RESEARCH ARTICLE

Anatomical and Functional Correlates of Persistent Pain in Parkinson's Disease

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ABSTRACT: Background: The pathophysiology of pain in Parkinson's disease (PD) is still poorly understood, although it is conceivable that supraspinal mechanisms may be responsible for pain generation and maintenance.

Methods: We examined brain functional and anatomical changes associated with persistent pain in 40 PD patients, 20 with persistent pain and 20 without pain. We also examined 15 pain-free healthy participants of similar age, gender, and cognitive state as a control group. We assessed pain by the King's Parkinson's Pain Scale, the Visual Analogue Scale for pain, and the Leeds Assessment for Neuropathic Symptoms and Sign. All patients underwent structural, diffusion tensor imaging, and resting-state functional MRI. We compared clinical characteristics, whole-brain cortical thickness, subcortical volumes, diffusion tensor imaging scalar measures, and functional connectivity by network based statistics.

Results: The group with PD and persistent pain showed significant thinning in the bilateral temporal pole, left-medial orbitofrontal cortex, bilateral superior and left-inferior parietal areas, pars orbicularis, and right superior frontal, posterior cingulated, and precentral cortex. There were no significant subcortical volume and white matter differences between PD subgroups. Functional MRI showed a decrease of brain activity in the left frontal inferior orbital in PD patients with persistent pain, with greater activity bilaterally in the cerebellum and in the right inferior temporal areas. Only PD patients with persistent pain showed an accumbens–hippocampus disconnection without white matter and subcortical alterations.

Conclusions: We showed that persistent pain in PD is associated with supraspinal structural and functional changes. We also highlighted the contribution of frontal, prefrontal, and insular areas in nociceptive modulation and accumbens–hippocampus disconnection.

Key Words: chronic pain; Parkinson's disease; neuropathic pain; neuroimaging; fMRI

Pain is one of the most common nonmotor symptoms in Parkinson's disease (PD) with a prevalence ranging from 40% to 85%, heterogeneous clinical presentation, and a disabling impact on quality of life.[1,2] Pain is reported already at the onset of the disease,[3] it negatively affects rehabilitation strategies, and increases relatives and caregivers' burden.[4] Nonetheless, it is often underrecognized and undertreated.[5,6]

Pain can occur as a consequence of dystonic muscle contraction at the end of levodopa effect, secondary to comorbidities such as osteo-arthrosis or disk herniation,[7] and as a result of peripheral neuropathy.[4,7] Indeed, it is now evident that with advancing disease, a significant number of patients present abnormal nociceptive processing, reporting a lower pain threshold than healthy controls.[8] Pain threshold may also be

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variably modulated by levodopa treatment, regardless of its aetiology.[9] However, pain does not constantly improve with dopaminergic therapy[10] and may also respond to other treatments, including deep brain stimulation,[11] suggesting that other supraspinal mechanisms, not directly influenced by dopamine, are involved in its modulation.

The experience of pain is associated with psychological and neurophysiological responses and is processed by a broad neural network, which includes sensory-discriminative, motivational-affective, and cognitive areas.[12,13] Specific brain alterations are found in several persistent pain conditions with a different pathophysiology, such as irritable bowel syndrome, fibromyalgia, headache, or neuropathic pain. Regions found consistently involved are somatosensory areas, the insula, anterior cingulate cortex (ACC), prefrontal cortex (PFC), thalamus (Th), and periaqueductal gray matter.[14] Some (PFC, Th Insula, ACC, and hippocampus) are also linked to the pars compacta of substantia nigra (SNpc), providing the neural bases for a PD-specific network involvement in pain processing.[15-17]

However, to date there are no studies investigating whether pain in PD is associated with structural alteration, whereas functional imaging has confirmed the role of the insula and ACC as well as prefrontal and somatosensory cortices.[10,18]

Nonetheless, the exact mechanisms of nociceptive processing and modulation in PD remain unclear.[19] In this study, we assessed both structural and functional cerebral changes associated with persistent pain in PD patients. Persistent pain was assessed using the King's PD pain scale that has been specifically developed for the assessment of PD pain and recently applied in clinical trials.[20,21]

Methods

Participants

From February 2013 to May 2015, a total of 188 consecutive PD inpatients were examined at the Parkinson Disease Unit of IRCCS San Camillo Hospital, in Venice, Italy. All patients underwent extensive clinical, neuropsychological, behavioral, and MRI evaluations. The patients' inclusion criteria were a diagnosis of idiopathic PD according to the UK Brain Bank criteria,[22] an ability to understand study purposes and procedures, and a willingness to participate in the study. To maximize subjective feedback from self-reported questionnaires and take into account cognitive and psychological aspect that might influence pain,[17] a Mini-Mental State Examination score (MMSE)[23] ≥ 24 and Beck Depression Index-II score (BDI-II[24] < 30 were considered inclusion criteria.

Exclusion criteria were the presence of previous neurosurgical procedures (including deep brain stimulation); severe psychosis or psychological diseases, which may hinder perception or self-reporting of pain; peripheral neuropathy as a result of comorbidities, such as Herpes zoster or posttraumatic neuropathies; and diffuse vascular lesions on MRI scan (as seen on FLuid Attenuated Inversion Recovery(-FLAIR)). A total of 25 age-matched and pain-free healthy controls (HC) were also included and underwent the same clinical and neuroimaging assessment protocols.

