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ORIGINAL ARTICLE

Regional changes in the type 1 cannabinoid receptor are associated with cognitive dysfunction in Parkinson's disease

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Abstract

Purpose The endocannabinoid system plays a regulatory role in a number of physiological functions, including motor control but also mood, emotion, and cognition. A number of preclinical studies in Parkinson's disease (PD) models demonstrated that modulating the type 1 cannabinoid receptor (CB_1R) may improve motor symptoms and components of cognitive processing. However, the relation between CB_1R, cognitive decline and behavioral symptoms has not been investigated in PD patients so far. The aim of this study was to examine whether CB_1R availability is associated with measures of cognitive and behavioral function in PD patients.

Methods Thirty-eight PD patients and ten age- and gender-matched controls underwent a [^{18}F]MK-9470 PET scan to assess CB_1R availability, as well as volumetric MR imaging. Neuropsychological symptoms were evaluated using an extensive cognitive and behavioral battery covering the five cognitive domains, depression, anxiety, apathy, and psychiatric complications, and were correlated to CB_1R availability using vowel-wise regression analysis ($P < 0.05$, corrected for familywise error).

Results PD patients with poorer performance in episodic memory, executive functioning, speed and mental flexibility (range P 0.003–0.03) showed lower CB_1R availability in predominantly the midcingulate cortex and middle to superior frontal gyrus ($T_{\text{peak-level}} > 4.0$). Also, PD patients with more severe visuospatial dysfunction showed decreased CB_1R availability in the precuneus, midcingulate, supplementary motor cortex, inferior orbitofrontal gyrus and thalamus ($T_{\text{peak-level}} = 5.5$). These correlations were not related to cortical gray matter atrophy. No relationship was found between CB_1R availability and mood or behavioral symptom scores.

Conclusions Decreased CB_1R availability in the prefrontal and midcingulate cortex in PD patients is strongly correlated with disturbances in executive functioning, episodic memory, and visuospatial functioning. Further investigation of regional CB1R expression in groups of PD patients with mild cognitive impairment or dementia is warranted in order to further investigate the role of CB1R expression in different levels of cognitive impairment in PD.

Keywords Parkinson's disease · Cognition · CB_1R · PET · Behavior · Dementia

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide, affecting about 1% of the population over the age of 60 years [1]. PD is characterized by dopaminergic cell loss in the basal ganglia, which is considered to underlie the motor symptoms of the disease [2]. However, in the last decades, PD has been considered a multisystem disease, rather than a pure movement disorder, comprising various behavioral and psychiatric manifestations such as sleep disturbances, anxiety, depression, and psychotic symptoms as well as cognitive deficits occurring even in the early stages [3–6]. As many as 40% of the PD patients with normal cognition at baseline develop mild cognitive impairment (PD with mild cognitive impairment, PD-MCI) in the early stages (first 3 to 6 years) of the disease [5, 6], and around 75% of PD patients develop dementia 10–15 years after the initial diagnosis of PD. Therefore, a crucial goal of future therapeutic approaches in PD is the development of a neuroprotective agent that has beneficial effects on the progression of both motor and cognitive decline [7].

Numerous experimental studies have suggested a possible contribution of disturbance of the endocannabinoid system (ECS) [8–11] to the symptomatology of PD. A type 1 cannabinoid receptor (CB_1R) PET study in PD patients using [^{18}F]MK-9470 found significant regional alterations in CB_1R availability, but not relation to levodopa-induced dyskinesia (LID) severity [12]. These changes may represent compensatory mechanisms, but could also aggravate symptomatology. A number of preclinical studies of both CB_1R agonists and antagonists showed improvement of motor impairment in PD models [8–11, 13–16] despite their opposing effects on CB_1R activity.

Besides the possible CB_1R involvement in motor symptoms in PD models, a variety of experimental procedures have focused on the role of the CB_1R in different components of cognitive processing [17–19]. CB_1R plays a critical role in short- and long-term synaptic plasticity and memory formation [20–22]. A number of behavioral tasks conducted in rats have shown that CB_1R agonists disrupted different stages of spatial and non-spatial memory [17, 22], non-associative learning, different aspects of short- and long-term recognition memory (storage and retrieval), and retention of spatial memory [23–25]. These effects appeared to be CB_1R dependent since pharmacological CB_1R inhibition enhances spatial memory [26]. Also, CB_1R signaling represents an important modulator of emotional-, feeding-, stress-, and mood-related psychiatric conditions, including depression, anxiety, and posttraumatic stress disorder [27, 28].

Whether CB_1R signaling is related to cognitive and psychiatric problems in human PD, it is still unknown.

