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BRIEF REPORT

Impaired Gait, Postural Instability, and Rigidity in Relation to CB1 Receptor Availability in Parkinson's Disease

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ABSTRACT: Background: In Parkinson's disease (PD), postural instability and gait disorder (PIGD) symptoms are associated with a worse prognosis for an unknown reason.

Objective: The objective was to explore the relationship between cannabinoid receptor type 1 (CB1R) availability and motor symptoms in PD with [^{18}F]FMPEP-d_2 positron emission tomography (PET).

Methods: Fifteen individuals with PD underwent [^{18}F]FMPEP-d_2 PET to measure cerebral CB1R availability. The Unified Parkinson's Disease Rating Scale motor part (UPDRS-III) was used to evaluate the motor symptoms.

Results: A negative correlation was observed between [^{18}F]FMPEP-d_2 V_T and PIGD score ($P = 0.002$) as well as rigidity subscore ($P < 0.001$). Both clusters covered widespread areas of both hemispheres. In contrast, tremor or bradykinesia did not correlate to [^{18}F]FMPEP-d_2 V_T.

Conclusions: Gait, postural instability, and rigidity in PD are associated with decreased CB1R availability, unlike tremor or bradykinesia, suggesting that the endocannabinoid system has a role in the pathophysiology of different motor symptoms in PD. © 2024 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: Parkinson's disease; PET; CB1R; ECS; UPDRS

The endocannabinoid system (ECS) is a complex neuromodulatory system that plays an important role in central nervous system development,[1] synaptic plasticity,[2] and cognitive processes,[3] among others. The most abundant cannabinoid receptor in the brain is cannabinoid receptor type 1 (CB1R). High densities of CB1R are found in basal ganglia,[4,5] which makes the ECS an interesting study target for basal ganglia diseases like Parkinson's disease (PD).

The Postural Instability and Gait disorder (PIGD) subtype in PD has been associated with more functional disability, faster disease progression, and more nonmotor disturbances[6-10] compared to the tremor-dominant subtype. The pathogenic mechanisms underlying the heterogeneity and the different motor subtypes in PD are still unclear.

We have previously studied the ECS *in vivo* in subjects with idiopathic PD using positron emission tomography (PET) and [^{18}F]FMPEP-d_2, an inverse agonist radioligand with a high affinity and selectivity for the CB1R. We showed that subjects with PD, who had discontinued their usual antiparkinsonian medication at least 12 hours before scanning, had lower CB1R availability compared to healthy controls. The decrease in CB1R availability was seen widely across different brain areas, including basal ganglia, cortical areas, white matter, and cerebellum. We also found that when the subjects were on their usual antiparkinsonian

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medication, the CB1R availability was significantly increased toward the normal level, indicating that antiparkinsonian medication affects the CB1R availability.[11]

This study aimed to further characterize the ECS disturbance in PD by exploring the relationship between CB1R availability and different motor symptoms in PD with [^{18}F]FMPEP-d_2 PET.

Patients and Methods

Patients and Study Design

The study was approved by the Ethics Committee of the Hospital District of Southwest Finland and was conducted according to the World Medical Association Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) and following Good Clinical Practice guidelines. Written informed consent was obtained from all participants according to the Declaration of Helsinki.

The study sample consisted of 15 subjects with PD (Table 1). Recruited participants fulfilled the UK Brain Bank Research criteria for the diagnosis of idiopathic PD. To confirm the clinical diagnosis of PD, all participants also underwent [^{18}F]FDOPA high-resolution research tomograph (HRRT) PET examination to ensure typical nigrostriatal dopaminergic hypofunction characteristic of PD. All subjects were on their individual standard PD medication. The details on the dopaminergic medication for each subject are presented in Supporting Information. None of the participants used hormone replacement therapy or reported smoking of any kind. The exclusion criteria have been described previously.[11]

TABLE 1 *Demographics and characteristics: demographic and clinical information on subjects*