The pain subscales of the 36-item Short Form(SF-36) Health Survey[25] (items 21 and 22) were used to define a clear division between the PD-Pain group and the PD-Ctrl group. Patients were enrolled in the PD-Pain group if they reported severe or very severe pain (item 21) or to have pain interfering with everyday activities quite a bit or extremely (item 22). In the PD-Pain group, we only enrolled patients who had (1) persistent pain for more than 3 months and (2) pain experienced on a recurrent or daily basis (item 2 of King's Parkinson's Disease Pain Scale [KPP] > 2).[20,21] PD patients and healthy participants declaring no pain or very little pain that did not interfere with normal activities were included in the PD-Ctrl and HC groups, respectively. We decided to use both the SF-36 and KPP scales to better characterize pain symptoms. The 2 scales together can assess pain intensity, frequency, and its impact on daily activities. Moreover, the KPP has also been used in recent clinical trials to test the effect of pain medications.[20]

This study was approved by the ethical committee of the IRCCS San Camillo Hospital. Written informed consent was obtained from each individual according to the Declaration of Helsinki after an extensive explanation of the aim and experimental procedures of the study (Protocol 2013.08).

Study Procedure

All patients underwent a complete clinical assessment, an extensive neuropsychological evaluation,[26,27] and a MRI imaging acquisition within the first week after hospital admission.

Demographic (age, gender, education), clinical (disease duration, comorbidities, medications, Unified Parkinson Disease Rating Scale [UPDRS-parts II and III][28]; Hoehn and Yahr [H&Y],[29] and pain symptoms), cognitive and behavioral status (MMSE,[23] BDI-II,[24] State Trait Anxiety Inventory [STAI-Y1 and −Y2][30] were assessed. Dopaminergic medications were stable during the entire assessment period, and the scanning procedures were always set at the same time of day in the medication ON-state to avoid biases because of diurnal variations. The levodopa equivalent dose (LEED)[31] was calculated, and other medications were noted.

To comprehensively evaluate the pain of the PD and healthy participants, we used the following 3 tools: the KPP scale,[20,21] a Visual Analogue Scale (VAS),[32] and Leeds Assessment of Neuropathic Symptoms and Signs (LANSS).[33] The KPP scale is a validated comprehensive questionnaire and was chosen for its ability to discriminate different types of pain and evaluate its intensity and daily frequency.[26] The scale has 7 domains investigating musculoskeletal, chronic, visceral, nocturnal, motor fluctuation–related, radicular, and oro-facial pain during the last month. One or more items address every domain. Higher scores are associated with more frequent or more intense pain.[21] The LANSS scale was developed to discriminate whether pain had predominantly neuropathic features, and it includes 7 items investigating different symptoms such as burning pain, electroshock-like pain, pins and needles sensations, and hyperalgesia. Scores can range from 0 to 24, and a score of 12 or higher indicates that pain is likely to have a neuropathic origin.[33]

Secondary outcomes assessed functional and motor severity of Parkinson's disease (UPDRS part-II, III and H&Y) and psychological (BDI-II, STAI-Y1, and STAI-Y2) and cognitive characteristics (MMSE). Data relative to secondary outcomes and their validity and accuracy can be found in previous studies.[26,27]

MRI Acquisition

Patients underwent structural diffusion tensor imaging (DTI), and functional resting state MRI with a 1.5 T Achieva Philips scanner (Philips Medical Systems, Best, The Netherlands) with an 8-channel head coil. MRI protocol included (1) a whole-head 3-dimensional sagittal T1-weighted-3D-TFE (repletion time [TR] = 8.3 milliseconds, echo time [TE] = 4.1 milliseconds, flip angle = 8°, matrix resolution [mr] = 288 × 288, slice thickness [ST] = 0.87 mm), (2) echo-planar imaging sequence (TR = 1929.2 milliseconds, TE = 45 milliseconds, slices = 25, ST = 5.2 mm, acquired voxel size [mm] = 2.875 × 2.875; mr = 80 × 80; FA = 90°, SENSE-factor = 2, volumes = 240), and (3) Diffusion Weighted Imaging (DWI) sequence (TR = 11067.3 milliseconds, TE = 80.3 milliseconds, slices = 67, ST = 2 mm, acquired voxel size [mm] = 2, mr = 128 × 128, flip angle = 90°, SENSitivity Encoding(SENSE)-factor = 2, volumes = 33, diffusion direction = 32; diffusion B-value = 800, number of acquisitions = 3).

Participant's heads were accurately immobilized with pillows to minimize head movement artifacts. During data acquisition, participants were instructed to lie quietly in the scanner, close their eyes, and remain awake. The echo-planar imaging field of view was set parallel to the intercommissural line to guarantee a whole-brain analysis. MRI scans with cerebral small vessel disease (assessed in T1) periventricular white matter (WM) hypo intensity in T1, evidence of space-occupying lesions, and head motion artefacts were excluded.

