RESEARCH ARTICLE

Apathy and brain alterations in Parkinson's disease: a multimodal imaging study

Olaia Lucas-Jiménez[1] (iD), Natalia Ojeda[1], Javier Peña[1], Alberto Cabrera-Zubizarreta[2], María Díez-Cirarda[1], Juan Carlos Gómez-Esteban[3], María Ángeles Gómez-Beldarrain[4] & Naroa Ibarretxe-Bilbao[1]

[1]Department of Methods and Experimental Psychology, Faculty of Psychology and Education, University of Deusto, Bilbao, Spain
[2]OSATEK, MR Unit Hospital of Galdakao, Galdakao-Usansolo, Spain
[3]Neurodegenerative Diseases Group, Biocruces Health Research Institute, University of Basque Country, Barakaldo, Spain
[4]Department of Neurology, Hospital of Galdakao, Galdakao-Usansolo, Spain

Correspondence
Naroa Ibarretxe-Bilbao, Faculty of Psychology and Education, University of Deusto, Avda Universidades 24, 48007 Bilbao, Spain.
Tel/Fax: + 34 944 139 000 (ext. 2892);
E-mail: naroa.ibarretxe@deusto.es

Abstract

Objective: Apathy is a common nonmotor symptom in Parkinson's disease (PD) affecting 40% of patients. The aim of the study was to investigate brain changes and correlates of frontal, striatal, and limbic pathways related to subclinical symptoms of apathy in PD patients. **Methods**: Thirty-two PD patients divided into low-subclinical symptoms of apathy (LSA) ($n = 18$) and high-subclinical symptoms of apathy (HSA) ($n = 14$) and 25 healthy controls (HC) underwent a T1-weighted, diffusion-weighted, and resting-state functional MRI. Apathy was evaluated with the Lille Apathy Rating Scale. Voxel-based morphometry, tract-based spatial statistics, and resting-state functional connectivity (FC) analyses were performed with a region-of-interest approach. **Results**: HSA-PD showed increased white matter axial and mean diffusivity compared with HC and increased white matter axial diffusivity compared with LSA-PD. HSA-PD showed decreased fronto-striatal and fronto-limbic FC compared with HC and decreased fronto-striatal FC compared with LSA-PD. LSA-PD showed decreased fronto-limbic but increased fronto-striatal FC (hyperconnectivity) compared with HC. No significant differences in grey matter were found. Fronto-striatal FC and white matter axial and mean diffusivity were associated with symptoms of apathy in HSA-PD. The fronto-striatal hyperconnectivity was associated with lower symptoms of apathy in LSA-PD. **Interpretation**: Findings suggest distinct brain alterations in PD groups with subclinical symptoms of apathy. The increased pattern of activation in LSA-PD, accompanied with lower apathetic symptomatology, might be the initial manifestation of compensatory mechanisms for dysfunctional limbic pathway. The same pattern of hyperconnectivity has been found in other pathologies and the implication of these abnormalities as a cross-disease model for initial apathy symptomatology is further discussed.

Introduction

Apathy is one of the most common and disabling nonmotor symptoms in Parkinson's disease (PD) that manifests simultaneously in goal-directed behavior, cognitive, and affective features.[1] Recent meta-analyses have shown that the prevalence of apathy is close to 40% in PD.[2,3] Apathy has been associated with poor cognitive performance and dementia.[4–7] Although the neurochemical substrates of apathy remain poorly characterized, dopamine deficits affecting fronto-striatal and limbic regions have been suggested to play an important role in the pathophysiological bases of apathy in PD.[8] Previous studies highlighted frontal, limbic, and striatal involvement of apathy in PD. However, no studies have investigated the first symptoms of apathy in PD patients when the diagnosis of apathy has not yet been established. PD has a long pre-symptomatic evolution during which compensatory

mechanisms occur to delay the clinical onset of disabling nonmotor symptoms such as cognitive dysfunction or mood disorders.[9] Nevertheless, data from early PD patients with first symptoms of apathy are difficult to obtain as most studies have been performed once the diagnosis and treatments have been established.

Studies using T1-weighted magnetic resonance imaging (MRI) showed grey matter atrophy in the temporal, frontal, and parietal lobes, insula, and nucleus accumbens.[10–12] The only study of diffusion weighted imaging did not report any difference in white matter integrity between PD with or without apathy and healthy controls (HC).[11] Finally, regarding resting-state functional MRI, studies showed decreased functional connectivity (FC) in fronto-striatal regions in apathetic PD patients compared to nonapathetic PD and HC.[13,14] Only a limited number of neuroimaging studies have investigated apathy in PD. The majority of studies only included one single imaging modality, making it difficult to investigate structural and functional MRI changes related to apathy in PD.[8,15] Finally, no studies have evaluated the brain differences between low and high symptoms of apathy in PD patients with MRI. Only one study took into account the apathy level, they investigated the performance of individuals with PD, with or without clinically significant levels of apathy, on a spatial search task (money reward vs valueless token) during PET. In the high-apathy group reduced activity was found in left amygdala, left striatum, bilateral ventromedial prefrontal cortex, and midbrain relative to the low-apathy group.[16]

Therefore, the objective of the study was to investigate brain changes and correlates of frontal, striatal and limbic pathways related to subclinical symptoms of apathy through three different neuroimaging modalities (grey matter, white matter, and resting-state FC) in nonapathetic PD patients. We thought that this type of studies could help to elucidate whether there are compensatory mechanisms underlying apathy symptoms in PD patients. Moreover, they could help to investigate biomarkers in patients with PD and finally, how the results could be extrapolated so that both groups (with high and low apathy) can benefit from more specific treatments. Based on the previous findings that found frontal and striatal deficits in apathetic PD patients,[13,14] we hypothesized that PD patients with high symptoms of apathy would also show fronto-striatal deficits compared with PD patients with low symptoms of apathy and HC.