	Mean ± SD	Min.	Max.
Number of subjects (male/female)	8/7	-	-
Age (y)	66 ± 6	52	74
Disease duration (y)	10 ± 5	2	18
H&Y	2.5	1.5	3
UPDRS-III (OFF medication) score	23 ± 8	8	36
Gait+Postural Instability score	2 ± 1	0	4
Rigidity score	5 ± 3	0	12
Bradykinesia score	2 ± 1	1	3
Tremor score	3 ± 2	0	7
LEDD (mg)	602 ± 189	226	1007
Injected activity of [^{18}F]FMPEP-d_2 (MBq)	201 ± 12	174	220
Smoking of any kind	-	-	-
Hormone replacement therapy	-	-	-
BMI (kg m^{-2})	29 ± 6	23	36

Abbreviations: SD, standard deviation; H&Y, Hoehn and Yahr scale; UPDRS-III, Unified Parkinson's Disease Rating Scale, Part III; LEDD, levodopa equivalent daily dose; MBq, Mega Becquerel; BMI, body mass index.

Evaluation of Motor Symptoms

The Unified Parkinson's Disease Rating Scale motor part (UPDRS-III) was evaluated during the OFF stage (levodopa was discontinued for a minimum of 12 hours in advance, dopamine agonists and MAO-B inhibitors a minimum of 24 hours in advance). The evaluation was performed by a clinical neurologist. The focus of our study was to compare different motor features with [^{18}F]FMPEP-d_2 distribution volume (V_T). Therefore, we calculated UPDRS-III subscores for rigidity (sum of items 22a-e), body bradykinesia (item 31), tremor (sum of items 20a-e and 21a-b), and a composite of gait (item 29) and postural instability (item 30) (PIGD score).[12]

Radiochemistry

[^{18}F]FMPEP-d_2 was prepared as described previously.[13] The radioligand was obtained in high radiochemical purity (>95%) and had a molar activity of 200 ± 15 MBq/nmol at the time of injection.

Imaging Procedures

Structural MRI was performed using a 3T scanner (Philips Ingenuity TF PET/MR, Philips Medical Systems, Cleveland, OH, USA) and utilized in the analyses as described previously.[11] The OFF state [^{18}F]FMPEP-d_2 examinations were performed using a HRRT PET scanner (Siemens/CTI, Knoxville, TN, USA) as described previously[11] for a total emission data scan range of 0–60 and 90–120 minutes. Concomitant blood sampling was performed as described previously.[11]

PET Imaging Analyses

PET data processing and kinetic modeling were carried out as described previously.[11] The voxel level [^{18}F]FMPEP-d_2 V_T images, calculated with Logan's method within 30–120-minute period, were normalized to MNI152 space using clinical toolbox,[14] and spatially smoothed using an 8-mm full-width at half maximum Gaussian filter. Before statistical analyses, V_T images were flipped so that the left hemisphere corresponded to the contralateral side to the most affected body side and the right to the ipsilateral side. Details of imaging procedures and analyses are also provided in Supporting Information.

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Statistical Analyses

Statistical analyses were performed using *SPM12* software (Wellcome Trust Centre for Neuroimaging, London, UK) running in MATLAB (The MathWorks, Natick, MA). Associations between [^{18}F]FMPEP-d_2 V_T and with different UPDRS-III subscores were investigated with multiple regression, where age and sex were included as controlling variables. No grand mean scaling or global normalization was done. An explicit mask was used. All results were corrected for multiple comparisons using false discovery rate (FDR) at $P < 0.05$, and the cluster extent threshold was set such that only significant clusters were displayed. The statistical patterns were visualized using *MRIcroGL* software (https://www.nitrc.org/projects/mricrogl).