Cortical Thickness and Subcortical Volume Analysis

Gray matter (GM) changes within PD groups were analyzed comparing cortical thickness.[34] Cortical thickness and subcortical volumes were obtained with FreeSurfer-5.3 Software[35] that computes the curvature of the GM and WM interfaces to characterize sulci and gyri and inflates the whole brain into a sphere for the purpose of surface-based nonrigid registering of participants according to the Talairach standard atlas.[35,36] The human cortex is then divided into 34 regions of interest in each hemisphere[36] and in subcortical WM and GM volumetric structures (including the hippocampus, amygdala, caudate, putamen, accumbens, and ventricles).[35]

Tract-Based Spatial Statistical Analysis

WM microstructural brain tissue integrity was assessed using DTI measures of fractional anisotropy (fractional anysotropy (FA); unspecific microstructural alteration), mean diffusivity (MD; cellular membrane or cellular density alteration), and radial diffusivity (demyelination).[37] Native data were processed using the dt_recon Freesurfer tool. Preprocessing steps included dual-step registration to standard Montreal Neurologic Institute(MNI) space and selection of WM tracts less affected from between-subjects' variability by means of skeletonization Functional MRI of the Brain(FMRIB)-Software-Library(FSL)'s procedure (http://www.fmrib.ox.ac.uk/fsl/). See the supplementary material for further details.

Resting State Analysis

To analyze if persistent pain is associated with abnormalities in regional neuronal spontaneous activity, we compared MRI-based fractional amplitude of low frequency fluctuations (fALFF)[38] between the PD-Pain and PD-Ctrl groups. fMRI data preprocessing was run using the dpabi-Resting-State fMRI Data Analysis Toolkit (4.0 version, http://rfmri.org/dpabi)[39] and included (1) slice timing, (2) spatial realignment, (3) nuisance covariates regression, (4) temporal band pass filtering (0.01Hz-0.073 Hz), (5) ALFF and fALFF calculation, and (6) 2-step normalization to the MNI template. See the supplementary materials for details.

Region-Of-Interest(ROI)-based Resting-State Brain Networks-Based Statistical Analysis

To assess if functional connectivity in areas involved in acute and chronic pain are different among PD subgroups and HC, the resting state signal coherence

between the pain networks' ROIs was compared using a network-based statistical analysis (NBS).[40] The resting state fMRI in the HC were as previously described for PD patients. Based on recent literature,[41] we chose 20 regions known to be associated with pain: left and right sensory areas(S1 and S2), left and right insula, supplementary motor regions, anterior and posterior cingulate cortices, left and right thalamus, left and right hippocampus, left and right amygdala, periaqueductal gray matter, left and right nucleus accumbens, and left and right cerebellum areas. Thresholds were set at 0.70 of probability and masked using a mean GM mask previously obtained by Statistical Parametric Mapping release8-Data Processing & Analysis of Brain Imaging (SPM8-DPABI) segmentation of a sample T1-weighted-3D. Raw means were extracted from each ROI using the dpabi tool and then included in NBS using the GraphVar (0.62 version) tool (https://www.nitrc.org/projects/graphvar/).[42]

The preprocessing procedure of the fMRI correlation matrix included (1) band pass filtered raw signal extraction from the ROIs, (2) correlation matrix generation, (3) values normalization, (4) generation of permuted matrix, (5) T-based threshold, and (6) network model generation (see the supplementary materials for details). After preprocessing, network models were considered for each participant if they reach an explorative $P < .1$ and a node size > 3.

Statistical Analysis

Statistical analyses included between-group comparisons of demographic and clinical variables of PD-Pain versus PD-Ctrl groups. Continuous and dichotomous variables were compared among groups running nonparametric Mann–Whitney *U* and chi-squared tests. Pearson correlations were used to analyze the degree of association between clinical, demographic, and neuropsychologic variables. All statistics were performed using SPSS version 20 (IBM SPSS, Chicago, Illinois).

Between-group differences for the cerebral GM thickness and subcortical volumes were assessed by general linear model (GLM) surface-based analysis. Statistical maps were generated using Freesurfer's QDEC 1.4 (Query, Design, Estimate, Contrast) application. QDEC fits a GLM at each surface vertex to explain the data from all participants in the study. The results were obtained with a full-width/half max of 15 mm. Age, disease duration, LEED, and intracranial volume were used as covariates for each group. We applied Monte Carlo nonparametric testing, correcting for multiple comparisons across space for cerebral thickness. For the cortical thickness analysis, a $P < .05$ clusterwise Monte Carlo corrected threshold was used, and a $P < .005$ uncorrected threshold was used only for exploratory purposes. A $P < .05$ Sidak correction for multiple comparisons across areas was adopted for subcortical volumes.

For DTI, we used the FSL tool Tract-Based Spatial Statistics(TBSS)[43] to compare diffusion measures between PD patients' subgroups, including age, disease duration, LEED, and intracranial volume in the model, as covariates for each group separately. In addition, fALFF GLM comparisons were performed voxel by voxel between PD subgroups with the FSL randomize tool.[39] Statistical results for the DTI and fALFF were corrected for multiple comparisons using the FSL randomize tool, with 5000 permutations, and the randomize option threshold-free cluster enhancement (TFCE)[43] was applied with threshold at $P < .05$. We adopted a nonparametric permutation-based Family-Wise Error (FWE) multiple correction. This approach has been indicated as adequate to minimize false positive findings.[44]

Finally, nonparametric analysis of variance was run among suprathreshold connections in the PD-Pain, PD-Ctrl, and pain-free HC groups to rule out possible brain alterations specific to PD but not related to pain. The *F* test for multiple comparisons was performed at the $P < .05$ level of significance.