Materials and Methods

Participants

The sample included 32 nonapathetic and nondemented PD patients recruited from the Department of Neurology at the Galdakao Hospital and from the PD Biscay Association (ASPARBI) and 25 HC matched by age, sex, and years of education. PD patients were recruited for the study if they fulfilled the UK PD Society Brain Bank diagnostic criteria checked by a neurologist specialized in movement disorders. Other inclusion criteria were as follow: (1) age between 45 and 75; (2) Hoehn and Yahr disease stage ≤ 3; (3) Unified PD Rating Scale (UPDRS) evaluated and scored by the neurologist. The exclusion criteria were as follow: (1) the presence of dementia as defined by the DSM-IV-R and the Movement Disorders Society clinical criteria for PD-dementia; (2) scores on the Mini Mental State Examination (MMSE) < 26; (3) the presence of other neurological illness/injury (e.g., traumatic brain injury); (4) unstable psychiatric disorders (e.g., schizophrenia); (5) presence of visual hallucinations evaluated with Neuropsychiatric Inventory Questionnaire (NPI); (6) Anxiety or fatigue symptomatology evaluated with the NPI; and (7) diagnosis of depression or a score > 5 on Geriatric Depression Scale (GDS-15).[17] GDS-15 is a suitable instrument with high internal consistency[18] and it has been validated to the Spanish language.[19] From the initial sample of 44 PD patients, one PD patient was excluded due to MMSE scores, three patients refused to attend MRI acquisition and eight patients were excluded from the MRI analysis ($n = 1$ visual difficulties, $n = 2$ artifacts, $n = 1$ dilated ventricles, $n = 1$ traumatic brain injury, $n = 1$ cerebral hemorrhage, $n = 1$ metal shavings and $n = 1$ morphine treatment). Hence, MRI analyses were carried out on 32 PD patients. One patient was taking no medication and 31 were on anti-Parkinsonian treatment. Their Levodopa equivalent daily dose (LEDD) was registered.[20] The clinical and sociodemographic characteristics of the sample are shown in Table 1. Differences were investigated between excluded ($n = 8$) and included ($n = 32$) PD patients (Mann–Whitney U), and no significant differences were found in MMSE, GDS-15, years of education, age, UDRS III, disease duration or LEDD.

Ethics statement

The study protocol was approved by the Ethics Committee at the Health Department of the Basque Mental Health System in Spain and the Ethics Committee of the University of Deusto. All subjects were volunteers and provided written informed consent prior to their participation in the study, in accordance with the Declaration of Helsinki of 1975.

Assessment of apathy

The Lille Apathy Rating Scale (LARS),[21] which is valid for PD patients and allows to assess apathy independently of

Table 1. Sociodemographic and clinical variables of the sample.

	HSA-PD ($n = 14$) Mean (SE) (95% CI)	LSA-PD ($n = 18$) Mean (SE) (95% CI)	HC ($n = 25$) Mean (SE) (95% CI)	Statistic	P
Age (years)	69.64 (1.92) (65.28 to 73)	66.28 (1.32) (63.63 to 68.87)	68.64 (1.52) (65.43 to 71.41)	$F = 1.07$	0.351
Gender (male)	9 (64.3%)	9 (50%)	15 (60%)	$\chi^2 = 0.740$	0.691
Education (years)	12.46 (1.20) (10.17 to 14.88)	10.94 (1.10) (8.85 to 12.18)	11.16 (0.91) (9.42 to 12.84)	H = 1.63	0.443
MMSE	27.92 (0.26) (27.47 to 28.42)	28.17 (.31) (27.56 to 28.77)	28.80 (0.26) (28.23 to 29.26)	$F = 1.99$	0.146
GDS-15	2.50 (0.65) (1.30 to 3.77)	2.00 (0.54) (1.09 to 3.17)	1.22 (0.23) (0.80 to 1.72)	H = 2.53	0.282
LARS	−21.79 (1.53) (−24.43 to −18.34)	−29.50 (0.39) (−30.29 to −28.72)	−28.68 (1.12) (−30.55 to −26.08)	H = 24.67	<0.001[a,b]
MCI	9 (64.3%)	10 (55.55%)	−	$\chi^2 = 0.249$	0.725
UPDRS I	1.85 (0.34) (1.15 to 2.50)	1.39 (0.23) (0.95 to 1.88)	−	$U = 87.00$	0.212
UPDRS III - motor	24.92 (2.96) (19.73 to 31.28)	17.61 (2.00) (14.27 to 22.05)	−	$U = 68.50$	0.052
Disease duration (years)	6.32 (1.44) (3.68 to 9.37)	6.08 (1.10) (4.15 to 8.44)	−	$U = 125.00$	0.969
LEDD	702.44 (123.33) (470.20 to 957.09)	807.36 (135.37) (584.85 to 1104.25)	−	$t = -0.560$	0.580
Hoehn & Yahr				$\chi^2 = 0.093$	0.993
1	2	3	−		
1.5	1	1	−		
2	10	13	−		
2.5	0	0	−		
3	1	1	−		

[a] = significant differences between HSA-PD and LSA-PD; [b] = significant differences between HSA-PD and HC.
HSA-PD, High-subclinical symptoms of apathy Parkinson's disease group; LSA-PD, Low-subclinical symptoms of apathy Parkinson's disease group; HC, Healthy controls; SE, Standard error; CI, Confidence interval; F, ANOVA analysis; H, Kruskal–Wallis analysis; χ^2, Chi squared analysis; T, T-test analysis; MMSE, Mini-Mental State Examination; GDS-15, Geriatric Depression Scale (15 items); LARS, Lille Apathy Rating Scale; MCI, Mild Cognitive Impairment; UPDRS, Unified Parkinson Disease Rating Scale; LEDD, Levodopa Equivalent Daily Dose.