Results

A statistically significant negative correlation was observed between [^{18}F]FMPEP-d_2 V_T and PIGD score ($P = 0.002$). That is, the lower the [^{18}F]FMPEP-d_2 V_T, the higher the PIGD scores were. A large cluster (266,770 voxels) was located widespread over both hemispheres, covering several areas of temporal, parietal, and frontal lobes; cerebellum; and white matter (WM) (Fig. 1A). Similarly, a statistically significant negative correlation was observed between [^{18}F]FMPEP-d_2 V_T and rigidity subscore ($P < 0.001$). A large cluster (627,855 voxels) was located widespread over both hemispheres covering several areas of temporal, parietal, frontal, and occipital lobes; thalamus; basal ganglia; cerebellum; and WM (Fig. 1B). In contrast, tremor ($P = 0.995$) or bradykinesia ($P = 0.980$) subscore or UPDRS-III total score ($P = 0.144$) did not correlate significantly with [^{18}F]FMPEP-d_2 V_T.

Results were essentially replicated using nonparametric testing, an ROI-based approach, and correction for partial volume effects. Details of supplementary analyses are provided in Supporting Information.

Additionally, we studied the relationship between [^{18}F]FMPEP-d_2 binding and [^{18}F]FDOPA uptake, but the [^{18}F]FMPEP-d_2 and [^{18}F]FDOPA correlation analysis did not survive multiple comparison correction using FDR at $P < 0.05$.

Discussion

In this study, we investigated the relationship between CB1R availability and different motor features

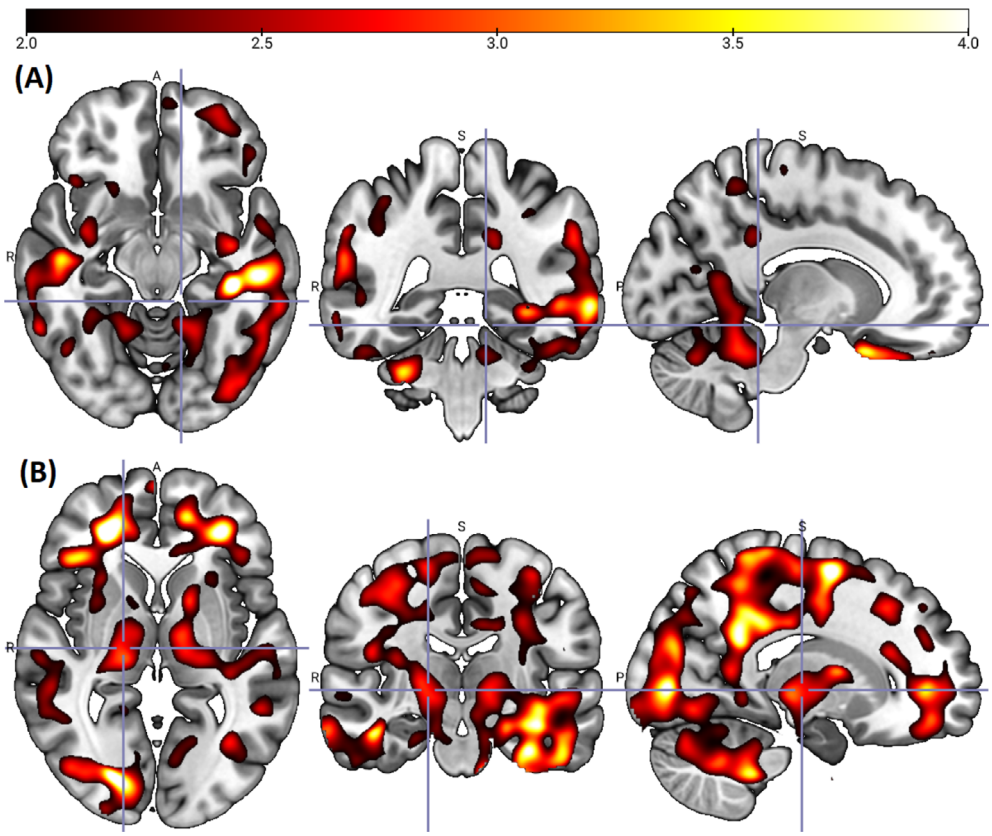

FIG. 1. Whole-brain statistical parametric mapping analysis shows lower cannabinoid receptor type 1 density correlating to higher gait and postural instability (**A**) and rigidity (**B**) subscore. Color bar represents t value, which corresponds to the level of significance at the voxel level. R, right hemisphere corresponding to the ipsilateral to the most affected body side. A, anterior; P, posterior; S, superior.