Results

Demographic and Clinical Features of Participants

A total of 40 PD patients (28 men and 12 women) and 15 pain-free HC (12 men and 3 women) fulfilled the selection criteria and were enrolled in the study. Mean patient age was 66.64 (standard deviation [SD] 10.07), and disease duration was 10.49 years (SD 5.02). Of the PD patients, 20 (11 men and 9 women) were included in the PD-Pain group, and 20 patients (17 men and 3 women) were classified as PD-Ctrl. Mean HC age was 61 (SD 8.30), MMSE > 28, and BDI was 8.00 (SD 8.98). Demographic and clinical features of PD patients are summarized in Table 1.

The PD subgroups were similar in age, severity of the disease (H&Y), motor severity (UPDRS III), and motor aspects of experiences of daily living (UPDRS II), with a trend for greater prevalence of women in the cohort with pain. Cognitive and psychological aspects (MMSE, BDI, STAI-Y1, and STAI-Y2) were also similar in the 2 groups. PD-Pain patients had longer disease duration ($P = .045$), received less levodopa therapy ($P = .035$), and presented greater pain scores ($P = .0001$, $P = .0004$, and $P = .004$ for KPP, VAS, and LANSS, respectively). The KPP global score strongly correlated with the VAS and LANSS scores ($P < .0001$). In addition, all 7 domains of the KPP score were correlated ($P < .05$). All PD-Pain patients scored musculoskeletal, chronic, and visceral pain domains, and in at least 2 other domains of the scale

TABLE 1. Demographics of Parkinson and healthy controls subgroups

	PD-Pain		PD-Ctrl		
	Mean	SD	Mean	SD	*P* value
Demographics					
Gender, male/female	11/9		17/3		.0845[a]
Age, y	64.60	9.32	68.05	10.81	.1894
Years of disease	12.20	3.83	9.05	5.63	**.0451**
Disease-specific assessment					
UPDRS II	16.37	7.13	13.25	7.32	.1691
UPDRS III	26.90	14.13	24.31	14.56	.3889
H&Y (1.5/2/2.5/3/3.5/4)	1/5/9/2/1/2		1/9/5/5/0/0		.2545*
LEED	942.60	367.68	1186.65	401.16	**.0349**
Cognitive and psychological assessment					
BDI	10.45	5.52	8.90	6.56	.2606
STAI-Y1	36.65	9.37	35.44	11.12	.6929
STAI-Y2	40.95	7.39	37.72	9.48	.3128
MMSE	26.36	1.90	26.28	2.60	.7451
Pain					
SF 36 Pain intensity	4.00	0.46	1.30	0.57	**.0001**
SF 36 Pain impact	4.95	0.51	1.80	0.95	**.0001**
LANSS	11.00	6.68	1.30	3.56	**.0001**
VAS	1075.37	339.29	291.50	362.66	**.0001**
King's Parkinson's Disease Pain Scale					
Musculoskeletal Pain	10.60	2.04	3.30	3.67	**.0001**
Chronic and Visceral	13.40	3.87	2.15	3.22	**.0001**
Fluctuation-related Pain	8.45	7.71	0.30	1.34	**.0001**
Nocturnal Pain	8.85	6.47	1.20	2.55	**.0001**
Oro-facial Pain	3.25	5.48	0.05	0.22	**.0039**
Edema/swelling	4.95	5.05	0.00	0.00	**.0001**
Radicular Pain	4.25	3.40	0.00	0.00	**.0001**
Total King's PD-Pain	53.75	19.28	6.55	6.61	**.0001**
ICV	1438140	143487.7	1511479	191107.2	.2674

Bold *P* value fonts indicate variables with significant difference. PD, Parkinson's disease; LANSS, Leeds Assessment of Neuropathic Symptoms and Signs; VAS, Visual Analogue Scale; UPDRS, Unified Parkinson Disease Rating Scale (parts II and III); H&Y, Hoehn and Yahr; BDI, Beck Depression Index; STAI, State Trait Anxiety Inventory (Y1, part 1; Y2, part 2); MMSE, Mini-Mental State Examination; LEED, levodopa equivalent dose; SF36, pain subscales of the 36-item Short Form(SF-36) Health Survey[14] (items 21 and 22); ICV, intracranial volume.
[a]Tests for between-group independent comparison were the Mann–Whitney *U* and chi-squared tests.

(oro-facial domain >0 in 45% and edema/swelling domain >0 in 60% of the PD-Pain subgroup). By contrast, no persistent or frequent pain symptoms were reported in the PD-Ctrl group. Of the PD-Ctrl patients, 13 were completely pain free, and the others reported only low intensity scores in fewer than 3 subitems (eg, mild score related to physical exercise or digestive functions).

Disease duration positively correlated with King's PD-Pain score ($P<.017$). Age negatively correlated with the edema/swelling domain of King's PD-Pain score ($P=.033$). There was no correlation between pain scores and disease severity (H&Y, UPDRS-III), functional impairment (UPDRS-II), LEED, psychological status, or cognitive performances global score in any pain assessment measure.