Accordingly, in this cross-sectional study of a large cohort of PD patients, we used an extensive test battery covering different cognitive and behavioral domains to explore whether in vivo CB_1R availability is associated with specific cognitive and behavioral symptoms that are significantly different from healthy controls.

Material and methods

The study was approved by the Ethics Committee Research UZ/KU Leuven, Leuven, and was performed in accordance with the latest version of the Declaration of Helsinki. All participants provided written informed consent before entering the study.

Study population

A total of 38 PD patients (mean age ± SD, 63.7 ± 8.7; age range 43.3–85.0 years; 14 F/24 M), with a diagnosis according to the UK Parkinson's Disease Society Brain Bank criteria, were recruited in the Movement Disorders Clinic of the University Hospitals Leuven, Belgium. The patients sample included in the current study was a different cohort of PD patients respect to the one included in the previous study [12]. All PD patients were levodopa-responsive and none had signs suggestive of progressive supranuclear palsy, multiple system atrophy, or corticobasal degeneration. Subjects with other neuropsychiatric diseases than PD, major internal medical conditions, previous stereotactic brain surgery, a history of alcohol abuse or other drugs (including marijuana) were excluded. All patients were on medication, and a levodopa daily equivalent dose (LEDD) was calculated as previously described [29].

A group of 10 healthy subjects were used as control group (CON; age, 59.1 ± 11.7 years; age range 40.4–76.6 years; 4 F/6 M). Inclusion/exclusion criteria and recruitment procedure for healthy controls have been previously described [30]. The control subjects were part of a database to study age and gender variability of [^{18}F]MK-9470 binding and were randomly selected for this study to form an age- and gender-matched group [30].

All subjects underwent physical examination, blood and urine testing, and magnetic resonance imaging (MRI, see below) to exclude major internal and other cerebral pathology. Urine toxicology for cannabis and other important addictive drugs was performed as described previously [12].

Motor, neuropsychological, and behavioral assessment

PD patients were clinically evaluated on the day of PET using the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn-Yahr (HY) scale in the "ON" medication condition. In addition, all CON and PD subjects underwent cognitive screening as well as extensive neuropsychological assessment

using a test battery covering different cognitive domains (episodic memory, executive functioning, attention/working memory, visuospatial function, and language function) affected in PD. Specifically, we used Mini-Mental State Examination (MMSE) as a measure of general cognitive functioning; Rey Auditory Verbal Learning Test (RAVLT) to assess episodic memory; Trail Making Test part A and B (TMT A and TMT B), and Stroop test as measure of mental speed, attention, and executive functioning (response inhibition); Digit Symbol (DS) substitution test from Wechsler Adult Intelligence Scale as measure of visuospatial and psychomotor function; digit span for working memory capacity; letter verbal fluency, animal verbal fluency test, Boston Naming Test, and National Adult Reading Test for language function.

To evaluate mood and behavioral symptoms, the Beck Depression Inventory (BDI), the State-Trait Anxiety Inventory form Y (STAI-Y), the Apathy Evaluation Scale (AES), and the Neuropsychiatric Inventory were administered. Psychiatric complications due to drug intake in PD were assessed using the Scales for Outcomes in Parkinson's disease-Psychiatric Complications (SCOPA-PC).

CB_1R PET imaging

The [^{18}F]MK-9470 precursor was obtained from Merck Research Laboratories and labeled on-site using ^{18}F-ethylbromide, as described previously [31]. The final product was obtained after high-performance liquid chromatography (HPLC) separation and had a radiochemical purity of > 95%. [^{18}F]MK-9470 PET imaging was conducted in 3D mode on a HiRez Biograph16 PET-CT camera (Knoxville, TN, USA). Prior to PET imaging, the subjects' head was fixed using a vacuum pillow to avoid excessive head movements and a low dose CT scan (80 kV tube potential, 11 mAs) was conducted for attenuation correction. All subjects fasted for at least 4 h prior to [^{18}F]MK-9470 PET imaging. 60-min [^{18}F]MK-9470 PET acquisitions (6 × 10 min) were started 120 min after the slow intravenous injection of 176.0 ± 18.9 MBq in the PD patients and 179.8 ± 21.4 MBq in CON under standard conditions with low ambient stimuli. Specific radioactivity at time of injection was 160.6 ± 75.4 GBq/μmol in PD and 148.7 ± 77.5 GBq/μmol in CON. Image reconstruction was performed using a 3-dimension ordered-subsets expectation-maximization iterative reconstruction with 5 iterations and 8 subsets and post smoothing with a 3D isotropic Gaussian (full-width-at-half-maximum [FWHM] of 6 mm).