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of PD. We found that gait and postural instability and rigidity were associated with decreased CB1R availability measured as [^{18}F]FMPEP-d_2 V_T in several brain areas. In contrast, we did not see any association between tremor or bradykinesia and [^{18}F]FMPEP-d_2 V_T, which supports the hypothesis of different pathophysiological mechanisms underlying different motor subtypes and symptoms in PD.

The typical motor symptoms of PD include bradykinesia, rigidity, tremor, postural instability, and gait problems. However, individual patients' symptoms vary considerably, and three major clinical phenotypes have been described based on the predominant motor feature: tremor-dominant, akinetic-rigid, and PIGD subtypes. Several studies have found that the tremor-dominant subtype is associated with slower progression, while patients who have or progress to the PIGD subtype have a poorer prognosis and are at an increased risk for developing dementia.[6,15,16] The pathophysiological basis for the different phenotypes is not fully understood.

Dopaminergic depletion is the main neuropathological change behind PD-related motor symptoms and the rationale for using dopaminergic medication. Although dopamine replacement reduces rigidity and bradykinesia efficiently, the effect on tremor and PIGD symptoms can be minor. Similarly, imaging studies have shown a significant correlation between striatal dopamine loss and bradykinesia and rigidity although such an association has been weaker or not been observed with tremor.[17,18] PD pathology is not restricted to the dopaminergic system, and significant changes have also been observed in other neurotransmitter systems, which most likely contribute to the clinical phenotypes of PD. For example, decreased serotonergic transporter availability has been shown to correlate with the severity of tremor[19]; gait impairment has been associated with cholinergic deficit[20]; and the akinetic-rigid motor subtype has more severe noradrenergic loss than the tremor dominant subtype.[21] The current study expands this knowledge by showing that decreased CB1R availability is associated with gait and postural instability and rigidity, whereas such an association is not observed with tremor and bradykinesia.

Animal studies have shown that CB1R can modify both the dopaminergic system[22] and the noradrenergic system.[23] Our previous work showed an interaction between CB1R and the dopaminergic system as we found that subjects with PD had lower CB1R availability in the OFF stage compared to healthy controls. In the ON stage the availability increased toward normal levels.[11] But the dopaminergic deficit alone hardly explains the findings of the current study because the correlation between reduced [^{18}F]FMPEP-d_2 V_T and increased rigidity and PIGD scores was also seen in the cerebellar and occipital regions, where the dopaminergic projections are low. Instead, noradrenergic and cholinergic projections reach these regions and might explain some of the findings.

We found a significant correlation between decreased [^{18}F]FMPEP-d_2 V_T and rigidity and the PIGD score in several brain areas, including the WM. Although CB1R is most abundant in cortical regions, hippocampus, entorhinal cortex, and basal ganglia,[24] they are also present in WM.[25] WM forms connections between cortical and subcortical gray matter regions, and PIGD and non-tremor-dominant PD patients are believed to have more severe deficits within cortico-striato-thalamo-cortical circuitry compared to tremor-dominant PD patients.[26]

Considering that high densities of CB1R are found in basal ganglia, the ECS is of interest when developing new treatments for basal ganglia disorders such as PD. The role of CB1R in movement control is supported by CB1R knock-out mouse studies exhibiting a phenotype with hypoactivity and reduced movement.[27,28] Furthermore, based on animal studies, targeting the ECS might have beneficial effects on PD-related motor symptoms.[29] Thus far, only a few studies investigating cannabinoids in subjects with PD have been published. The results have been conflicting, probably due to small subject samples, various agents used, or being open-label. Also, the effects have been evaluated only by UPDRS total scores and not on different motor symptoms separately. The current study results support further exploring how targeting the ECS might affect different motor symptoms of PD instead of the total UPDRS motor score.