depression,[22] consists of 33 items, including nine subscales. The subscales included reduction in everyday productivity, lack of interest, lack of initiative, extinction of novelty seeking and motivation, blunting of emotional responses, lack of concern, poor social life, and extinction of self-awareness. These subscales were summed into a total apathy score with a possible range of −36 to 36, being LARS scores closer to −36 indicative of normality and scores closer to 36 indicative of apathy. The visual binning analysis with SPSS software[23] created two distinct categorical variables based on the LARS standard score distribution. PD patients were stratified into equal quartiles on the basis of LARS with cut off points of ±2 standard deviations. Two groups of nonapathetic PD patients were formed, high-subclinical symptoms of apathy group (HSA-PD) ranging from −26 to −16 ($n = 14$) and low-subclinical symptoms of apathy group (LSA-PD) ranging from −36 to −27 ($n = 18$). These two groups represent nonapathetic PD patients with the LARS scale, but with symptomatology of apathy (subclinical symptoms).

For apathy correlates, subscales were performed in four factors according to the validation of a Spanish version of the LARS for PD.[22] The sign of the measures were adjusted so that higher scores indicated less apathy symptoms. Factor 1, "Intellectual Curiosity", included the subscales everyday productivity, lack of interest, and lack of initiative; factor 2, "Emotion", grouped subscales extinction of novelty seeking and motivation, and poor social life; factor 3, "Action Initiation", was composed by subscale lack of concern; and factor 4, "Self-awareness", included subscales blunting of emotional responses, and extinction of self-awareness.

Mild cognitive impairment (MCI) assessment

Classification for PD-MCI followed Level II of Movement Disorders Society Task Force criteria corresponding to a comprehensive assessment.[24] PD patients that did not fulfill these specific criteria were classified as PD with normal cognition (PD-NC). The details of the PD-MCI

classification have been extensively described in a previous study.[25] According to this criteria, we have investigated the MCI in our sample. In the HSA-PD group 5 PD-NC patients and 9 PD-MCI patients were found. In LSA-PD group, 8 PD-NC patients and 10 PD-MCI patients were found. No significant differences in the number of patients with MCI between groups were found ($\chi^2 = 0.249$, $P = 0.725$; see Table 1). These data were introduced as a covariate in the neuropsychological and neuroimaging analyses to control for the influence of cognitive impairment.

Neuroimaging data acquisition and pre-processing

Neuroimaging data acquisition

Neuroimaging data were acquired on a 3-Tesla MRI (Philips-Achieva) at OSATEK, Hospital of Galdakao. A T1-weighted scan was acquired in sagittal orientation (TR = 7.5 msec, TE = 3.5 msec, matrix size = 228 × 218 mm; flip angle = 9°, FOV = 250 × 250 mm, slice thickness = 1.1 mm, gap = −0.6 mm, 300 slices, acquisition time = 4 min 55 sec, voxel size = 1.10 × 1.15 × 1.20 mm). An accelerating factor was used for the T1 acquisition. Diffusion-weighted images were obtained, in an axial orientation in an anterior–posterior phase direction, using a single-shot EPI sequence (TR = 7540 msec, TE = 76 msec, matrix size = 120 × 117 mm; flip angle = 90°, FOV = 240 × 240 mm, slice thickness = 2 mm, no gap, 66 slices, acquisition time = 9 min 31 sec, voxel size = 2.00 × 2.05 × 2.00 mm) with two identical repetitions (32 uniformly distributed directions [b = 1000 sec/mm^2] and 1 b = 0 sec/mm^2). In all cases first sequence was used. The resting-state functional MRI was acquired in an axial orientation in an anterior-posterior phase direction, using a sequence sensitive to blood oxygen level-dependent (BOLD) contrast and a multislice gradient echo EPI sequence (TR = 2100 msec, TE = 16 msec, matrix size = 80 × 78 mm, flip angle = 80°, FOV = 240 × 240 mm, slice thickness = 3 mm, slice gap = 0.25 mm, 40 slices, 214 volumes, acquisition time = 7 min 40 sec, voxel size = 3.00 × 3.07 × 3.00 mm).

Neuroimaging data pre-processing and definitions of regions of interest (ROI; See Fig. 1) are described in Supplementary Material S1.

Neuroimaging data analysis

Grey and white matter

Grey matter and white matter differences between groups were analyzed with a randomized tool (5000 permutations) and with threshold-free cluster enhancement (TFCE) and with cluster-based in FSL with ROI-to-ROI methodology. Total Intracranial Volume (TIV), UPDRS-III (motor) and MCI were introduced as covariates in between-group analysis. Statistical threshold for analysis was set at $P < 0.05$ corrected for multiple comparisons using family wise error (FWE) and exploratory analyses using $P < 0.001$ (uncorrected, $K > 30$ voxels) were also explored.

Resting-state FC

FC differences were assessed with ROI-to-ROI methodology with CONN Functional Connectivity Toolbox 15.h. TIV, UPDRS-III, MCI and LEDD data were used as covariates because apathy in PD is at least partly dopamine-dependent syndrome.[26,27] Statistical threshold was set at $P < 0.05$ corrected for multiple comparisons using false discovery rate (FDR) and exploratory analyses using $P < 0.001$ (uncorrected, $K > 30$ voxels) were also explored.

Statistical analysis

Normality of data was tested using the Shapiro-Wilk test. Categorical data were analyzed with the Chi-squared ($\chi2$) test. Significant differences in variables were compared using the Analysis of Variance (ANOVA) test or Kruskal–Wallis test for three-group comparisons and two-tailed *t*-tests or U-Mann–Whitney test for two-group comparisons. Significant results' average of each participant was extracted for correlational analyses. To obtain adjusted mean differences we used bootstrapping. Effect size was calculated with Cohen's *d*. To study brain correlates of apathy, Spearman Rho correlations between significant neuroimaging results (structural and resting-state functional MRI) and four factors of apathy were performed in HSA-PD and LSA-PD and HC. Additionally, further post hoc analyses were also carried out to examine the relationship between structural and resting-state functional MRI in HSA-PD and LSA-PD patients and HC using the Spearman Rho correlation test. For the correlations, outliers were excluded and the scores were initially adjusted for TIV, UPDRS-III, LEDD, and MCI by means of linear regressions and the resulting nonstandard residuals were utilized in the correlations.