MR imaging and volumetric brain assessment

Apart from CB_1R PET imaging, all subjects underwent high-resolution MRI, both volumetric T1-weighted (T1w) magnetization prepared rapid acquisition gradient echo (MPRAGE) and T2-weighted MR images, on a 1.5 Tesla Vision Scanner (Siemens, Germany). The following acquisition parameters were used: repetition time, 10 ms; echo time, 4 ms; flip angle, 8°; voxel size, 1 × 1 × 1 mm. Before starting the voxel-based morphometry (VBM) analysis, T1w MR images were manually reoriented to place their native-space origin at the anterior commissure. Images were then pre-processed using the Computational Anatomy Toolbox (CAT12) (Gaser and Dahnke, 2016) for SPM12 (www.fil.ac.uk/spm/) in Matlab R2017b (The Mathworks, Inc., Natick, MA, USA), including bias-field and noise removal, skull stripping, segmentation into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF), normalization to MNI space using DARTEL, and finally after preprocessing, scans were smoothed with a Gaussian kernel of 8 mm (FWHM). The preprocessed images were entered into a statistical unpaired *t* test analysis, with total intracranial volume (TIV, i.e., the sum of GM, WM, and CSF) as confound to correct for different brain sizes. Data were then explored at a voxel-level $p_{height} < 0.001$ (uncorrected) and cluster extent (K_{EXT}) of 200 voxels.

Image processing and statistical analysis

Parametric maps of CB_1R availability were calculated using modified standardized uptake values (mSUV = [activity concentration × (subject's body weight + 70/2)/injected activity]), a previously validated quantification method which gives reliable estimates of the total volume of distribution of [^{18}F]MK-9470, as determined by full kinetic modeling [32]. All PET processing procedures were automatically performed using the brain PNEURO tool of PMOD (v. 3.7, PMOD Technologies, Zurich, Switzerland). PET images were first rigidly registered to the corresponding individual volumetric T1w MR images. Individual T1w MR-PET images were nonlinearly spatially normalized to the standard Montreal Neurological Institute (MNI) space MRI template in PMOD. In case of lateralized clinical affliction, image data were flipped so that "left" corresponded to the most affected hemisphere.

In PD patients, the correlations between the CB_1R availability and clinical characteristics, when significantly different from CON, were analyzed with a multiple regression analysis in SPM12 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, UK), one for each independent cognitive and behavioral measure. For all the whole-brain voxel-by-voxel correlation analyses, age was included as nuisance variable as upregulation of [^{18}F]MK-9470 availability with aging has been observed [30]. Moreover, based on the possible effect of disease duration on aging and cognitive performance [33], all the correlation analyses were also controlled for disease duration. All mSUV CB_1R images were first smoothed with an isotropic Gaussian kernel of 10 mm FWHM. To exclude extracerebral, WM and ventricular activity, a smoothed (10 mm) mask obtained by the

average GM from the age-matched CON group was applied to correlation analysis. For regional analysis, proportional scaling to the global CB_1R value was used. For the whole-brain voxel-based correlation analyses, the statistical threshold was set at a P value of less than 0.05, corrected for familywise error ($P_{FWE} < 0.05$), with a minimal cluster extent $K_{EXT} > 200$ voxels (~ 1.6 cm^3).

Conventional statistics were carried out using Graphpad Prism 7.0 (Graphpad Software, La Jolla, CA, USA). Shapiro–Wilk tests were used to test the distribution of variables against normality. Non-parametric Mann–Whitney U t test or parametric t test with Welch's correction were used as appropriate. Significance was accepted at the 95% probability level.

Results

Demographic and clinical features

In total, 38 PD patients and 10 age- and gender-matched healthy CON were included in the study. Demographic and clinical characteristics are summarized in Table 1. PD patients had an average disease duration of 6.5 ± 3.9 years (range 1–14 years), which was positively associated with age ($P = 0.04$) as expected. The mean total LEDD was 531 ± 273 mg (levodopa, 274 ± 256 mg/day; dopamine agonist, 188 ± 122 mg/day; entacapone, 129 ± 66 mg/day; amantadine, 13 ± 48 mg/day; rasagiline, 36 ± 48 mg/day).

Three fifths of PD patients received a HY score of stage between 1 and 1.5 (UPDRS-III: 13.5 ± 14.0), and the remaining 40% of patients had a HY score between 2 and 3 (UPDRS-III: 21.8 ± 10.4), measured during the ON state. Nine PD patients (24%) had levodopa-induced dyskinesia (LID; average score on the dyskinesia items 32–34 of the UPDRS IV of 2.1 ± 2.3).