In conclusion, our study supports the hypothesis that the pathophysiological basis behind different motor symptoms and subtypes in PD is heterogeneous and further expands this by including the ECS as a potential contributor. A better understanding of the pathophysiological differences in different PD motor subtypes may result in more advanced and individualized treatment. More studies with larger sample sizes and subjects with various motor and nonmotor symptoms are needed to further understand the role of the ECS in PD and the interaction between the ECS and the dopaminergic system. ■

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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References

1. Harkany T, Guzmán M, Galve-Roperh I, Berghuis P, Devi LA, Mackie K. The emerging functions of endocannabinoid signaling during CNS development. Trends Pharmacol Sci 2007;28(2):83–92. https://doi.org/10.1016/j.tips.2006.12.004
2. Lu HC, MacKie K. An introduction to the endogenous cannabinoid system. Biol Psychiatry 2016;79(7):516–525. https://doi.org/10.1016/j.biopsych.2015.07.028
3. Kruk-Slomka M, Dzik A, Budzynska B, Biala G. Endocannabinoid system: the direct and indirect involvement in the memory and learning processes—a short review. Mol Neurobiol 2017;54(10):8332–8347. https://doi.org/10.1007/s12035-016-0313-5
4. Bisogno T, Berrendero F, Ambrosino G, et al. Brain regional distribution of endocannabinoids: implications for their biosynthesis and biological function. Biochem Biophys Res Commun 1999;256:377–380. https://doi.org/10.1006/bbrc.1999.0254
5. Herkenham M, Lynn AB, Little MD, et al. Cannabinoid receptor localization in brain. Proc Natl Acad Sci U S A 1990;87:1932–1936. https://doi.org/10.1073/pnas.87.5.1932
6. Jankovic J, McDermott M, Carter J, et al. Variable expression of parkinson's disease: a base-line analysis of the datatop cohort. Neurology 1990;40(10):1529–1534. https://doi.org/10.1212/wnl.40.10.1529
7. Aleksovski D, Miljkovic D, Bravi D, Antonini A. Disease progression in Parkinson subtypes: the PPMI dataset. Neurol Sci 2018;39(11):1971–1976. https://doi.org/10.1007/s10072-018-3522-z
8. Poletti M, Frosini D, Pagni C, et al. Mild cognitive impairment and cognitive-motor relationships in newly diagnosed drug-naive patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2012;83(6):601–606. https://doi.org/10.1136/jnnp-2011-301874
9. Van Der Heeden JF, Marinus J, Martinez-Martin P, Rodriguez-Blazquez C, Geraedts VJ, Van Hilten JJ. Postural instability and gait are associated with severity and prognosis of Parkinson disease. Neurology 2016;86(24):2243–2250. https://doi.org/10.1212/WNL.0000000000002768
10. Choi SM, Kim BC, Cho BH, et al. Comparison of two motor subtype classifications in de novo Parkinson's disease. Park Relat Disord 2018;54:74–78. https://doi.org/10.1016/j.parkreldis.2018.04.021
11. Ajalin RM, Al-Abdulrasul H, Tuisku JM, et al. Cannabinoid receptor type 1 in Parkinson's disease: a positron emission tomography study with [^{18}F]FMPEP-d2. Mov Disord 2022;37(8):1673–1682. https://doi.org/10.1002/mds.29117
12. Walker IM, Cousins KA, Siderowf A, et al. Non-tremor motor dysfunction in Lewy body dementias is associated with AD biomarkers. Park Relat Disord 2022;100:33–36. https://doi.org/10.1016/j.parkreldis.2022.05.022
13. Lahdenpohja S, Keller T, Forsback S, et al. Automated GMP production and long-term experience in radiosynthesis of CB1 tracer [^{18}F]FMPEP-d2. J Label Compd Radiopharm 2020;63(9):408–418. https://doi.org/10.1002/jlcr.3845