A total of 6 patients in the PD-Ctrl group and 3 patients in the PD-Pain group were on benzodiazepines or antidepressants. In both groups there were patients on additional medications, such as cardioaspirin or melatonin. All patients in the PD-Pain group were on analgesic medication (16 in monotherapy, mainly paracetamol and 4 in association with codeine or oxycodone). Only 3 of 20 patients in the PD-Ctrl group occasionally take paracetamol.

Cortical and Subcortical Pattern Associated With Pain in Parkinson's Patients

The PD-Pain patients showed significant thinning ($P<.05$ Monte Carlo corrected) in the right superior frontal gyrus, namely, the dorso-lateral prefrontal cortex (DLPFC), when compared with the PD without pain participants. Moreover, widespread cortical thinning (uncorrected $P<.005$ threshold) was also found in the temporal pole bilaterally, left pars opercularis, superior parietal, postcentral, medial orbitofrontal cortex, and in parts of the superior temporal sulcus. In the right hemisphere, significant thinning was found in posterior insular cortex (pIC), lateral occipital cortex, posterior cingulate cortex (PCC), supramarginal area, and superior temporal gyrus (see Table 2, Fig. 1A).

TABLE 2. Significant cortical thickness differences between PD-Pain and PD-Ctrl

Desikan atlas	Clusterwise MC p-value	Max *P* value	Size, mm^2	TalX	TalY	TalZ	NVtxs
Left hemisphere							
Temporal pole		0.00008	101.45	−30.5	4.2	−31.7	209
Pars opercularis		0.00036	183.21	−44.4	6.4	6.6	455
Superior parietal		0.00271	12.1	−32.6	−42.2	43.0	34
Postcentral		0.00320	24.42	−40.5	−26.5	50.5	60
Inferior parietal		0.00396	10.68	−39.6	−74.8	33.4	18
Banksts		0.00464	3.5	−43.5	−53.1	9.2	7
Medial orbitofrontal		0.00467	7.39	−6.9	27.9	−11.7	14
Right hemisphere							
Lateral occipital		0.00007	30.6	−80.6	6.3	6.3	560
Temporal pole		0.00010	31	3.2	−30.1	−30.1	111
Insula (posterior pars)		0.00029	35.5	−9.1	−3.8	−3.8	345
Posterior cingulate		0.00074	12.8	−35.5	39.2	39.2	171
Superior frontal	**0.00110**	**0.00335**	**14.7**	**46.7**	**36.7**	**36.7**	**88**
Superior frontal (SMA aal)		0.00411	9.7	−5.2	52.5	52.5	32

GLM surface-based cortical thickness analysis. Age, disease duration, LEED, and intracranial volume were used as covariates. Bold font indicates areas significant after Monte Carlo correction (clusterwise threshold of $P < .05$). Local maxima that were significant after $P < .005$ uncorrected are reported. No significant between-group changes in subcortical volumes were found after Sidak correction for multiple comparisons (P value $< .05$). Banksts, bank of the superior temporal sulcus; TalX, TalY, TalZ. X,Y, and Z in Talairach coordinate system; NVtxs, number of vertices; size, cluster surface area; clusterwise MC *P* value, clusterwise Monte Carlo-corrected *P* value; SMA, supplementary motor area; aal, Automated Anatomical Labeling atlas; LEED, levodopa equivalent dose.

There were no significant between-group changes in the subcortical volumes.

WM microstructural integrity was assessed comparing FA, RD, and MD maps along the WM region with low morphological variation across population. No region survived either TFCE-FWE correction ($P < .05$) or exploratory uncorrected $P < .01$ thresholds for each index comparing PD with and without pain.

Changes in Regional Spontaneous Brain Activity Associated With Pain in Parkinson's Patients

A total of 2 patients in each PD group had acquisition artifacts during fMRI (relative movement > 1.5 mm) and were excluded from analysis. PD-Pain patients showed a reduction of fALFF in the frontal inferior orbital of the left hemisphere (Table 3, Fig. 1B). On the contrary, greater fALFF activity was found bilaterally in the cerebellum area and in the temporal inferior areas of the right hemisphere.

ROI-Based Network Comparison in Parkinson's Patients and HC

The *F* test analysis showed a significant difference between the HC, PD-Ctrl, and PD-Pain groups in the right Nucleus Accumbens (NAc)–left hippocampus connection. After post hoc comparisons, we found that this disconnection between the NAc and left hippocampus was determined solely by the PD-Pain cohort ($T = 3.54$, $P < .05$ corrected; see Fig. 2).

Discussion

We investigated functional and structural brain correlates of persistent pain in PD using both an exhaustive clinical evaluation and neuroimaging techniques. This is the first report linking a comprehensive clinical assessment of persistent pain with anatomical and functional neuroimaging.