Outcomes of the neuropsychological assessments are summarized in Table 2. The PD group performed significantly worse than CON on RAVLT total ($P = 0.019$), RAVLT retention ($P = 0.033$), TMT A ($P = 0.003$), TMT B ($P = 0.014$), Stroop word reading and color naming ($P = 0.044$ and $P = 0.038$ respectively), and Digit Symbol (DS) substitution test ($P = 0.029$). None of the language-related assessments showed significant group differences between CON and PD.

As for mood and behavioral symptoms, PD patients reported significantly lower scores on STAI-Y 1 and higher scores on AES and SCOPA-PC than CON.

Table 1 Demographic and clinical characteristics of participants

	CON	PD
No. subjects, F/M	10 (4/6)	38 (14/24)
Age, year	59.15 ± 11.72 (40.4–76.6)	63.70 ± 8.73 (43.4–85.0)
Disease duration, year[a]	–	6.47 ± 3.93 (1–14)
HY stage[b]	–	1.54 ± 0.70 (0–4)
Predominant clinical side, L/BIL/R	–	19 / 3 / 16
LEDD, mg	–	531.28 ± 272.57 (100–1075.5)
UPDRS-I		1.74 ± 2.31 (0–10)
UPDRS-II		7.50 ± 6.35 (1–32)
UPDRS-III	–	16.55 ± 13.25 (5–75)
UPDRS-IV	–	2.34 ± 2.84 (0–11)

CON, control subjects; *PD*, Parkinson's disease patients; *F*, female; *M*, male; *HY*, Hoehn-Yahr; *L*, left; *R*, right; *BIL*, bilateral; *LEDD*, levodopa daily equivalent dose; *UPDRS*, Unified Parkinson's Disease Rating Scale

Data is expressed as mean ± standard deviation (range)

[a] HY and UPDRS scores were obtained in the medication "on" state

[b] Disease duration refers to time since first motor symptoms as reported by the patient

Volumetric MRI changes in PD patients

A voxelwise VBM analysis, corrected for total intracranial volume, showed a single significant cluster of GM volume atrophy covering the right superior and middle temporal gyrus of PD, compared to CON ($P_{height} < 0.001$, uncorrected for multiple comparisons; $K_{EXT} > 200$; Supplementary Fig. 1). When age and gender were included as covariate variables, the results remained unchanged (Supplementary Table 1).

CB_1R availability and cognitive function

Cognitive impairments in episodic memory, attention, and visuospatial functioning were associated with a relative decrease in CB_1R availability in specific cortical brain regions (Figs. 1 and 2). More specifically, PD patients with poorer performance in episodic memory (RAVLT total) showed lower relative CB_1R availability in two clusters comprising the middle cingulum (at cluster level $P_{FWE\text{-}cor} = 0.005$, $T_{peak\text{-}level} = 4.98$, $K_{EXT} = 881$) and superior medial frontal gyrus (at cluster level $P_{FWE\text{-}cor} = 0.006$, $T_{peak\text{-}level} = 4.05$, $K_{EXT} = 840$) (see Fig. 1 and Table 3). The whole-brain voxel-based SPM analysis showed that performance on the Digit Symbol (DS) substitution test, a measure of visuospatial function, executive function, and processing speed, was positively correlated with relative CB_1R availability in a cerebral-wide cluster ($P_{FWE} < 0.05$, corrected for multiple comparisons). In particular, significant clusters were observed in the precuneus and middle cingulum (at cluster level $P_{FWE\text{-}cor} = 0.001$, $K_{EXT} = 5245$; $T_{peak\text{-}level} = 5.49$), thalamus, (supplementary) premotor cortex and inferior orbitofrontal gyrus (see Fig. 2 and Table 3 for peak cluster locations). There were no significant relationships between CB_1R availability and Stroop test scores.

Table 2 Neuropsychological assessments in Parkinson's disease patients and controls

