RESEARCH ARTICLE

Early Limbic Microstructural Alterations in Apathy and Depression in De Novo Parkinson's Disease

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ABSTRACT: Background: Whether structural alterations underpin apathy and depression in de novo parkinsonian patients is unknown. The objectives of this study were to investigate whether apathy and depression in de novo parkinsonian patients are related to structural alterations and how structural abnormalities relate to serotonergic or dopaminergic dysfunction.

Methods: We compared the morphological and microstructural architecture in gray matter using voxel-based morphometry and diffusion tensor imaging coupled with white matter tract-based spatial statistics in a multimodal imaging case-control study enrolling 14 apathetic and 13 nonapathetic patients with de novo Parkinson's disease and 15 age-matched healthy controls, paired with PET imaging of the presynaptic dopaminergic and serotonergic systems.

Results: De novo parkinsonian patients with apathy had bilateral microstructural alterations in the medial corticostriatal limbic system, exhibiting decreased fractional anisotropy and increased mean diffusivity in the anterior striatum and pregenual anterior cingulate cortex in conjunction with serotonergic dysfunction. Furthermore, microstructural alterations extended to the medial frontal cortex, the subgenual anterior cingulate cortex and subcallosal gyrus, the medial thalamus, and the caudal midbrain, suggesting disruption of long-range nondopaminergic projections originating in the brainstem, in addition to microstructural alterations in callosal interhemispheric connections and frontostriatal association tracts early in the disease course. In addition, microstructural abnormalities related to depressive symptoms in apathetic and nonapathetic patients revealed a distinct, mainly right-sided limbic subnetwork involving limbic and frontal association tracts.

Conclusions: Early limbic microstructural alterations specifically related to apathy and depression emphasize the role of early disruption of ascending nondopaminergic projections and related corticocortical and corticosubcortical networks which underpin the variable expression of nonmotor and neuropsychiatric symptoms in Parkinson's disease. © 2019 International Parkinson and Movement Disorder Society

Key Words: apathy; depression; multimodal imaging, diffusion-weighted MRI; Parkinson's disease

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Apathy is a frequently underestimated and disabling neuropsychiatric condition characterized by decrease in the initiation, enactment, and achievement of goal-directed behaviors.[1-3] Importantly, apathy may intrude at any stage in the course of Parkinson's disease and may have diverse pathological underpinnings.[3-5] In particular, ventral striatal and mesocorticolimbic dopaminergic depletion plays an important role in apathy, depression, and anxiety in advanced parkinsonian patients.[1-6] However, recent studies demonstrate that serotonergic, but not dopaminergic, dysfunction is related to apathy in both newly diagnosed parkinsonian patients[7] and in patients with rapid eye movement sleep behavior disorder who are at high risk of developing Parkinson's disease.[8] Moreover, MRI and functional PET studies have revealed that apathy, depression, and anxiety are related to widespread abnormalities of anatomy, connectivity, and metabolism in limbic and premotor corticosubcortical networks in advanced parkinsonian patients.[3-5] However, morphological changes are variable, ranging from widespread reduced cortical gray-matter density,[9] differences in the shape of the nucleus accumbens,[10] or no morphological differences,[11] possibly undermined by the confusing role of cognitive and disease-related deficits in advanced parkinsonian patients. Consequently it is currently unknown whether morphological or microstructural alterations may underpin apathy, depression, and anxiety in newly diagnosed, drug-naive (de novo) and cognitively unimpaired parkinsonian patients and how structural alterations relate to serotonergic or dopaminergic dysfunction.

We hypothesized that apathy, depression, and anxiety may result from structural alterations as early as in de novo parkinsonian patients, involving the disruption of long-range monoaminergic projections originating in the brainstem and focal morphological and microstructural alterations in the limbic system, which can be untangled using multimodal imaging. We therefore investigated morphological and microstructural abnormalities in gray and white matter in a 3-group case-control study comparing de novo parkinsonian patients with and without apathy, depression, and anxiety and age-matched healthy participants, using whole-brain voxel-based morphometry (VBM) and voxel-based analysis of diffusion tensor metrics[12] in the limbic system, the brainstem, and white-matter tracts. Furthermore, we investigated how microstructural alterations relate to functional disorders of the presynaptic dopaminergic and serotonergic systems assessed with 2 specific PET radiotracers binding to the dopamine transporter (DAT; using [11C]-N-(3-iodoprop-2E-enyl)-2-beta-carbomethoxy-3-beta-(4-methylphenyl)-nortropane ([^{11}C]-PE2I) and serotonin transporter (SERT; using [11C]-N,N-dimethyl-2-(-2-amino-4-cyanophenylthio)-benzylamine, [^{11}C]-DASB) respectively.[7]