Results

Sociodemographic variables

No significant differences were found between LSA-PD, HSA-PD, and HC in sociodemographic variables or
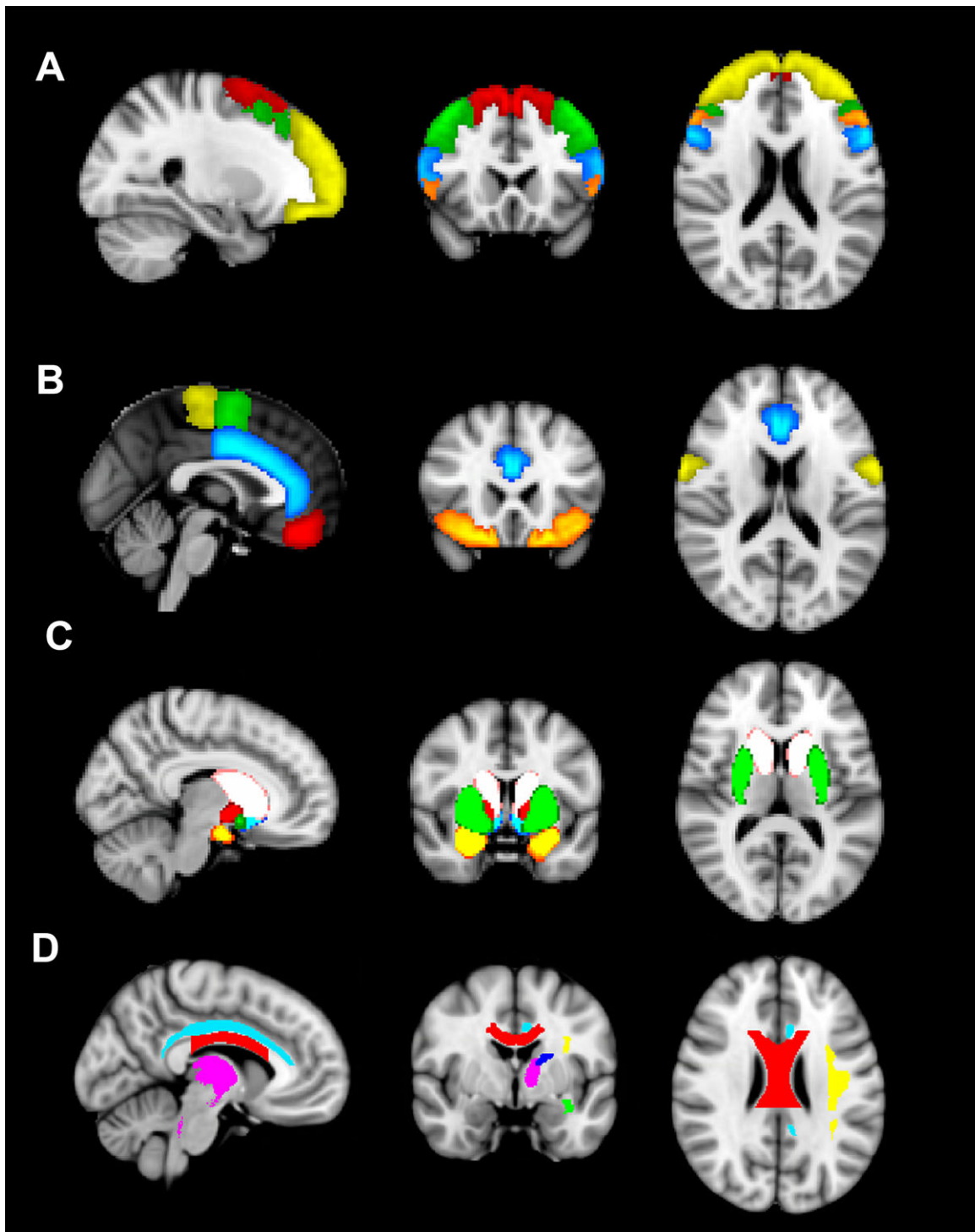
Figure 1. ROI masks for MRI analyses. (A) Frontal pole is shown in yellow, superior frontal gyrus in red, middle frontal gyrus in green, inferior frontal gyrus pars opercularis in blue-light, and inferior frontal gyrus pars triangularis in orange. (B) Frontal orbital cortex in orange, cingulate gyrus-anterior division in blue-light, juxtapositional lobule cortex/supplementary motor area in green, frontal medial cortex in red, precentral gyrus in yellow. (C) Amygdala in orange-yellow, caudate in white and pink, putamen in green, the nucleus accumbens in blue-light, pallidum in red. (D) Anterior thalamic radiation in purple, internal capsule in blue, uncinated fasciculus in green, superior longitudinal fasciculus in yellow, body of corpus callosum in red, cingulum in blue-light (left-side).

cognitive scores such as MMSE, UPDRS I or MCI criteria. A tendency in UPDRS-III (motor) was found ($P = 0.052$) between LSA-PD and HSA-PD (see Table 1). Because of that, subsequent neuroimaging analyses were also performed with UPDRS-III (motor) as covariate.

Neuroimaging group-wise comparisons

Grey and white matter

No significant differences were found in grey matter analyses between groups.