	CON	PD	*P* value
Cognition			
MMSE	29.0 ± 1.2 (27–30)	28.3 ± 2.9 (15–30)	0.80
RAVLT total, A1-A5	51.7 ± 13.1 (34–71)	40.4 ± 13.1 (6–61)	0.019*
RAVLT retention, A7	11.7 ± 3.4 (4–15)	8.7 ± 4.0 (1–15)	0.033*
RAVLT recognition, A8	14.2 ± 1.1 (12–15)	12.7 ± 2.4 (6–15)	0.06
TMT A, s	31.9 ± 12.6 (20–60)	66.9 ± 122.6 (21–795)	0.003*
TMT B, s[§]	75.9 ± 32.0 (49–153)	136.9 ± 126.2 (52–600)	0.014*
Stroop word reading	46.8 ± 6.6 (38–63)	62.8 ± 45.1 (36–320)	0.044*
Stroop color naming	61.3 ± 12.6 (47–81)	74.6 ± 27.0 (36–320)	0.038*
Stroop interference	97.7 ± 17.6 (70–122)	136. ± 94.7 (69–520)	0.14
DS forward	5.6 ± 1.1 (4–7)	5.6 ± 1.0 (4–7)	0.99
DS backward	4.4 ± 1.1 (3–6)	4.6 ± 1.0 (3–7)	0.71
Digit Symbol substitution	68.8 ± 14.8 (46–89)	57.3 ± 14.2 (32–94)	0.029*
Block patrons	64.2 ± 5.7 (50–68)	61.8 ± 6.2 (41–68)	0.16
VF animal	21.5 ± 3.7 (16–26)	18.1 ± 6.3 (5–37)	0.22
VF N	10.5 ± 3.2 (6–15)	10.6 ± 5.0 (0–20)	0.98
VF A	11.3 ± 3.4 (7–16)	10.8 ± 5.2 (0–25)	0.78
VF K	11.8 ± 3.9 (6–16)	12.6 ± 5.6 (3–25)	0.99
BNT	55.6 ± 3.1 (49–59)	53.5 ± 5.8 (34–59)	0.33
NART	44.0 ± 4.2 (38–50)	44.8 ± 7.6 (18–50)	0.29
Mood and behavior			
BDI	4.8 ± 4.7 (1–16)	8.1 ± 7.9 (0–32)	0.19
STAI-Y 1	48.6 ± 4.6 (43–57)	44.7 ± 5.2 (30–54)	0.037*
STAI-Y 2	48.6 ± 4.6 (41–55)	48.3 ± 4.8 (37–57)	0.87
AES	19.6 ± 2.1 (18–24)	28.5 ± 12.7 (18–75)	0.005*
SCOPA-PC	–	1.9 ± 1.9 (0–6)	–
NPI	1.1 ± 2.9 (0–9)	5.5 ± 9.8 (0–41)	0.11

PD, Parkinson's disease patients; *CON*, control subjects; *MMSE*, Mini-Mental State Examination; *RAVLT*, Rey Auditory Verbal Learning Test; *BNT*, Boston Naming Test; *TMT*, Trail Making Test; *NART*, National Adult Reading Test; *DS*, Digit span; *VF*, verbal fluency; *BDI*, Beck Depression Inventory; *STAI-Y*, State-Trait Anxiety Inventory form Y; *AES*, Apathy Evaluation Scale; *SCOPA-PC*, psychiatric complications questionnaire; *NPI*, Neuropsychological Inventory

[§] All TMT B completion times were included, rather than a maximum of 300 s

*Results surviving either non-parametric unpaired Mann–Whitney *t* test or parametric unpaired *t* test with Welch's correction if unequal SD between CON and PD ($P < 0.05$, no multiple testing correction)

Data is expressed as mean ± standard deviation (range)

None of the above results were different when unflipped CB_1R images were used or when LEDD (i.e., dopaminergic medication doses) was included as additional nuisance variable in the multiple regression analyses (see Supplementary Fig. 2).

CB_1R availability and motor measures, mood, and behavioral symptoms

No correlations of CB_1R availability with HY stage, disease duration, LEDD, UPDRS-III motor, and UPDRS-IV scores were found, even at the less stringent threshold of $P_{height} < 0.001$ (uncorrected for multiple comparisons).

We also searched for correlations between CB_1R availability and mood and behavioral symptoms, when significantly different from CON. However, there was no significant correlation between CB_1R availability and STAI-Y 1, AES nor SCOPA-PC measures neither in the PD group, nor in the CON group.

Discussion

Besides motor symptoms, cognitive impairment and behavioral disturbances are characteristic of PD, occurring even in the first years of the disease [3–6, 34]. Therefore, future