Subjects and Methods

Participants

Fifteen apathetic and 15 nonapathetic newly diagnosed patients were recruited in our cohort of patients with de novo Parkinson's disease at the Lyon and Grenoble University Hospitals between December 2012 and January 2015 and satisfied the following inclusion criteria as previously reported[7]: (1) age ≤70 years; (2) diagnosis of parkinsonian syndrome within the 2 years prior to enrollment; and (3) absence of exclusion criteria listed in the UKPDSBB diagnostic criteria. Exclusion criteria were (1) presence of cognitive impairment (Mattis Dementia Rating Scale[13] score <130, or Frontal Assessment Battery[14] score <15); (2) current or past dopaminergic medication; (3) concomitant medical or psychiatric condition other than apathetic, depressive, and anxiety disorders; and (4) intractable resting tremor. Patients were evaluated for apathy using the Lille Apathy Rating Scale (LARS) and Starkstein Apathy Scale (SAS)[2] and assigned to the apathetic group for LARS score ≥−21.[15] One apathetic patient and 2 nonapathetic patients had developed atypical symptoms challenging the initial diagnosis during follow-up since 2016 and were excluded from the cohort, resulting in 14 apathetic and 13 nonapathetic parkinsonian patients in this study, next to 15 age-matched healthy participants. All participants were assessed for depressive symptoms using the Beck Depression Inventory (BDI-II),[16] for anxiety trait using the Spielberger State-Trait Anxiety Inventory (STAI-YB),[17] and for disease-related impairment using the MDS-UPDRS rating scale and the PDQ-39 questionnaire for quality of life. The study (project 2012.722) was approved by the local Ethics Committee. All participants provided written informed consent.

MRI and PET Acquisitions

MRI acquisitions were performed on a Sonata system (1.5T, Siemens) with an 8-element phased-array head coil. The MR imaging protocol included a 3-D T1-weighted sequence (repetition time (TR), 1970 milliseconds; echo time (TE), 3.93 milliseconds; flip angle, 15°) generating 176 stacked contiguous slices (voxel size, 1 mm isotropic). Whole-brain diffusion-weighted imaging was performed using a 2-D spin echo-planar imaging sequence (TR, 6900 milliseconds; TE, 86 milliseconds; flip angle, 90°) yielding a volume of 51 axial sections (voxel size, 2.5 mm isotropic) repeated twice in 24 diffusion-gradient directions with b = 1000 s/mm^2, along with 4 null diffusion-weighted volumes (b = 0 s/mm^2).[18] Independent PET acquisitions for both the dopamine transporter using [11C]-PE2I and the serotonin transporter using [11C]-DASB were performed in all patients of this de novo cohort and their results reported previously.[7] However, we reproduced the analysis of the PET DAT and SERT labeling

presented in Maillet et al (2016) as 3 patients were excluded from this cohort because of atypical disease progression since 2016.

Diffusion Tensor Imaging

Preprocessing of diffusion-weighted images was performed using customary commands in the FMRIB's Software Library (FSL5.0.9 and 5.0.11).[18] Individual whole-brain diffusion-weighted volumes scanned twice were corrected for head motion and eddy current distortions and combined to increase signal-to-noise ratio with rotated b-vectors.[18,19] Individual brain masks from the Brain Extraction Tool were used for diffusion-weighted volumes. Voxelwise diffusion tensor indices were estimated using the *dtifit* algorithm of the FMRIB's Diffusion Toolbox (FDT v3.0)[20] and summarized as fractional anisotropy (FA), mean diffusivity (MD), and mode of anisotropy (MO) using their conventional definition, thereby approximating a set of orthogonal invariants of the diffusion tensor model when anisotropy is low (as in gray matter).[12]

Individual FA maps were realigned to a common space (FMRIB58_FA_1mm) using nonlinear registration, and transformations maps were applied to MD and MO volumes, smoothed with an isotropic Gaussian kernel (σ = 2 mm) for voxelwise gray-matter analysis. White-matter analysis was performed using tract-based spatial statistics (TBSS)[18] used to register local FA maxima to the white-matter tracts skeleton derived from the study participants and replicated in a sensitivity analysis using the most representative subject FA image as template. Specifically, the mean FA image was created from the aligned FA maps and thinned to create a mean FA skeleton that represents the centers of all tracts common to the group at the 0.2 threshold. Each subject's aligned FA data were then projected onto this skeleton, and the resulting distance maps were used to project MD and MO values for voxelwise cross-subject statistics.

Voxel-Based Morphometry

Morphological abnormalities were evaluated in gray matter across the whole brain using the standard optimized FSL-VBM procedure.[21] First, structural images were brain-extracted and gray matter-segmented before nonlinear registration to the MNI 152 standard space. The resulting images were averaged and flipped along the x axis to create a left-right symmetric, study-specific gray-matter template with an equal number (13) of participants from each group. Second, all native gray-matter images were nonlinearly registered to this study-specific template, "modulated" to correct for local expansion (or contraction), and smoothed with an isotropic Gaussian kernel (σ = 2 mm).

Statistical Analysis of Clinical and Neuropsychological Data

Data were tested for the normal distribution assumption using the Shapiro test and summarized as median, interquartile range, and range. Suitable nonparametric tests for between-group comparisons involved the Fisher exact test for categorical variables and the Kruskal-Wallis H test for continuous variables, followed by pairwise post hoc comparisons using Dunn's test with Benjamini and Hochberg correction controlling for false discovery rate using R 3.3.2.[22]

Statistical Analysis of Neuroimaging Data

Statistical analysis was performed using voxelwise nonparametric permutation-based inference with the FSL *randomise* algorithm in the General Linear Model framework.[23] Permutation number was 5000 for each contrast. Spatial correction for multiple comparison was performed for all statistical inference using threshold-free cluster enhancement (TFCE) controlling for the family-wise error (FWE) rate,[24] with $P \leq 0.05$.