HSA-PD showed increased axial diffusivity in one significant cluster located in the body of corpus callosum (uncorrected $P < 0.001$) compared with HC (See Table 2 and Fig. 2). Furthermore, the HSA-PD group showed increased mean diffusivity in five significant clusters located in left anterior thalamic radiation, left uncinate fasciculus, left cingulum and left superior longitudinal fasciculus (uncorrected $P < 0.001$) compared with HC (See Table 2 and Fig. 2). HSA-PD showed increased axial diffusivity in a significant cluster located in the right body of corpus callosum (FWE-corrected $P < 0.05$) compared with LSA-PD group (See Table 2 and Fig. 2). No significant differences were found between LSA-PD and HC.

Resting-state FC

HSA-PD showed significantly reduced fronto-striatal and fronto-limbic FC compared with HC (See Table 3 and Fig. 3A). HSA-PD showed significantly lower fronto-striatal FC compared with LSA-PD group (See Table 3 and Fig. 3B). In addition, LSA-PD showed significantly reduced fronto-limbic FC but increased fronto-striatal FC (hyperconnectivity) compared with HC (See Table 3 and Fig. 3C). Post hoc analysis assessing structural MRI and resting-state functional MRI relationship are shown in Supplementary Material S1 (See Fig. S1.1).

Brain correlates of apathy

In HSA-PD, the altered fronto-striatal FC between left inferior frontal gyrus and left pallidum correlated with the "Emotion" factor ($\rho = 0.703$, $P = 0.007$) and between the left orbitofrontal cortex and right putamen with the "Intellectual Curiosity" factor ($\rho = 0.698$, $P = 0.008$) (See Fig. S1.2). Moreover, the increased white matter mean diffusivity and axial diffusivity correlated with the "Action Initiation" factor ($\rho = -0.720$, $P = 0.008$; $\rho = -0.664$, $P = 0.018$) (See Fig. S1.2). In LSA-PD, the hyperconnectivity between the left inferior frontal gyrus and right caudate correlated significantly with the "Emotion" factor ($\rho = 0.522$, $P = 0.032$) (See Fig. S1.2). No significant

correlations were found in HC. Additionally, significant correlation between UPDRS III and hyperconnectivity in LSA-PD patients was found ($\rho = -0.564$, $P = 0.018$), indicating that the lower the motor symptoms, the higher the hyperconnectivity (See Fig. S1.2).

Discussion

This is the first study assessing the association between subclinical symptoms of apathy and brain changes. This study used a multimodal neuroimaging approach to explore apathy symptoms in PD by combining T1-weighted MRI, diffusion-weighted MRI and resting-state functional MRI. The results revealed that distinct structural and functional brain alterations are present in HSA-PD and LSA-PD patients and those apathy symptoms were associated with these alterations. These changes were observed using TIV, UPDRS-III (motor), LEDD and MCI data as covariates.

Although there are some studies which have demonstrated structural grey matter brain changes in apathetic PD patients, we have not found significant reduced brain grey matter volume between groups. These results could reveal that grey matter atrophy is not yet present because the diagnosis of apathy in our sample has not been established in HSA-PD and LSA-PD patients with LARS. There are few studies assessing apathy in PD using T1-weighted imaging and some of them reported reduced grey matter in temporal, frontal, parietal, insula,[10,12] and accumbens[11] in apathetic PD patients, although these results were not reported in another study.[14] Although grey matter significant results at corrected level were not found, the regions altered in white matter and FC results are in line with the areas that have been found altered in previous grey matter studies.

A few studies used diffusion-weighted MRI to examine the neural substrates of apathy in PD patients investigating fractional anisotropy values[11,28] and different results were found. In one study, no significant differences were found in this index while in the other very recent study, significant fractional anisotropy differences in the corpus callosum between apathetic and nonapathetic PD patients were found, and those differences correlated with LARS scores.[28] In our study, we assessed white matter changes in fractional anisotropy, axial diffusivity, mean diffusivity, and radial diffusivity indexes. As a previous study, we did not find significant differences in fractional anisotropy at corrected level. However, HSA-PD patients revealed significant increased axial diffusivity in the corpus callosum compared with LSA-PD and HC. Moreover, an increased mean diffusivity was found in the left cingulum, left uncinated fasciculus, left anterior thalamic radiation and left superior

Table 2. Group-wise comparisons in white matter indexes.

Index	Cluster Size (voxels)	MNI coordinate			t-value	P-value	Effect size (Cohen's d)
		x	y	z			
HSA-PD > HC							
AD							
Body of corpus callosum	526	−16	−15	35	2.79	<0.001	0.93
MD							
Left superior longitudinal fasciculus	522	−23	−11	45	1.81	<0.001	0.60
Left anterior thalamic radiation	276	−19	−17	51	1.54	<0.001	0.51
Right uncinate fasciculus	202	43	17	−18	1.03	<0.001	0.34
Left cingulum	197	−7	−36	32	3.14	<0.001	1.04
Left cingulum	72	−7	23	24	1.92	<0.001	0.64
HSA-PD > LSA-PD							
AD							
Body of corpus callosum	5267	5	13	22	4.40	0.014*	1.56