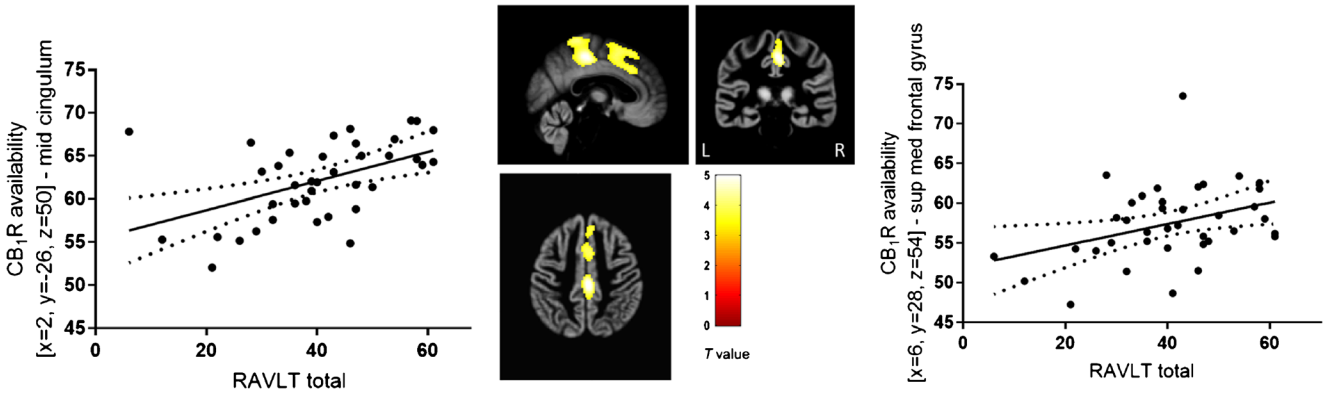

Fig. 1 Positive correlation between CB_1R availability and Rey Auditory Verbal Learning Test (RAVLT) total score in Parkinson's disease (PD) patients. Results of the voxel-based statistical parametric map analysis showing the positive correlation between CB_1R availability and RAVLT total score in PD patients. Clusters overlaid onto the average gray matter from the age-matched healthy control group. Significance is shown with a T statistic color scale, which corresponds to the level of significance at the voxel-level. Scatter plots of relative CB_1R availability (mSUV) values at the maximal peak location for each significant cluster located on the middle cingulum and superior medial frontal gyrus

neuroprotective agents should ideally have beneficial effects not only on the progression of motor symptoms, but also on cognitive decline [7]. Several mechanisms are likely to contribute to cognitive decline in PD, and a variety of biomarker studies, some using novel structural and functional imaging techniques, have documented in vivo brain changes associated with cognitive impairment [35].

The endocannabinoid system (ECS) plays a regulatory role in a number of physiological functions, including motor control, mood, emotion, and cognition [17, 19, 36–39]. Preclinical studies in different experimental PD models demonstrated that modulating endocannabinoid signaling, in particular CB_1R, may improve motor symptoms [8–11, 13–16]. However, although it has been established that CB_1R signaling is involved in cognitive functions, such as memory and learning [17–19, 22, 25, 26], the relation between CB_1R signaling and cognitive decline in PD has been never investigated so far.