As derived from study design and hypotheses, direct between-group comparisons were performed using 2-tailed 2-sample permutation tests (t tests), independently for each modality. Specificity of the results was further tested in parkinsonian patients, excluding controls, using multivariable linear regression for the following clinical and neuropsychological scales, using age and sex as covariates: LARS, BDI-II, STAI-YB, SAS, and MDS-UPDRS part III. Anatomical VBM comparisons were conducted in the whole-brain gray-matter mask derived from the FSL-VBM segmentation routines. Total intracranial volume was calculated as the product of the inverse of the determinant for the linear transformation matrix to the MNI152_T1_1mm_brain template by the template size for each subject and considered in regression analysis.[25] Diffusion tensor metrics in gray matter were analyzed in an a priori defined mask restricting the analysis to the brainstem and limbic corticostriatothalamic system derived from the Hammers atlas.[7] White-matter analysis was conducted in the study-specific white-matter tract skeleton mask. Variance smoothing (σ = 2 mm) was used with 3-dimensional TFCE for VBM and gray-matter diffusion analysis, whereas standard 2-dimensional TFCE was used for TBSS with no variance smoothing. TFCE-FWE spatially corrected results are depicted as P-value maps and reported in tables, using the Talairach Daemon atlas for anatomical labeling in gray matter and the Johns Hopkins University ICBM-DTI-81 White Matter Labels and Johns Hopkins University White Matter Tractography atlases in FSL for white matter. In addition, conjunction analysis for the conjunction null hypothesis[26] using independent multimodal methods was performed to test for the co-occurrence of both functional PET and microstructural diffusion abnormalities related to apathy,

TABLE 1. Demographic, clinical, and neuropsychological characteristics in patients with Parkinson's disease and healthy controls

	Patients with Parkinson's disease				
	Nonapathetic patients	Apathetic patients	Healthy controls	Three-group comparison *P* value	Pairwise group comparison *P* value (FDR corrected)
Clinical variables					
n	13	14	15		
Male sex (%)	8 (61.5)	11 (78.6)	9 (60)	0.55	
Age (years), median (IQR) [range]	54 (19) [32–69]	62.5 (10.2) [45–69]	55 (14) [43–69]	0.17	
Apathy (LARS score), median (IQR) [range]	−28 (6) [−34 to −24]	−17 (7.8) [−21 to 2]	−30 (5.5) [−34 to −14]	<0.001	A vs NA < 0.001; A vs HC < 0.001
Apathy (Starkstein score), median (IQR) [range]	7 (6) [1–12]	17 (4.2) [13–26]	6 (3.5) [0–20]	<0.001	A vs NA < 0.001; A vs HC < 0.001
Depression (BDI-II score), median (IQR) [range]	5 (2) [2–23]	15 (4.5) [5–21]	4 (8.5) [0–17]	<0.001	A vs NA = 0.002; A vs HC < 0.001
Trait anxiety (STAI-YB score), median (IQR) [range]	37 (12) [29–55]	49.5 (11.2) [33–63]	31 (15) [20–57]	0.0013	A vs NA = 0.015; A vs HC < 0.001
Global cognition (MDRS score), median (IQR) [range]	142 (4) [134–144]	141 (4) [137–144]	139 (5) [131–144]	0.16	
Cognition-frontal (FAR score), median (IQR) [range]	18 (0) [15–18]	17 (2) [15–18]	17 (2.5) [14–18]	0.09	
Global quality of life (PDQ-39 score), median (IQR) [range]	31 (32) [9–73]	46.5 (16.5) [19–70]	-	0.08	
Motor impairment (MDS-UPDRS part III, off), median (IQR) [range]	29 (11) [9–45]	31.5 (5.6) [25–47]	-	0.31	
Global nonmotor impairment (MDS-UPDRS part I), median (IQR) [range]	5 (4) [3–16]	10 (5.5) [5–20]	-	0.005	
Global motor impairment (MDS-UPDRS part II), median (IQR) [range]	5 (7) [2–19]	10.5 (3.1) [4–21]	-	0.2	
Total intracranial volume (cm^3), median (IQR)	1527.8 (66.6)	1482.0 (81.3)	1517.6 (78.2)	0.09	

A, apathetic parkinsonian patients; NA, nonapathetic parkinsonian patients; HC, healthy controls; FDR, false discovery rate; IQR, interquartile range; LARS, Lille Apathy Rating Scale; BDI-II, Beck Depression Inventory II; STAI-YB, State-Trait Anxiety Inventory; MDRS, Mattis Dementia Rating Scale; FAB, Frontal Assessment Battery; PDQ-39, Parkinson's Disease Quality-39 questionnaire; MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale.

using the spatially uncorrected *z*-score maps resulting from the LARS regression analysis adjusted for age and sex and thresholded at *z* score ≥2.6 ($P < 0.005$).

Results

Clinical and Neuropsychological Characteristics

Demographic and clinical characteristics of the 3 groups are summarized in Table 1. De novo drug-naive parkinsonian patients of both sexes were free of cognitive impairment and had moderate motor impairment, similar in both apathetic and nonapathetic patients ($P = 0.31$). Apathetic patients had severe apathy (≥−9) or moderate apathy (Table 1) and greater depressive symptoms compared with nonapathetic parkinsonian patients ($P = 0.002$) and healthy controls ($P < 0.001$). Three apathetic patients had moderate depressive symptoms (BDI-II score ≥21), but no patient had severe depression. Similarly, apathetic patients had greater anxiety trait scores, but of intermediate severity, compared with nonapathetic patients ($P = 0.015$) and healthy controls ($P < 0.001$).

