Abstract

Purpose: Patients with Parkinson's Disease (PD) commonly experience Olfactory Dysfunction (OD). Our study examined hippocampal volumetric and resting-state functional magnetic resonance imaging (rs-fMRI) variations in a Healthy Control (HC) group versus a cognitively normal PD group, further categorized into PD with No/Mild Hyposmia (PD-N/MH) and PD with Severe Hyposmia (PD-SH).

Methods: We calculated participants' relative Total Hippocampal Volume (rTHV) and performed Spearman's partial correlations, controlled for age and gender, to examine the correlation between rTHV and olfactory performance assessed by the Odor Stick Identification Test for the Japanese (OSIT-J) score. Mann-Whitney U tests assessed rTHV differences across groups and subgroups, rejecting the null hypothesis for $p < 0.05$. Furthermore, a seed-based rs-fMRI analysis compared hippocampal connectivity differences using a one-way ANCOVA covariate model with controls for age and gender.

Results: Spearman's partial correlations indicated a moderate positive correlation between rTHV and OSIT-J in the whole study population ($\rho = 0.406$; $p = 0.007$), PD group ($\rho = 0.493$; $p = 0.008$), and PD-N/MH subgroup ($\rho = 0.617$; $p = 0.025$). Mann-Whitney U tests demonstrated lower rTHV in PD-SH subgroup compared to both HC group ($p = 0.013$) and PD-N/MH subgroup ($p = 0.029$). Seed-to-voxel rsfMRI analysis revealed reduced hippocampal connectivity in PD-SH subjects compared to HC subjects with a single cluster of voxels.

Conclusions: Although the design of the study do not allow to make firm conclusions, it is reasonable to speculate that the progressive involvement of the hippocampus in PD patients is associated with the progression of OD.

Keywords:

Parkinson Disease; hippocampus; resting-state functional MRI

List of abbreviations

- BOLD = Blood Oxygen Level Dependent
- CSF = Cerebrospinal Fluid
- fMRI = functional MRI
- GLM = General Linear Model
- FA = Fractional Anisotropy
- GM = Grey Matter
- HC = Healthy Controls
- MD = Mean Diffusivity
- MNI = Montreal Neurological Institute
- MRI = Magnetic Resonance Imaging
- OD = Olfactory Dysfunction
- OSIT-J = Odor Stick Identification Test for the Japanese
- p = p-value
- p-FWE = Family Wise corrected p-value
- PD = Parkinson's Disease
- PD-M/NH = Parkinson's Disease patients with No/Mild Hyposmia
- PD-SH = Parkinson's Disease patient with sever hyposmia
- ROI = Region Of Interest
- rs-fMRI = resting state functional Magnetic Resonance Imaging
- rTHV = relative total hippocampal volume
- T1W-3D = T1-weighted three-dimensional
- T2*-Echo-Planar Imaging
- WM = White Matter

1. Introduction

Parkinson's Disease (PD) is one of the most common neurodegenerative disorders globally. Specifically, in the United States of America, the estimated incidence ranges from 108 to 212 per 100,000 among individuals aged over 65 [Willis et al., 2022]. In addition to classical motor symptoms such as tremor, rigidity, and akinesia/bradykinesia [Moustafa et al., 2016], other recently investigated non-motor symptoms can be associated with this disease. Olfactory Dysfunction (OD) in PD has been extensively studied in recent years, with several studies indicating its presence in up to 90% of symptomatic PD patients [Schapira et al., 2017], as well as during the prodromal stage of the disease [Ercoli et al., 2022].

The exact mechanisms behind OD in PD are still under investigation, but the progressive deposition of aggregates of α-synuclein [Gómez-Benito et al., 2020], from the periphery (olfactory bulbs) to central cerebral structures, appears to play a pivotal role [Fullard et al., 2017]. From a macroscopic perspective, the progression of PD is characterized by the gradual atrophic involution not only of the olfactory bulbs but also of several central cerebral regions, including the caudate, nucleus accumbens, hippocampus, and posterior cortical regions [Torres-Pasillas et al., 2023]. Among these structures, the hippocampus has drawn attention from researchers due to its critical role in the central processing of olfactory stimuli [Compston, 2010; Dickson, 2018; Dintica et al., 2019; Kubota et al., 2020; Roh et al., 2021]. A recent study by *Roh et al.* [Roh et al., 2021] highlighted that PD patients with marked hyposmia exhibited more pronounced bilateral hippocampus hypotrophy compared to normosmic PD subjects, suggesting that the volume reduction of the hippocampus implies underlying issues in the central olfaction process.

Over the last two decades, several functional Magnetic Resonance Imaging (fMRI) studies have analyzed the neural activity and brain networking of PD patients with OD, both in resting state (rs-fMRI) [Yoneyama et al., 2018; Georgiopoulos et al., 2019; Wang et al., 2022; Fan et al., 2022; Du et al., 2023] and/or following an olfactory task [Westermann et al., 2008; Welge-Lüssen et al., 2009; Hummel et al., 2010; Su et al., 2015; Tremblay et al., 2020]. These studies have been conducted globally or by focusing on specific circuits involved in odor identification and processing. Four of these studies [Westermann et al., 2008; Welge-Lüssen et al., 2009; Hummel et al., 2010; Su et al., 2015], while differing in study design and analysis technique, revealed impairments in hippocampal activity within the broader context of brain network analysis. However,

to the best of our knowledge, no fMRI studies have specifically examined the relationships between the hippocampus and other cerebral areas in relation to OD in PD.