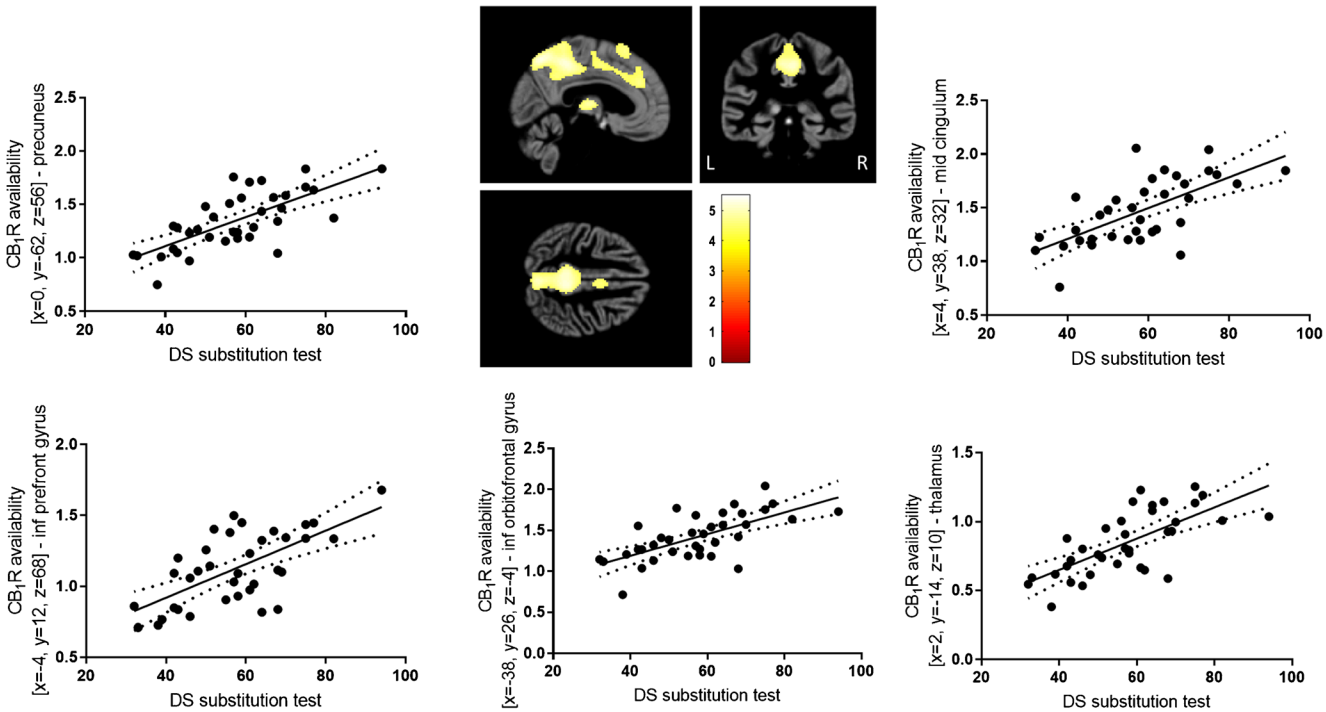

Fig. 2 Positive correlation between CB_1R availability and Digit Symbol (DS) substitution test in Parkinson's disease (PD) patients. Results of the voxel-based statistical parametric map analysis showing the positive correlation between CB_1R availability and DS substitution test in PD patients. Clusters overlaid onto the average gray matter from the age-matched healthy control group. Significance is shown with a T statistic color scale, which corresponds to the level of significance at the voxel-level. Scatter plots of relative CB_1R availability (mSUV) values at the maximal peak location for each significant cluster

Table 3 Results of the voxel-based correlation analysis between CB_1R availability and cognitive assessments in Parkinson's disease patients

Cluster-level		Voxel-level		Peak voxel MNI coordinate			Cluster location
$p_{FWE\text{-}corr}$ §	k_{EXT}	p_{unc}	T	x	y	z	
RAVLT total							
0.005	881	$9.2 \cdot 10^{-6}$	4.98	2	−26	50	Mid cingulum
		$9.8 \cdot 10^{-5}$	4.18	4	−36	68	Paracentral lobule (BA4)
0.006	840	$1.4 \cdot 10^{-4}$	4.05	6	28	54	Sup medial frontal gyrus (BA8)
		$1.8 \cdot 10^{-4}$	3.95	2	12	56	Supplementary motor cortex (BA6)
		$2.7 \cdot 10^{-4}$	3.82	2	24	36	Mid cingulum
DS substitution test *							
0.001	3245	0.003	5.49	0	−62	56	Precuneus
				6	−38	50	Mid cingulum
				−4	−38	50	Mid cingulum
0.023	298	0.012	4.92	2	−14	10	Thalamus
0.018	457	0.018	4.75	−4	12	68	Supplementary motor cortex (BA6)
0.025	254	0.020	4.71	−38	26	−4	Inf orbitofrontal gyrus (BA47)
0.016	550	0.025	4.60	4	38	32	Mid cingulum

K_{EXT}, cluster size extent (number of $2 \times 2 \times 2$ mm^3 voxels); p_{corr}, corrected for multiple comparisons; p_{unc}, uncorrected for multiple comparisons; *RAVLT total*, Rey Auditory Verbal Learning Test total score (A1-A5); *DS*, Digit Symbol substitution test

$p_{FWE\text{-}corr}$ §, FWE-corrected clusters based on whole brain volumes

Clusters surviving at $P_{unc} < 0.001$, *$P_{FWE\text{-}corr} < 0.05$, with cluster extent $K_{EXT} > 200$ voxels

In this study, we have explored whether in vivo CB_1R availability is associated with specific cognitive and behavioral symptoms in PD patients. Cognitive functioning was assessed with an extensive neuropsychological test battery covering different domains (memory, executive functioning, attention, visuospatial function, processing speed, and language function).

PD patients with lower CB_1R availability in the midcingulate and superior frontal gyrus had worse episodic memory. Also, PD patients with more severe visuospatial dysfunction showed decreased CB_1R availability in a cerebral-wide cluster, more specifically in the precuneus, midcingulate, supplementary motor cortex, inferior orbitofrontal gyrus, and thalamus.