Gray-Matter Microstructural Alterations in the Limbic System

No difference in gray-matter microstructure was observed between nonapathetic parkinsonian patients and healthy controls in the limbic system (Supporting Table 1). Conversely, apathetic patients exhibited profound microstructural abnormalities with decreased FA and increased MD in the bilateral medial thalamus compared with nonapathetic patients and healthy controls. In addition, patients with apathy disclosed increased MD in the pregenual anterior cingulate cortex compared with nonapathetic patients (Supporting Table 1), which directly correlated with the severity of apathy, independently of age and sex (Fig. 1B and Table 2). Furthermore, the more severe the apathy the greater the decrease in FA in the medial frontal and subgenual anterior cingulate cortices, subcallosal gyrus, and anterior striatum (head of the caudate nucleus; Fig. 1A and Table 2). Moreover, MO increased with apathy severity in the

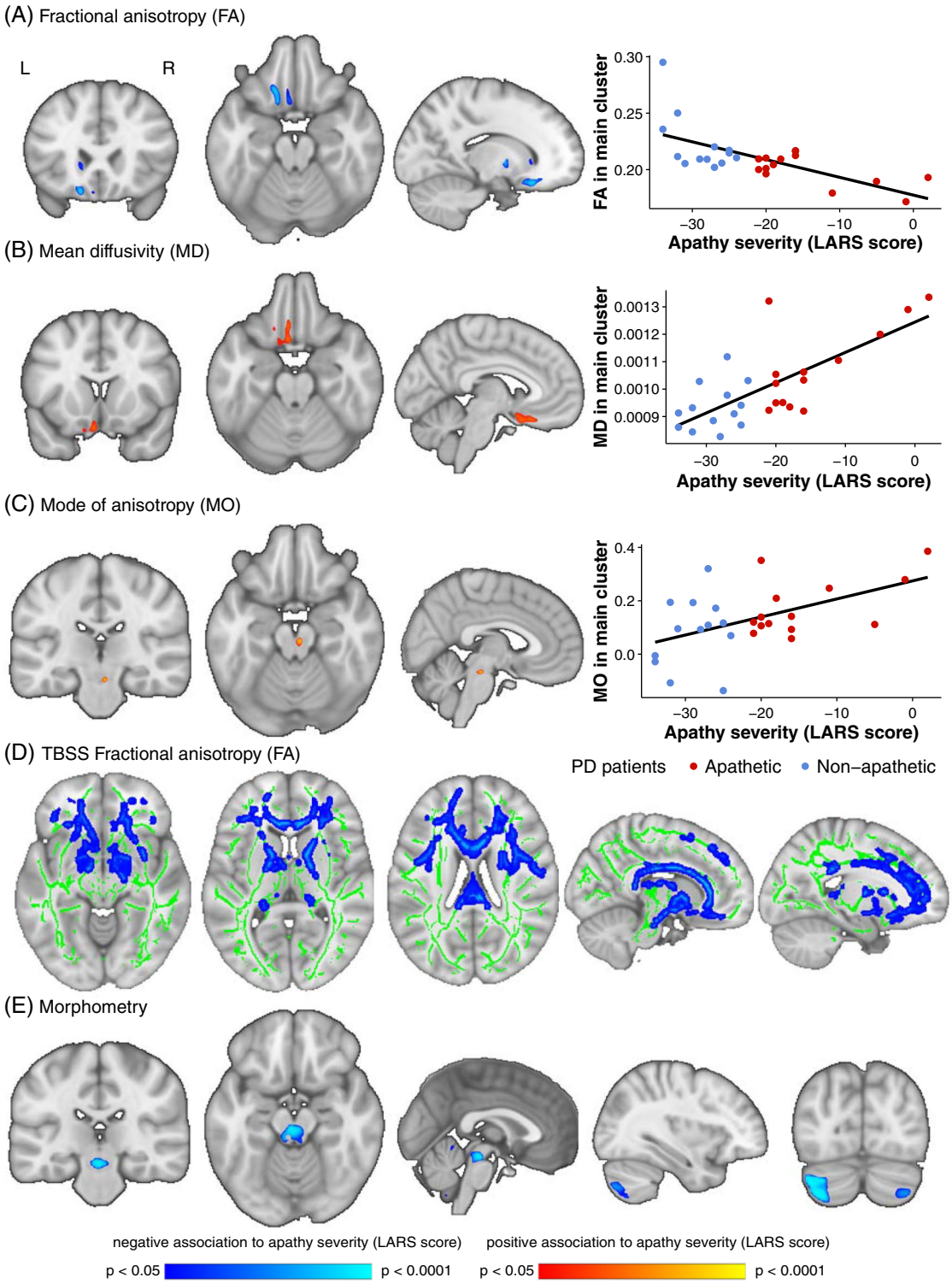

FIG. 1. Alterations related to the severity of apathy in patients with Parkinson's disease for microstructural grey matter (FA [A], MD [B], MO [C]) and white matter (TBSS FA [D]) organization, and gray-matter morphology (morphometry [E]). TFCE-FWE-corrected *P*-value maps for the regression analysis of the LARS score adjusted for age and sex are depicted next to the plot of the mean metric value in the main cluster and apathy severity in each participant. [Color figure can be viewed at wileyonlinelibrary.com]

caudal midbrain (Fig. 1C), contiguous to the morphological deformation observed on the midline, at the level of the decussation of the superior cerebellar peduncles (Fig. 1E). Specificity of these apathy-related alterations was confirmed in multivariable regression considering the Starkstein Apathy Scale, both apathy (LARS) and depression (BDI-II) scores together (all adjusted for age and sex) and in 2 sensitivity analyses conducted to