Our data indicate that persistent pain in PD is associated with relative thinning in several brain areas—DLPFC, Orbito-Frontal Cortex (OFC), posterior Insular Cortex (pIC), and PCC—and with local functional alterations in the OFC and cerebellum. Most structural alterations in the DLPFC, OFC, and pIC have been reported in other chronic pain conditions.[14]

DLPFC is part of the mesocortical system and receives dopamine projections from both the SN pars compacta and the ventral tegmental area (VTA).[15] It is a key area in the descending pain modulatory system,[45] consistent with its role in expectation, reward, and decision making.[46] The OFC is also well connected with the striatum and dopaminergic nuclei, and it is involved in expectation and rewards.[47] The OFC increases its activity to link several stimuli with their subjective emotional and affective value[47] or during pain inhibition.[48] Posterior IC is considered a central area for sensory integration, receiving significant inputs from nociceptive and nonnociceptive fibers.[49] It forms the main sensory area for inputs from the spinothalamic pathway.[49] pIC is also highly connected with primary and secondary sensory areas in the parietal lobe that are important during sensory-discriminative processing of inputs, including nociception.[50] Insular Cortex (IC) is considered a central area for nonmotor symptoms of PD patients. Christopher and

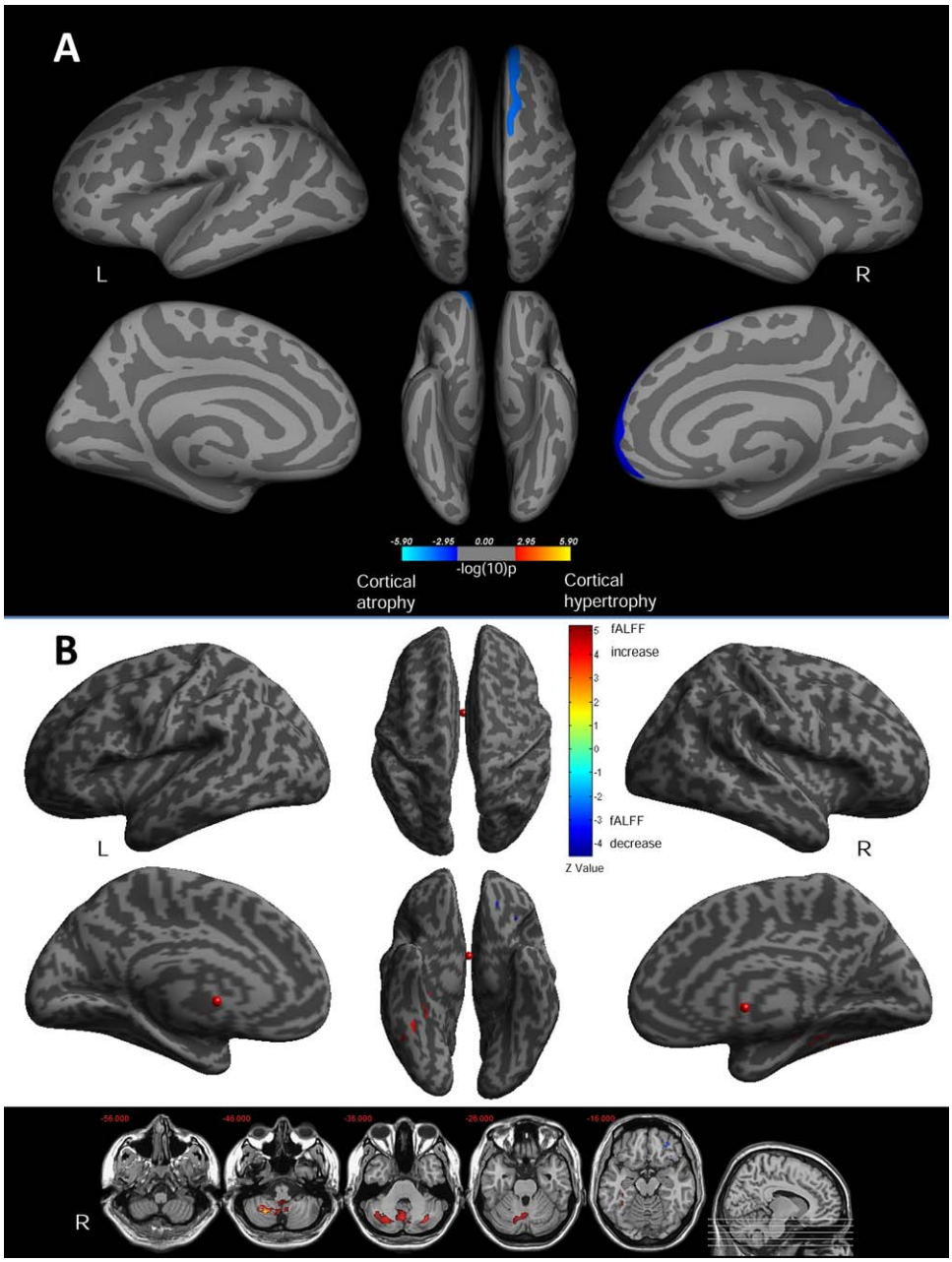

FIG. 1. Between-group (PD-Pain vs PD-Ctrl) differences in cortical thickness and in fractional amplitude of low frequency fluctuations (fALFF). Between-group (PD-Pain VS PD-Ctrl) differences in cortical thickness (**A**) and in fALFF (**B**). **A**: General linear model surface-based cortical thickness using age, disease duration, levodopa equivalent dose (LEED), and intracranial volume as covariates. Areas that were significant after Monte Carlo correction ($P<.05$) are shown. **B**: General linear model voxel-based comparison between PD-Pain and PD-Ctrl groups. Age, disease duration, and LEED were used as covariates. Only regions of significance after nonparametric Family-Wise Error-Threshold Free Cluster Enhancement(FWE-TFCE) correction at $P<.05$ are listed. Significant cerebellum clusters are overlaid onto a T1 MR template using C. Rorden's MRI tool (MRIcro) for visualization purpose. A detailed list of the areas is shown in Tables 2 and 3. [Color figure can be viewed at wileyonlinelibrary.com]