Cluster size denotes the extent of the cluster of significant voxels. MNI (Montreal Neurological Institute) coordinates refer to the location of the most statistically significant voxel in the cluster. HSA-PD, High-subclinical symptoms of apathy Parkinson's disease group; LSA-PD, Low-subclinical symptoms of apathy Parkinson's disease group; HC, Healthy controls; AD, Axial diffusivity; MD, Mean diffusivity. * FWE-corrected
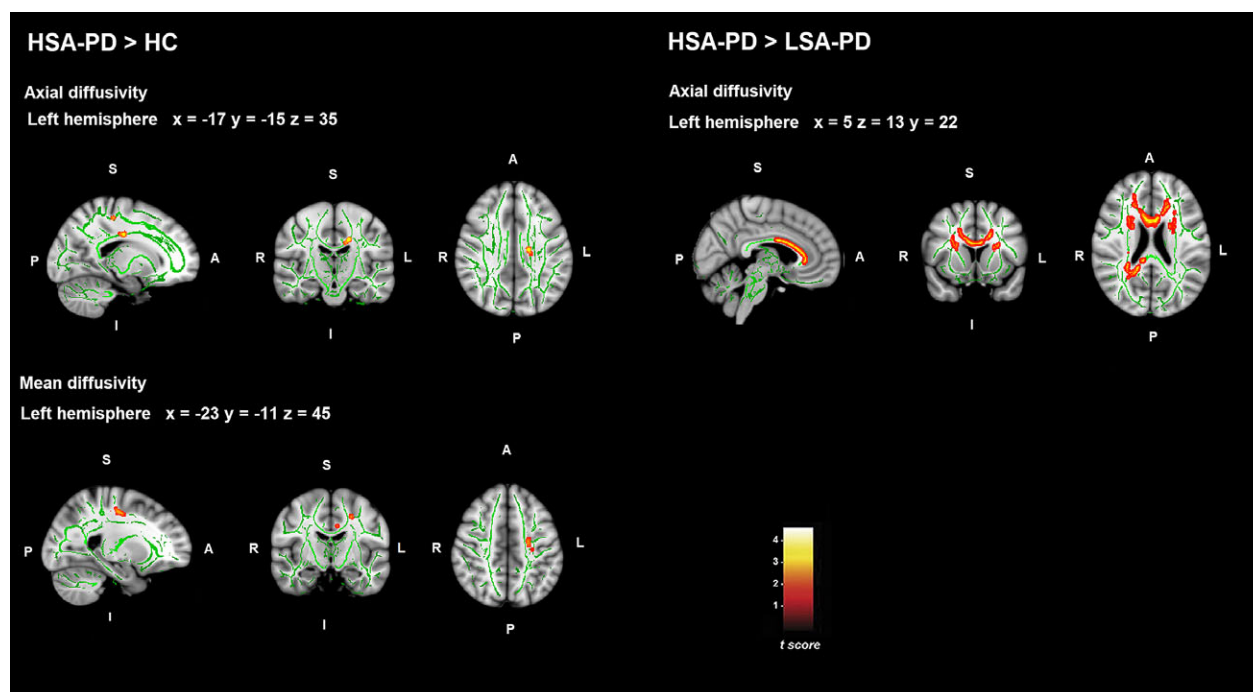

Figure 2. Group differences in white matter indexes. Significant white matter regions are shown in red-yellow; the white matter skeleton is shown in green. Results are shown at *P* < 0.05 FWE-corrected and *P* < 0.001 uncorrected. Coordinates are shown in MNI space (Montreal Neurological Institute). Significant voxels are thickened for easier visualization. Abbreviations: HSA-PD = High-subclinical symptoms of apathy Parkinson's disease group; LSA-PD = Low-subclinical symptoms of apathy Parkinson's disease group; HC = Healthy controls; S = Superior; I = Inferior; A = Anterior; P = Posterior; L = Left; R = Right.

longitudinal fasciculus in HSA-PD compared with HC. Axial diffusivity alterations may contribute to increased mean diffusivity that could refer to loss of tissue density. A very recent study[29] investigated white matter changes in PD patients without cognitive impairment and they also found higher mean and axial diffusivity in similar areas. Moreover, in the same study, PD patients with normal cognition did not show grey matter atrophy.[29]

Table 3. Group-wise comparisons in resting-state functional connectivity.

Seed	Target	*t*-value	*P*-value	Cohen's *d*
HSA-PD < HC				
Left Inferior frontal gyrus opercularis	Right putamen	3.36	0.007	1.12
	Left putamen	2.84	0.015	0.94
	Right pallidum	2.36	0.027	0.78
	Left pallidum	2.31	0.027	0.77
Left supplementary motor area	Right nucleus accumbens	2.90	0.026	0.96
Left fronto-orbital gyrus	Right putamen	3.57	0.004	1.19
	Right pallidum	3.31	0.005	1.10
	Left putamen	2.43	0.028	0.81
HSA-PD < LSA-PD				
Right superior frontal gyrus	Left putamen	2.85	0.038	1.01
Left precentral	Left pallidum	2.73	0.048	0.97
LSA-PD < HC				
Left Inferior frontal gyrus opercularis	Left putamen	3.30	0.009	1.02
Left amygdala	Left nucleus accumbens	2.87	0.027	0.88
Right superior frontal gyrus	Left putamen	−2.72	0.035	0.84
	Left caudate	−2.48	0.035	0.76
Left inferior frontal gyrus triangularis	Right caudate	−3.02	0.018	0.93

HSA-PD, High-subclinical symptoms of apathy Parkinson's disease group; LSA-PD, Low-subclinical symptoms of apathy Parkinson's disease group; HC, Healthy controls.

Taking into account the results of this type, whiter matter impairment in PD might be a sensitive sign preceding the neuronal loss in associated grey matter regions related to apathy. Authors interpreted the increased axial diffusivity as resulting from expansion of extracellular space caused by axon and myelin loss.[29] Despite these results, a recent review study[15] remarked the scarce investigation in mood disturbances in PD. One study assessing white matter volume in apathetic PD patients found white matter loss in frontal regions, cingulate region and the insula.[11] Interestingly, in other pathologies such as Alzheimer's disease, bilateral anterior thalamic radiations[30] and corpus callosum[31] alterations in white matter are strategic for the occurrence of apathy. However, white matter axial diffusivity results have to be interpreted with caution.

The results in resting-state functional MRI showed that HSA-PD patients revealed an FC decrement in fronto-striatal and fronto-limbic pathways compared with HC, but only fronto-striatal FC decrement when compared with LSA-PD patients. In the study by Baggio and colleagues, [14] they also found that apathetic PD patients showed FC reductions compared with HC mainly in limbic, striatal and frontal regions. Interestingly, dorsolateral prefrontal cortex–caudate circuits are key structures implicated in any form of apathy.[1] Comparing LSA-PD versus HC, significant FC decrements in fronto-limbic pathways were found between left amygdala and left nucleus accumbens.