TABLE 2. Alterations related to the severity of apathy in patients with Parkinson's disease for microstructural grey matter organization (FA, MD, MO) and morphology (morphometry)

Outcome; anatomical labels	Side	Cluster size, mm^3	*P*	MNI coordinates of peak voxel		
				x	*y*	*z*
Fractional anisotropy (FA) decrease						
Subcallosal gyrus and inferior frontal gyrus (BA 47) Medial frontal gyrus (BA 25)	L	519	0.011	−15	23	−20
Globus pallidus (internal and external)	L	188	0.016	−14	−2	0
Subcallosal gyrus and medial frontal gyrus (BA 25)	L	168	0.032	−4	16	−21
Caudate nucleus (head and body)	L	133	0.036	−11	8	2
Cingulate gyrus (BA 23)	L + R	97	0.014	0	−16	27
Caudate nucleus (head and body)	R	95	0.031	14	9	6
Caudate nucleus (head and body)	L	65	0.04	−14	23	−1
Mean diffusivity (MD) increase						
Subcallosal gyrus and inferior frontal gyrus (BA 47) Medial frontal gyrus (BA 25)	L	871	0.031	−5	13	−22
Pregenual anterior cingulate cortex (BA 32)	R	226	0.04	6	46	10
Uncus (BA 28)	R	134	0.018	25	−9	−36
Mode of anisotropy (MO) increase						
Midbrain	R	79	0.015	4	−24	−19
Morphometry: grey matter atrophy						
Cerebellum (posterior lobe)	L	661	0.001	−32	−78	−46
Cerebellum (posterior lobe)	R	305	0.011	34	−78	−46
Midbrain	L + R	97	0.004	0	−26	−16

MNI, Montreal Neurological Institute; L, left; R, right. BA, Brodmann area.
All cluster *P* values are corrected for spatial multiple comparisons using threshold-free cluster enhancement (TFCE) controlling for the family-wise error (FWE) rate with $P < 0.05$ for the regression analysis of the LARS score, adjusted for age and sex, across the whole-brain gray matter mask for voxel-based morphometry and the limbic gray-matter mask for voxel-based analysis of diffusion metrics. Anatomical labeling was obtained with the Talairach Daemon Label and edited for accuracy if necessary. (*x, y, z*) coordinates refer to the Montreal Neurological Institute (MNI) space coordinate system and are reported in millimeters.

further challenge the possible confounding effects of sex (excluding 8 women and restricting the analysis to the 19 men in the study) and of depressive symptoms (excluding 3 parkinsonian patients with moderate severity of depression [BDI-II score ≥21]). Furthermore, abnormalities related to the severity of depressive symptoms regardless of apathy were restricted to focal decrease in FA (Fig. 2A and Supporting Table 2), involving the right substantia nigra and posterior putamen. No microstructural abnormality was demonstrated in the corticostriatal system for anxiety and motor impairment.

White-Matter Microstructural Alterations

Widespread alterations related to apathy were observed in white-matter tracts (Fig. 1D and Supporting Table 3), whereas no alterations were observed for patients without apathy compared with healthy controls. Reduced FA was observed in callosal interhemispheric connections and projection fibers, including the forceps minor and frontal interhemispheric connections, as well as association fibers including the cingulate bundle, and anterior thalamic fibers. Decreased FA also related to the severity of depressive symptoms in anterior interhemispheric connections and limbic association tracts (Fig. 2B and Supporting Table 4).

Whole-Brain Voxel-Based Morphometry

No morphological differences were observed in nonapathetic parkinsonian patients compared with healthy controls (Supporting Table 1), and total intracranial volume was similar in all groups (Table 1). In contrast, apathetic patients exhibited decreased gray-matter volume compared with nonapathetic patients in the bilateral subgenual anterior cingulate cortex, left superior temporal gyrus, and right superior frontal gyrus. In addition, more severe apathy was associated with greater deformation in the caudal midbrain at the level of the superior cerebellar peduncle decussation, below and dorsal to the substantia nigra/ventral tegmental area complex, and in bilateral posterior cerebellum (Fig. 1E and Table 2). No morphological abnormality related to the severity of depression, anxiety, and motor impairment was observed in de novo parkinsonian patients.