colleagues[51] showed that the cortical thickness of the IC is not related to patients' cognitive status. Taken together, our data confirm the relevance that the prefrontal insular cortex covers in pain conditions.

On the contrary, to the best of our knowledge, the PCC is not associated with pain generation,[52] although it may be activated during noxious stimulation,[52] suggesting a role in the emotional evaluation of stimuli. PCC atrophy was found in AD, but its role in cognitive decline in PD is controversial.[53,54] Our data showed structural alterations of PCC associated with pain and not with cognitive or psychological features. Despite its unclear function, the PCC is well connected to the PFC and may link DLPFC and OFC and other cortical regions, possibly in association with the emotional evaluation that pain requires.[55]

Other very interesting results come from the functional MRI evaluation. NBS analysis was based on several ROIs chosen a priori and showed that a specific disconnection between the right NAc and the left

TABLE 3. Differences in fractional amplitude of low-frequency fluctuation (fALFF) between PD-Pain and PD-Ctrl

Hemisphere	AAL atlas	X (MNI)	Y (MNI)	Z (MNI)	# voxel	*Z* max	*P* value
Left	Frontal Inferior Orbital	−36	24	−18	10	−4.573	<.00001
	Cerebellum crus2	−33	−72	−39	57	4.121	.00038
Right	Cerebellum 8	30	−57	−45	587	5.188	<.00001
	Temporal Inferior	39	−54	−9	164	5.551	<.00001

General linear model comparison between PD-Pain and PD-Ctrl groups. Age, disease duration, and levodopa equivalent dose were used as covariates. Only regions that were significant after nonparametric FWE-TFCE correction ($P < .05$) are listed. AAL atlas, Automated Anatomical Labelling atlas; FWE-TFCE. Family-Wise Error-Threshold-Free Cluster Enhancement correction procedure.