Strikingly, LSA-PD patients also showed an increased fronto-striatal FC (hyperconnectivity) between the left inferior frontal gyrus and right caudate and between the right superior frontal gyrus and left caudate and left putamen compared with HC. This hyperconnectivity could suggest that LSA-PD patients recruited additional resources as a mechanism to maintain the lower symptomatology of apathy. Previous studies also showed that the increased FC might be the initial manifestation of altered brain function preceding cognitive deficits.[32,33] This idea is in line with others in which an extensive review using fMRI methods in several pathologies revealed that hyperconnectivity is a common response to neurological alteration.[34] It might be speculated that alterations such as hyperconnectivity in the pre-symptomatic phases could be the basis for the development of a biomarker, because, as the disease progresses, a critical loss of resources may result in gradual increment of FC in other areas,[33,34] specifically in striatal pathways.[35] Some autopsy-controlled studies in PD revealed associated pathology before the symptoms become recognizable and highlighted the relevance of nonmotor symptoms which appear before the cardinal motor symptoms.[36] For instance, in other pathologies such as Alzheimer's disease, hyperconnectivity was observed to reflect adaptive changes as an attempt to maintain cognitive performance.[37] Fronto-striatal brain changes have also been associated with cognitive disturbances. One study revealed that PD patients with executive impairments on set
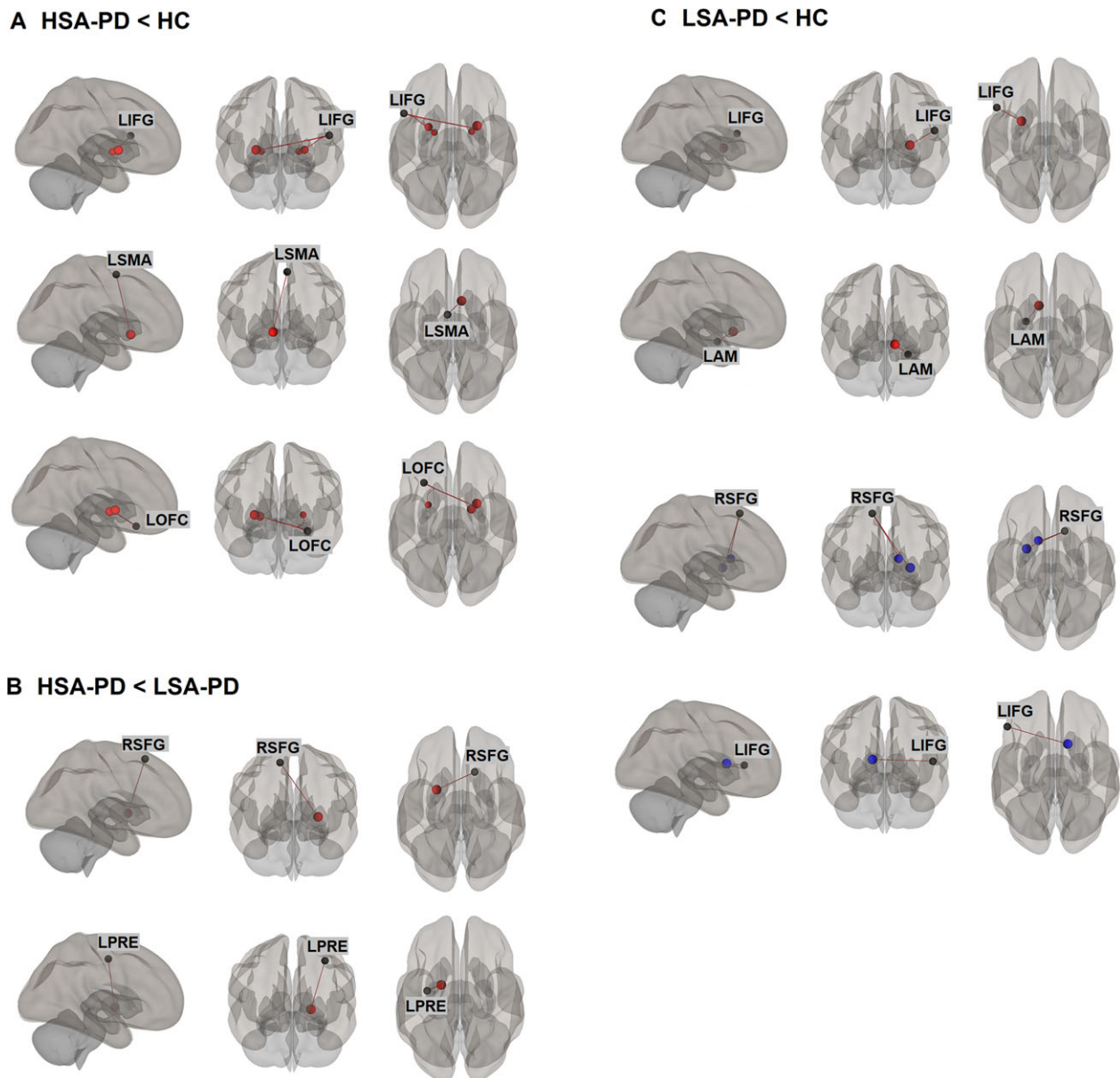
A HSA-PD < HC