Dopaminergic and Serotonergic Dysfunction

A bilateral decrease in DAT labeling using the PET radiotracer [11C]-PE2I was found in the ventral midbrain (including the substantia nigra, ventral tegmental area, and midbrain dopaminergic neurons), putamen, caudate nucleus, globus pallidus, thalamus, parahippocampal area, and subcallosal cortex in de novo parkinsonian patients with and without apathy compared with age-matched

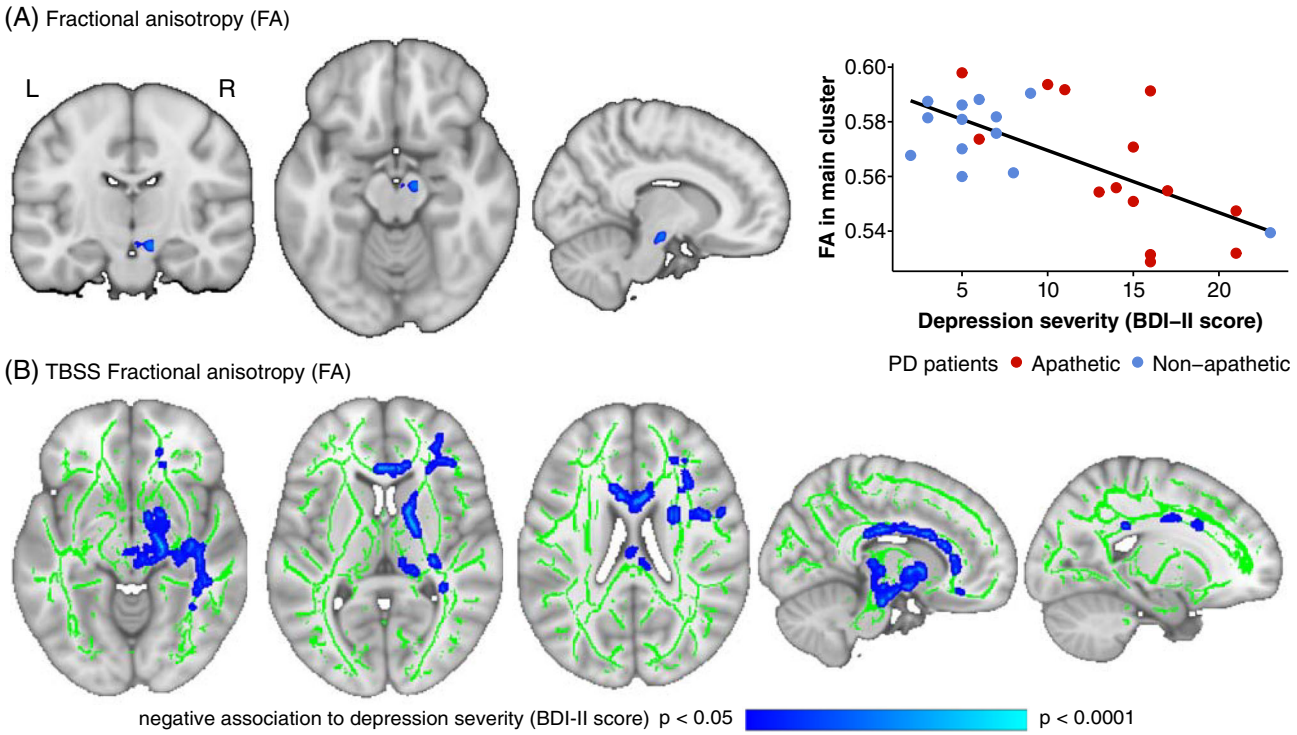

FIG. 2. Microstructural alterations (FA) related to the severity of depressive symptoms in patients with Parkinson's disease in gray matter (A) and white matter (B). TFCE-FWE-corrected *P*-value maps for the regression analysis of the BDI-II score adjusted for age and sex are depicted next to the plot of the mean metric value in the main cluster and depression severity in each participant. [Color figure can be viewed at wileyonlinelibrary.com]

healthy subjects (Supporting Table 5) in line with our previous findings.[7] No difference in DAT labeling was observed between apathetic and nonapathetic patients, whereas apathetic patients had lower SERT labeling bilaterally in the subgenual anterior cingulate cortex using [11C]-DASB PET imaging (Supporting Table 6). Nonapathetic parkinsonian patients did not differ in serotonergic function compared with healthy subjects. Bilateral decrease in SERT labeling further correlated with more severe apathy in the head of the caudate nucleus and anterior cingulate cortex.

Conjunction Analysis of Functional and Microstructural Alterations

To further investigate the association of functional (serotonergic) and microstructural alterations related to apathy, conjunction analysis of independent multimodal imaging investigations was performed (Fig. 3). This revealed the conjunction of decreased PET SERT labeling and decreased FA bilaterally in the head of the caudate nucleus (cluster size, 138 mm^3 [left] and 37 mm^3 [right]; z score = 2.98), together with increased MD in the left-sided head of the caudate nucleus (cluster size, 104 mm^3; z score = 2.94). In addition, decreased SERT labeling was colocalized with increased MD (cluster size, 107 mm^3; z score = 2.88) in the right pregenual anterior cingulate cortex. No conjunction of dopaminergic and structural abnormalities related to apathy or depression was found.

Discussion

This study shows for the first time that apathy in de novo, drug-naive, and cognitively unimpaired patients with Parkinson's disease is specifically associated with bilateral microstructural alterations in the medial corticostriatal limbic system early in the disease course. These microstructural alterations colocalize with dysfunction of serotonergic terminals in the head of the caudate nucleus and pregenual anterior cingulate cortex, as demonstrated using [^{11}C]-DASB PET imaging. Furthermore, microstructural abnormalities in de novo apathetic patients extend beyond the dysfunction of serotonergic terminals, involving the corticostriatothalamic circuit and caudal midbrain, where long-range nondopaminergic projections originate.