14. Rorden C, Bonilha L, Fridriksson J, Bender B, Karnath HO. Age-specific CT and MRI templates for spatial normalization. Neuroimage 2012;61(4):957–965. https://doi.org/10.1016/j.neuroimage.2012.03.020
15. Williams-Gray CH, Mason SL, Evans JR, et al. The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. J Neurol Neurosurg Psychiatry 2013;84(11):1258–1264. https://doi.org/10.1136/jnnp-2013-305277
16. García DS, Canfield H, De Deus FT, et al. Parkinson's disease motor subtypes change with the progression of the disease: results from the COPPADIS cohort at 2-year follow-up. J Parkinsons Dis 2022;12(3):935–955. https://doi.org/10.3233/JPD-213004
17. Pikstra ARA, Van Der Hoorn A, Leenders KL, De Jong BM. Relation of 18-F-dopa PET with hypokinesia-rigidity, tremor and freezing in Parkinson's disease. Neuroimage Clin 2016;11:68–72. https://doi.org/10.1016/j.nicl.2016.01.010
18. Pavese N, Evans AH, Tai YF, et al. Clinical correlates of levodopa-induced dopamine release in Parkinson disease: a PET study. Neurology 2006;67(9):1612–1617. https://doi.org/10.1212/01.wnl.0000242888.30755.5d
19. Pasquini J, Ceravolo R, Qamhawi Z, et al. Progression of tremor in early stages of Parkinson's disease: a clinical and neuroimaging study. Brain 2018;141(3):811–821. https://doi.org/10.1093/brain/awx376
20. Bohnen NI, Frey KA, Studenski S, et al. Gait speed in Parkinson disease correlates with cholinergic degeneration. Neurology 2013;81(18):1611–1616. https://doi.org/10.1212/WNL.0b013e3182a9f558
21. Kinnerup MB, Sommerauer M, Damholdt MF, et al. Preserved noradrenergic function in Parkinson's disease patients with rest tremor. Neurobiol Dis 2021;152:105295. https://doi.org/10.1016/j.nbd.2021.105295
22. Van Der Stelt M, Di Marzo V. The endocannabinoid system in the basal ganglia and in the mesolimbic reward system: implications for neurological and psychiatric disorders. Eur J Pharmacol 2003;480:133–150. https://doi.org/10.1016/j.ejphar.2003.08.101
23. Warren WG, Papagianni EP, Stevenson CW, Stubbendorff C. In it together? The case for endocannabinoid–noradrenergic interactions in fear extinction. Eur J Neurosci 2022;55(4):952–970. https://doi.org/10.1111/ejn.15200
24. Glass M, Dragunow M, Faull RLM. Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. Neuroscience 1997;77(2):299–318. https://doi.org/10.1016/S0306-4522(96)00428-9
25. Molina-Holgado E, Vela JM, Arévalo-Martín A, et al. Cannabinoids promote oligodendrocyte progenitor survival: involvement of cannabinoid receptors and phosphatidylinositol-3 kinase/Akt signaling. J Neurosci 2002;22(22):9742–9753. https://doi.org/10.1523/jneurosci.22-22-09742.2002
26. Boonstra JT, Michielse S, Temel Y, Hoogland G, Jahanshahi A. Neuroimaging detectable differences between Parkinson's disease motor subtypes: a systematic review. Mov Disord Clin Pract 2021;8(2):175–192. https://doi.org/10.1002/mdc3.13107
27. Zimmer A, Zimmer AM, Hohmann AG, Herkenham M, Bonner TI. Increased mortality, hypoactivity, and hypoalgesia in cannabinoid CB1 receptor knockout mice. Proc Natl Acad Sci U S A 1999;96(10):5780–5785. https://doi.org/10.1073/pnas.96.10.5780
28. Dubreucq S, Koehl M, Abrous DN, Marsicano G, Chaouloff F. CB1 receptor deficiency decreases wheel-running activity: consequences on emotional behaviours and hippocampal neurogenesis. Exp Neurol 2010;224(1):106–113. https://doi.org/10.1016/j.expneurol.2010.01.017
29. Stelt M, Fox SH, Hill M, et al. A role for endocannabinoids in the generation of parkinsonism and levodopa-induced dyskinesia in MPTP-lesioned non-human primate models of Parkinson's disease. FASEB J 2005;19(9):1140–1142. https://doi.org/10.1096/fj.04-3010fje

Supporting Data

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