamus, significantly correlated with histological measures of tau burden in the same regions.

As a perspective of this work, the use a full radiomics approach incorporating nonradiologic data as scores from easily available cognitive assessments such as the Montreal Cognitive Assessment or data from other exploration methods such as electroencephalogram, which has been proven to have great classification capacities of cognitive profiles in PD,<sup>42</sup> to build a multimodal model, could be a promising way not only for the profiling but also for the prognosis and the prediction of evolution. In the era of personalized medicine, the objective of such approaches is not to replace neuropsychological assessment but to provide a clinically suitable tool that is automatic and based on simple exploration as T1-weighted MRI imaging for the early identification of patients that need additional healthcare and to plan this personalized management, including extensive neuropsychological assessment if appropriate. ■

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