We demonstrate that specific brain circuit disorganization is already present in newly diagnosed parkinsonian patients with prominent apathy and mild depressive symptoms, whereas no significant anatomical abnormalities are found in drug-naive parkinsonian patients without neuropsychiatric symptoms. This is in line with case-control and large cohort studies indicating no extranigral morphological and diffusivity changes in cognitively unimpaired

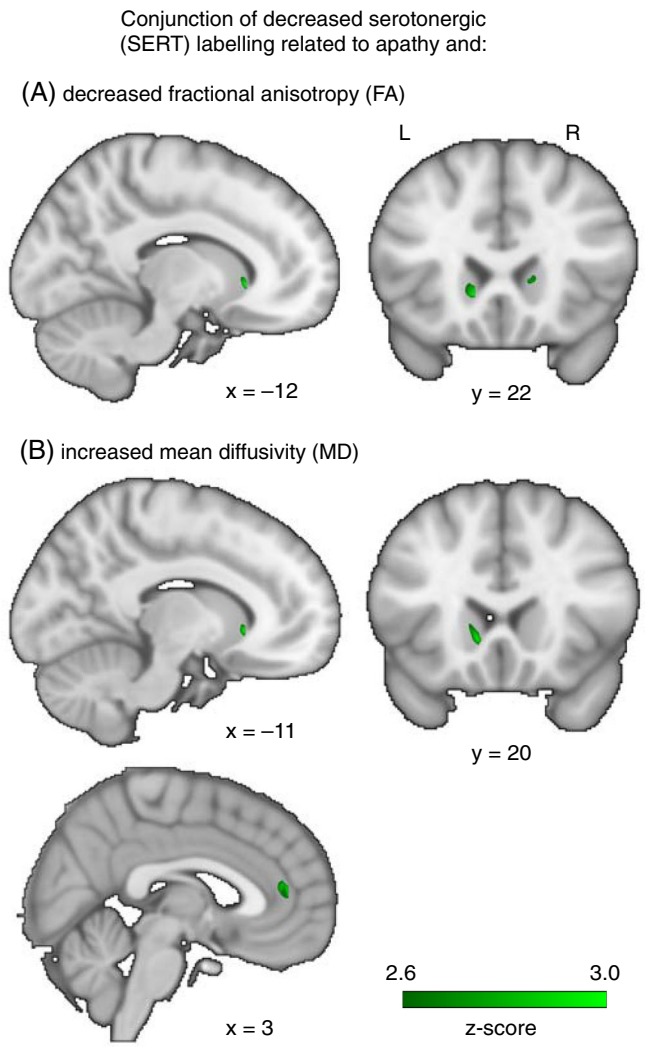

FIG. 3. Conjunction analysis showing the colocalization of both functional (serotonergic) and microstructural (FA [A] and MD [B]) alterations related to apathy. [Color figure can be viewed at wileyonlinelibrary.com]

early-stage parkinsonian patients without burdensome neuropsychiatric manifestations,[27-29] although early diffusivity changes are present in the substantia nigra[30] and may correlate with motor and nonmotor manifestations, albeit inconsistently.[31,32] Furthermore, 2 recent findings support that alteration in global connectivity may occur in the early stage of Parkinson's disease, pointing to a subnetwork of limbic structures (notably the right amygdala), and may associate with cognitive impairment and autonomic dysfunction but not anxiety, whereas apathy and depression were not evaluated.[33,34] Here, we demonstrate that early microstructural alterations related to apathy involve a bilateral and selective network of interconnected cortical and subcortical structures belonging to the corticostriatopallidothalamic limbic loop[35-37] including the medial frontal cortex, subgenual and pregenual anterior cingulate cortex, ventromedial caudate nucleus, globus pallidus, and medial thalamus. Moreover, white-matter abnormalities in the anterior interhemispheric and frontal projection tracts correlated with the severity of apathy, which supports the role of selective disorganization of reciprocal corticocortical, corticothalamic, and corticostriatopallidothalamic connections in apathy affecting parkinsonian patients.[4,5] Interestingly, disruption in this network was recently demonstrated in advanced parkinsonian patients with apathy, supporting structural alteration in the genu and body of corpus callosum, bilateral anterior corona radiata, left superior corona radiata, and left cingulum,[38,39] in addition to reduced functional connectivity, mainly in left-sided frontostriatal circuits.[11,38] Moreover, apathy in mid to advanced parkinsonian patients was associated with atrophy in the left nucleus accumbens[10,40] and head of the caudate nucleus[10] in which de novo apathetic patients in our study exhibited important microstructural alterations, but no atrophy, suggesting that diffusivity alterations may precede atrophy. Newly diagnosed apathetic patients also exhibited atrophy in the superior temporal gyrus, superior frontal gyrus, and the bilateral posterior cerebellar lobes, where glucose metabolism is negatively correlated with apathy in parkinsonian patients without dementia or depression.[41] However cortical atrophy patterns are heterogeneous and several studies in advanced parkinsonian patients did not find apathy-related atrophy,[10,11,38] whereas others disclosed widespread reduction of cortical gray-matter density[9,41] illustrating methodological differences and differential disease-related deficits in advanced patients. Altogether, our findings clearly demonstrate that apathy in de novo parkinsonian patients is related to selective disruption within the limbic circuit, characterized by increased disarray early in the disease course. These alterations specifically involve the medial corticostriatal limbic network, known to be implicated in goal-directed behaviors and emotion processing.[35-37] Interestingly, white-matter abnormalities are remarkably similar to the ones observed in patients suffering from apathy across other neurodegenerative conditions (including frontotemporal dementia,[42] Alzheimer's disease,[43] and small-vessel disease[44]), which emphasizes the transdiagnostic validity of the conceptual framework underpinning goal-directed behavior disorders.[4,45,46]