The posterior parietal, limbic and especially prefrontal cortices mediate the critical circuit for "top-down" modulation of attention, which is particularly affected in PD. The prefrontal cortex is highly interconnected to virtually all other subordinate cortical and subcortical structures. It receives inputs from all unimodal and multimodal association areas (i.e., visual, auditory, and the posterior parietal and ventral temporal lobes respectively), as well as from the limbic structures. Massive afferent projections from the dorsolateral prefrontal cortex and posterior parietal cortex arise from the basal ganglia. Lesions in these tracts account for the "frontal lobe" or executive deficits that typically occur in the subcortical dementia syndrome associated with basal ganglia disorders as PD. Both dopaminergic and ^{18}F-FDG PET studies have shown that cognitive impairment in executive function, attention, memory, and visuospatial function in PD are particularly related to frontal cerebral glucose metabolism deficits and striato-frontal dysfunction [4, 40–43]. Compared with PD patients with no cognitive impairment, hypometabolism was much more pronounced in the PD patients with dementia (PDD) than in PD-MCI, mainly in the posterior cortical areas, cingulum and precuneus. The result might suggest an association between posterior cortical hypometabolism and more severe cognitive impairment [4]. A recent tau PET study has shown increased signal in the inferior temporal gyrus and precuneus in patients with PDD, which was associated with more severe cognitive impairment [44]. In rs-fMRI study, PD-related nonmotor symptoms such as fatigue was associated with the amplitude of low-frequency fluctuations changes in the attention network and in the salience network, including midcingulate cortex [45]. The midcingulate (or dorsal anterior cingulate cortex) and precuneus zone has been shown to be specifically activated during tasks that require response selection [46], and is often engaged during episodic memory [47–49] and visuospatial processing [50].

Previous studies have consistently indicated that cannabinoid signaling is involved in cognitive regulation: a lower efficiency of the endocannabinoid system, probably due to a lowered expression of CB_1R, produced a decline in performance when attentional control and working memory processing is challenged [51, 52]. By using specific pharmacological agents acting on the endocannabinoid system and

genetically modified mice, Saravia et al. demonstrated the crucial involvement of CB_1Rs located in GABAergic cells in the cognitive impairment (including attention, working, and episodic memory) and neuronal plasticity changes in the HPC occurring during nicotine withdrawal [53]. In addition, acute treatments with the CB_1R agonist WIN55212-2 induced deficits in visuospatial attention measured on the Lateralized Reaction Time task [54]. Moreover, genetically determined lower prefrontal CB_1R levels are associated with abnormalities in neuronal networks related with verbal working memory in healthy cannabis users [55]. Since our PD patients reported a wide range in disease duration (from 1 to 14 years), and considering the known impact of age and disease duration on cognitive, mood, and behavioral symptoms [33, 34], all the correlation analyses were controlled for age and disease duration. Although there is evidence that depression is associated with cognitive impairment in PD [56], our (study) PD patients reported similar BDI scores compared to controls. For this reason, it is unlikely that the observed cognitive deficits are due to their affective state. Furthermore, we want to emphasize that the correlations between specific cognitive assessments and regional CB_1R availability were not related to cortical GM atrophy. Reduced volume of GM was only observed in a cluster covering the right superior and middle temporal gyrus of PD, when compared to controls. More severe and widespread GM reduction has been observed in PD with or without dementia, with a markedly longer disease duration [57, 58] compared with our cohort (average disease duration = 6.5 ± 3.9 years). Finally, performing an analysis where voxel-based CB_1R availability was scaled relatively to the individual global mean, we found a trend towards a relative increased CB_1R availability in PD in the prefrontal cortex, (anterior) cingulate cortex, and mesotemporal regions of PD patients compared to CON, in agreement with previous findings [12]. Similarly, also in line with the previous work, we found no differences in regional CB_1R availability between the group of advanced PD patients (i.e., with a disease duration > 5 years) with and without LID (range $P = 0.1$–0.5) [12].

Based on these findings, further investigation of regional CB_1R expression in PD patients with MCI and with dementia is warranted to further investigate the role of CB_1R expression in different impaired levels of cognition in PD. A limitation of the current study is the lack of longitudinal CB_1R PET and cognitive data. Follow-up will allow us to determine whether CB_1R imaging can contribute to the prediction and early diagnosis of dementia in PD. Finally, larger clinical studies are necessary to investigate the critical role of prefrontal endocannabinoid signaling in modulating specific domains of cognition.

In conclusion, the current study demonstrates that CB_1R availability in the PFC and midcingulate cortex in PD patients is strongly correlated with executive functioning, episodic memory and visuospatial function. Further exploration of the role of CB_1R in the neurobiology of early and late cognitive changes in PD is therefore warranted in order to further investigate the role of CB1R expression in different levels of cognitive impairment in PD.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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