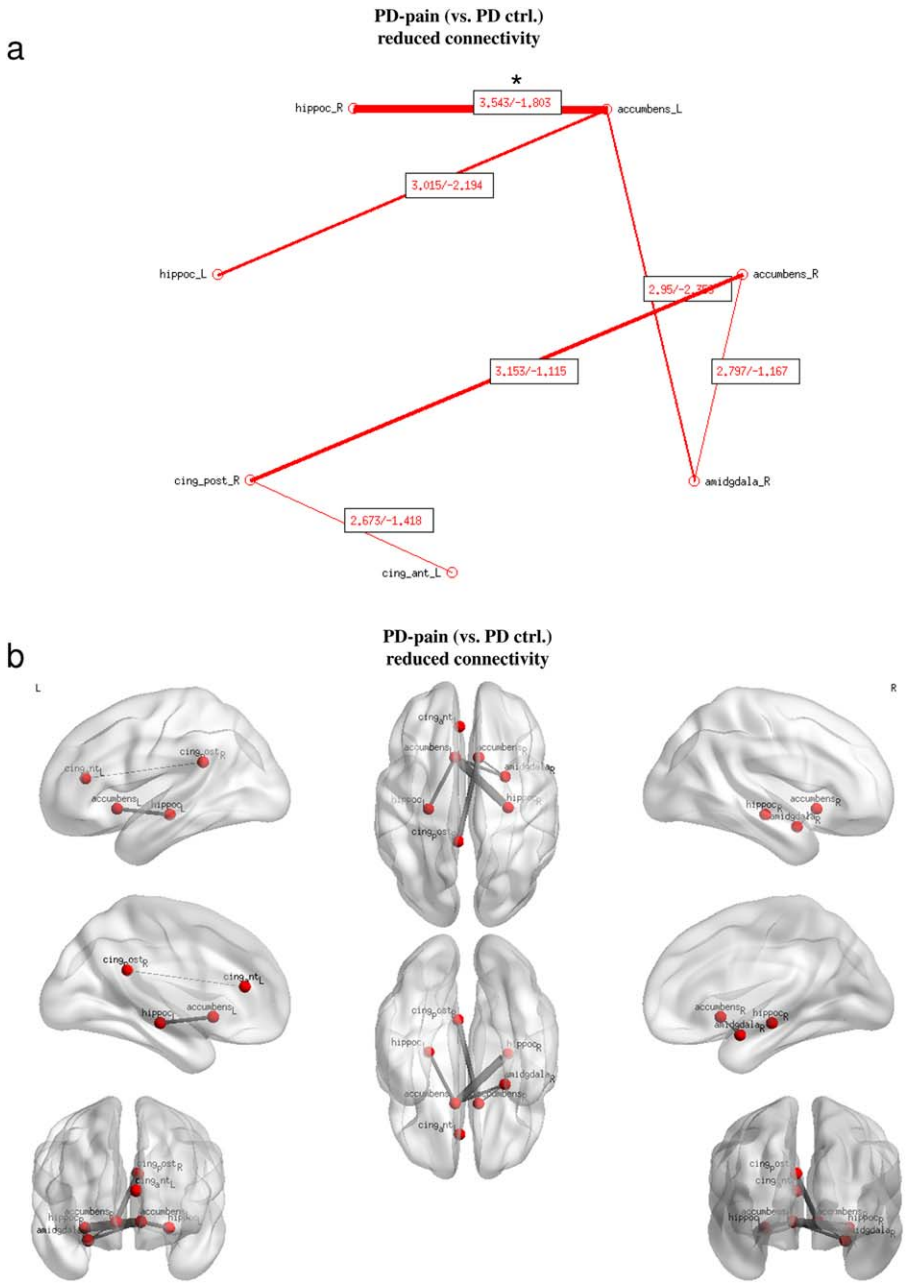

FIG. 2. PD-related connectivity changes in the pain network. **a**: Post hoc between-group network based statistics comparison. An explorative corrected threshold of $P < .1$ was used for visualization purpose. Red continuous line: network with significant reduction in PD-Pain as compared to PD without pain (PD-Ctrl); line thickness is proportional to *r* correlation value. *Significant disconnection after Monte Carlo randomization correction ($P < .05$). **b**: Third visualizations onto MNI standard template surface of network that were significant after post hoc comparison. Hippoc_R,L, right,-left-hippocampus; cing_post_R, right posterior part of the cingulate cortex; cing_ant_L, left anterior part of the cingulate cortex. [Color figure can be viewed at wileyonlinelibrary.com]

hippocampus—within the aforementioned network—might cover a central role in persistent PD pain. NAc receives modulatory inputs by the hippocampus and VTA.[56] NAc has recently emerged as a key structure in chronic and neuropathic pain. Both animal and human studies pointed out its role in the transition from subacute to chronic and neuropathic pain.[57,58] In our study, patients in the PD-Pain group had both chronic pain and neuropathic features, and the alteration of reward feedback because of reduced NAc-to-hippocampus interaction is consistent with the clinical presentation.

Other functional MRI studies used fALFF to present local alterations in the OFC, temporal areas, and cerebellar circuits in PD-Pain patients.[59] Our data demonstrate that OFC covers a major role in PD pain, showing both structural and functional alterations. The cerebellum receives projection from the basal ganglia and VTA and sends projections to a widespread network, including the frontal (eg, DLPFC), motor, somatosensory, and parietal regions.[60] Emerging evidence indicates that the cerebellum in PD presents specific structural changes and may be related to nonmotor manifestations.[61] Our results are also consistent with evidence demonstrating the functional alteration of the right cerebellum and parietal regions in the early onset of PD.[59] The role of the lingual cortex and temporal areas in pain is less established. They both have been classically ascribed to memory, word processing, and visual function. Lingual gyrus atrophy has been related to visual hallucination in PD,[62] and temporal pole hypotrophy to cognitive decline.[63]

Our clinical assessments were comprehensive, and PD groups with and without pain were well comparable in demographic, cognitive, psychological, and motor aspects, except for total LEDD, which was modestly lower in the PD-Pain patients possibly because of the greater prevalence of women. Clinical results are consistent with other neuroimaging evaluations. We found no differences in WM or in the subcortical regions typically related to PD's motor and cognitive impairment.[64] We are confident the presented results express persistent pain and lingual and temporal pole fALFF alterations that might therefore be related to additional nonmotor features, which may be addressed by future studies. Of note, fMRI is highly variable within subjects, and it may change under different conditions (eg, in ON and OFF phases). We carefully assessed all patients in the ON state to explain only those functional alterations that are dependent on persistent pain and not related to motor fluctuations.

We explored persistent pain with the KPP scale, the first specifically developed and validated for PD.[5,21] We acknowledge that our sample size was not very large, but the prevalence of patients with persistent pain without any previous peripheral cause that satisfied our criteria was relatively small. Indeed, our cohort was identified after screening 188 patients, and the participants were carefully evaluated before inclusion. Our data showed strong correlations across the domains of KPP, suggesting that common mechanisms may be responsible for the persistence of various pain manifestations. All PD-Pain patients reported positive scores in at least 5 domains of King's PD-Pain scale, confirming other published data that have showed a high prevalence and variability of pain in PD.[4]

In conclusion, we highlighted for the first time a network of brain regional alterations specifically associated to persistent pain in PD and not present in pain-free patients with similar cognitive, psychological, and clinical profiles. We propose that the present network is involved in pain processing regardless of its primary manifestation. Pain in PD is associated with distinct regional alterations in dopaminergic areas such as the OFC—which presents both functional and structural changes—and PFC. Other nondopaminergic areas such as the pIC, PCC, parietal regions, and cerebellum also showed structural and functional changes that might be related to sensory-motor and emotional responses to pain.

Further longitudinal studies are needed to improve our understanding of the supraspinal mechanisms of pain in PD. Our data strongly recommend that future research considers and controls for pain symptoms, as they are associated with important structural and functional cerebral changes. ■

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