In addition, patients with more severe apathy exhibited both decreased FA and increased MD in the head of the caudate nucleus, which receives dense projection from the subgenual anterior cingulate cortex.[36] Strikingly, apathy-related microstructural alterations and decreased SERT labeling were colocalized in the head of the caudate nucleus and pregenual anterior cingulate cortex. On the other hand, no difference in the dense mesolimbic dopaminergic bundle originating in the ventral tegmental area and projecting to the ventral striatum was found between apathetic and nonapathetic patients. This uniquely suggests that early microstructural abnormalities observed in the ventral striatum and pregenual anterior

cingulate cortex may correspond to the alteration of serotonergic terminals, which is also supported by recent lesion studies in animal models of Parkinson's disease. Indeed, we demonstrated that 3,4-methylene-dioxymethamphetamine (MDMA)-induced serotonergic lesions caused specific diffusivity changes in the caudate nucleus in monkeys, which are related to histologically confirmed microstructural alterations.[47] In light of these studies, we may speculate that disruption of serotonergic projections, which have characteristic anatomical features with large axonal varicosities and fuzzy and densely intertwined reticular organization, may specifically translate into profound abnormalities in diffusivity.[47,48]

Furthermore, we found that mode of anisotropy, which is sensitive to the orientation of crossing fibers,[12,49] is focally increased in the caudal central midbrain. This indicates bias toward elongated, more cigar-shaped (or equivalently less flattened, disc-shaped) principal fiber bundles.[12,49] These alterations positively correlate with the severity of apathy and are associated with morphological deformation located at the level of the decussation of the superior cerebellar peduncle where ascending serotonergic projections originating in both the medial and dorsal raphe nuclei join ventrally and form a complex reticulum of multiple small intertwined fascicles passing rostroventrally through the fibers of the superior cerebellar peduncle crossing in the midline.[48] Thus, apathy-related diffusivity abnormalities in the brainstem likely indicate that presynaptic dysfunction of serotonergic terminals in the ventral striatum and anterior cingulate cortex in de novo parkinsonian patients is associated with extranigral pathological processes in the caudal midbrain and selective disruption of ascending long-range serotonergic projections. Interestingly, serotonin depletion in the dorsal raphe nucleus also correlates with apathy in patients with rapid eye movement sleep behavior disorders who are at high risk of developing symptomatic synucleopathies.[8] Altogether these findings support that parkinsonian patients with early (or even prodromal) prominent nonmotor neuropsychiatric symptoms exhibit nondopaminergic degeneration in the caudal midbrain (corresponding to Braak stage 2), which may translate into widespread but specific supratentorial microstructural alterations.

Although apathy may be isolated, it is most often intermingled with depressive and anxious symptoms in Parkinson's disease as well as in other neurodegenerative disorders (frontotemporal dementia, Huntington's disease, Alzheimer's disease)[3,45] and psychiatric conditions.[36] However, the present study shows that diffusivity alterations in the caudal midbrain, caudate nucleus, anterior cingulate cortex, and medial frontal cortex were independently correlated with apathy when considering both apathy and depression together in multivariable regression. The specificity of apathy-related alterations was further confirmed by the sensitivity analysis excluding the patients with moderate depression scores. Moreover, depressive symptoms present in apathetic and nonapathetic parkinsonian patients were related to a distinct, mainly right-sided limbic subnetwork involving the genu of the corpus callosum and forceps minor, in line with previous findings,[50,51] whereas no specific association was found for anxiety. Although we observed no structural differences between de novo nonapathetic parkinsonian patients and healthy controls, we cannot exclude that replication studies combining higher-field MRI and registration with a stable representative study-specific template in a larger population may achieve greater power to detect subtle and localized differences.[52,53]

This unique multimodal imaging study demonstrates that not only functional, but also structural alterations affecting extranigral nondopaminergic structures are present in newly diagnosed parkinsonian patients with prominent apathy and mild depressive manifestations. Importantly, these patients were drug naive and free of cognitive impairment, which rules out the confounding effect of medication or cognitive deficits present in advanced parkinsonian patients. Moreover, multivariable regression and sensitivity analyses emphasize that apathy and depression have, at least in part, distinct pathological underpinnings in parkinsonian patients.[1-3,51]

Our results highlight the role of serotonergic dysfunction in early-stage parkinsonian apathy, which may apply to other neurodegenerative conditions compounded with apathy, notably in view of the efficacy of serotonergic drugs including agomelatine (a 5-HT2C receptor antagonist) in apathetic patients with frontotemporal dementia.[54] Thus the pathophysiology of apathy in Parkinson's disease may evolve with disease progression, with respect to the established role of the mesocorticolimbic dopaminergic dysfunction in apathy affecting advanced parkinsonian patients.[3,6,55]

Altogether our study highlights the diverse phenotypic expression of Parkinson's disease from the early disease stage and adds to the evidence that early neuropsychiatric clinical manifestations relate to specific functional and structural lesion patterns, which supports the existence of nonmotor subtypes and may represent key prognostic markers of disease progression.[56]

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Supporting Data

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