B HSA-PD < LSA-PD

C LSA-PD < HC

Figure 3. Group differences in resting-state functional connectivity. Seeds are the black points and targets are the red points (one-sided positive). Blue points indicate inverse differences (LSA-PD > HC one-sided negative). Results are shown at $P < 0.05$ FDR-corrected. (A) Differences between HSA-PD and HC. (B) Differences between HSA-PD and LSA-PD. (C) Differences between LSA-PD and HC. Abbreviations: HSA-PD = High-subclinical symptoms of apathy Parkinson's disease group; LSA-PD = Low-subclinical symptoms of apathy Parkinson's disease group; HC = Healthy controls; L = Left; R = Right; IFG = Inferior frontal gyrus; OFC = Fronto-orbital gyrus; SMA = Supplementary motor area; PRE = Precentral gyrus; SFG = Superior frontal gyrus; AM = Amygdala.

shifting and working memory tasks showed hypo-activation within the fronto-striatal loops connecting dorsolateral and ventrolateral prefrontal cortices, striatum and thalamus.[38]

Regarding the correlates of apathy, in HSA-PD patients, the lack of emotion and intellectual curiosity correlated with the altered fronto-striatal pathway, which is the most affected system when compared with HC or LSA-PD. Interestingly, the fronto-striatal hyperconnectivity in LSA-PD, which might be a compensatory mechanism of limbic dysfunction, correlated significantly with better emotion symptoms in apathy. This result goes in line with previous studies in which the disruption of emotional-affective mechanisms related to apathy are linked to the ventromedial prefrontal cortex, amygdala, and ventral striatum.[1,39] Moreover, a recent study showed

that an increase in apathy symptoms in PD predicted a decrease in the FC between the bilateral caudate and bilateral thalamus and between the right gyrus rectus and the right parahippocampal gyrus.[40] Finally, the structural-functional MRI relationship in HSA-PD patients was observed between white matter difusivity (mean and axial) alterations and reduced fronto-striatal FC. This alteration revealed that the higher the white matter mean and axial diffusivity, the lower the FC between left orbitofrontal cortex and left putamen. These findings could indicate that in the LSA-PD group a hyperconnectivity is present, but with greater subclinical symptoms of apathy (HSA-PD), the fronto-striatal pathway is affected showing an hypoconnectivity which is related with white matter mean and axial diffusivity alterations.

It is potentially interesting that in line with resting-state FC results, hyperconnectivity differences have been found in other pathologies, and that hyperconnectivity has been related to apathy symptoms.[41] Specifically, some studies reported increased FC in bipolar and schizophrenia patients involving frontal and limbic regions when compared with HC.[42,43] Moreover, this increased connectivity in this frontal-paralimbic network correlated with negative symptoms in bipolar patients.[42] In fronto-temporal dementia, even after controlling for structural atrophy, frontal hyperconnectivity was also associated with apathy scores.[44] These same results related to hyperconnectivity across various neuropsychiatric and neurodegenerative diseases could explain the underlying mechanism of apathetic symptomatology, and therefore, could be considered as a cross-disease model for early symptoms of apathy.

To our knowledge, this is the first study assessing the association between subclinical symptoms of apathy and brain changes combining three modalities of neuroimaging and exploring more than one index in DTI white matter values. The results showed that the affected pathway in LSA-PD was the limbic circuitry while in HSA-PD the fronto-striatal and fronto-limbic pathways were affected. In addition, DTI and resting-state functional MRI brain changes in HSA-PD patients are related in the same region. Finally, not only brain differences are present between groups, but also a relationship between apathy subclinical symptoms of the four subscales and those brain changes.

Limitations

Some limitations should be taken into account. The fulfillment of the UK PD Society Brain Bank diagnostic criteria was only checked by a single neurologist. An observance-expectancy effect may have occurred because participants were instructed not to sleep in resting-state.

In addition, PD patients were not diagnosed with apathy but the aim of the study investigated high and low subclinical symptoms of apathy. Future studies addressing apathy with caregivers' scales such as LARS-i[22] and the four apathy severity classes described in Sockeel and colleagues are needed. Employment of more sophisticated techniques to control crossing fibers in white matter analysis is needed. The use of different correction methods has to be considered. Finally, longitudinal studies are needed to assess the evolution of apathy symptoms in PD with whole-brain and ROI approaches.

Conclusions

Findings suggest distinct brain alterations in HSA-PD and LSA-PD patients. Brain changes may occur in the absence of detectable structural grey matter damage. Thus, the investigation of both brain functional and structural connectivity can provide different but complementary information for the understanding of neurobiological mechanisms underlying apathy effects. The initial response to the pathological process of apathy in PD could be the recruitment of additional resources in LSA-PD patients, which could be understood as a possible adaptive mechanism until the peak of available resources is reached. The current findings could help clinicians and researchers to be aware of the potential presence of apathy while symptoms are in the first stages. Early identification of apathy could be helpful to develop new therapies including the management of apathy as a key factor.

Acknowledgments

Authors' Contribution

Conception and design of the study: OLJ, NO, JP, and NIB. Acquisition and analysis of data: OLJ, NO, JP, ACZ, MDC, JCGE, MAGB, and NIB. Drafting a significant portion of the manuscript or figures: OLJ, NO, JP, MDC, and NIB.

Conflict of Interest

Nothing to report.

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Supporting Information

Additional Supporting Information may be found online in the supporting information section at the end of the article.

Figure S1. Post hoc Analyses: Structural MRI and resting-state functional MRI relationship. In HSA-PD patients, the increased white matter mean diffusivity and axial diffusivity correlated with the reduced FC between left orbitofrontal cortex and left putamen ($\rho = -0.818$, $P = 0.001$; $\rho = -0.811$, $P = 0.001$), indicating that the higher the white matter mean diffusivity and axial diffusivity, the lower the FC between left orbitofrontal cortex and left putamen. No correlations were found in LSA-PD or HC.

Figure S2. Scatterplots. (A) Correlations between apathy factors and functional connectivity and between apathy factors and mean and axial diffusivity in HSA-PD. (B) Correlation between emotion factor and hyperconnectivity in LSA-PD. (C) Correlation between UPDRS III and hyperconnectivity in LSA-PD.