Based on the aforementioned evidence, we designed a structural-functional combined exploratory cross-sectional study to compare hippocampal volumetric and seed-based rs-fMRI connectivity differences among healthy controls (HC), cognitively normal PD patients with No/Mild Hyposmia (PD-N/MH), and cognitively normal PD patients with Severe Hyposmia (PD-SH). This study utilized the freely available dataset from the research published by *Yoneyama et al.* [Yoneyama et al., 2018].

2. Materials and methods

2.1. Dataset

The dataset utilized for this research is the same one employed in the study published in 2018 by *Yoneyama et al.* [Yoneyama et al., 2018]. This dataset is freely and publicly available (License: CC0), was acquired from the OpenfMRI database, with the accession number ds000245 (https://openfmri.org/dataset/ds000245). The key details of the data used in this research project are summarized in the following sections; for more comprehensive information, readers are invited to refer to the original paper by *Yoneyama et al.* [Yoneyama et al., 2018].

2.2. Study population and olfaction assessment

The entire study population comprised 45 Japanese subjects, categorized into two groups: 1) the healthy control (HC) group, consisting of 15 HC, and 2) the PD group, consisting of 30 cognitively normal PD patients diagnosed according to the UK Brain Bank criteria [Hughes et al., 1992]. All PD patients were in Hoen and Yahr stages I-III [Hoehn & Yahr, 1967], with disease onset occurring after the age of 40.

Olfactory performance for all study subjects was assessed using the Odor Stick Identification Test for the Japanese (OSIT-J; Daiichi Yakuhin, Co., Ltd., Tokyo, Japan) [Saito et al., 2006]. The OSIT-J comprises 12 odorants familiar to the Japanese population and is widely utilized for olfactory evaluation in PD patients [Yoneyama et al., 2018]. Subsequent to this test, the PD group was further divided into two subgroups based

on: 1) the PD-N/MH subgroup, consisting of 15 PD patients with an OSIT-J score < 4, and 2) the PD-SH subgroup, consisting of 15 patients with an OSIT-J score ⩾ 6. The detailed procedures for subgroup definitions according to the OSIT-J score are outlined in the original publication by *Yoneyama et al.* [Yoneyama et al., 2018].

2.3. Imaging assessment

All subjects in the study population underwent an MRI scan using a Siemens Magnetom Verio 3.0 T scanner (Siemens, Erlangen, Germany) equipped with a 32-channel head coil. The sequences included in the dataset were as follows: a) a high-resolution structural T1-weighted three-dimensional (T1W-3D) sequence (repetition time = 2.5 s; echo time = 2.48 ms; acquisition axis = 192 sagittal; slice thickness = 1 mm; field of view = 256 mm; matrix = 256 × 256; total scan time = 349 seconds); and b) a functional T2*-Echo-Planar Imaging (T2*-EPI) sequence (repetition time = 2.5 s; echo time = 30 ms; acquisition axis = axial; number of slices = 39; inter-slice interval = 0.5 mm; slice thickness = 3 mm; field of view = 192 mm; matrix = 64 × 64; flip angle = 80°; total scan time = 8 min) acquired during the resting state, with the eyes closed. Regarding PD patients, the MRI scan was conducted while they were in the "ON" medication state.

2.4. Hippocampal volumetric analysis

In analogy to the research by *Porcu et al.* [Porcu et al., 2020], the relative total hippocampal volume (rTHV) was calculated for each subject in the study population using the HIPS automatic voxel-based segmentation online tool [Romero et al., 2017]. Specifically, the rTHV was automatically extracted from the structural T1W-3D sequence using the monospectral modality. This involved dividing the sum of the absolute volumes of the right and left hippocampus by the absolute intracranial volume. The rTHV was expressed as a percentage (%). An example of hippocampal segmentation is illustrated in Figure 1.

All segmentations underwent blind review by an expert neuroradiologist (M.P., with 10 years of radiological experience). In cases where the segmentation was deemed "not correct," the corresponding subject would have been excluded from the study population.

2.5. rs-fMRI data analysis

The rs-fMRI group analysis was conducted on the Matlab platform vR2020b (Mathworks, Inc., California, USA) using the CONN toolbox [Witfield-Gabrieli & Nieto-Castanon, 2012] release 22.a [Nieto-Castanon & Witfield-Gabrieli, 2022] and SPM release 12.7771 [Penny et al., 2011].

Following a similar approach to previous rs-fMRI studies [Porcu et al., 2020; Porcu et al., 2021], structural T1-3D and functional T2*-EPI sequence data underwent preprocessing using a defined pipeline [Nieto-Castanon, 2020].

Functional data were realigned using the SPM realign & unwarp procedure [Andersson et al., 2001]. All scans were coregistered to a reference image (first scan of the first session) using a least squares approach and a 6-parameter (rigid body) transformation [Friston et al., 1995]. Resampling was performed using b-spline interpolation to correct for motion and magnetic susceptibility interactions. Potential outlier scans were identified using ART [Whitfield-Gabrieli et al., 2011], considering acquisitions with framewise displacement above 0.9 mm or global Blood Oxygen Level Dependent (BOLD) signal changes above 5 standard deviations [Power et al., 2014]. A reference BOLD image was computed for each subject by averaging all scans excluding outliers. To minimize signal fluctuations in the initial scanning stage, the first 10 volumes of the T2*-EPI sequence were excluded from the analysis [Chiacchieretta & Ferretti, 2015].

Functional and anatomical data were then normalized to standard Montreal Neurological Institute (MNI) space [Collins et al., 1994] space, segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) tissue classes, and resampled to 2 mm isotropic voxels using a direct normalization procedure [Calhoun et al., 2017]. This was accomplished through SPM unified segmentation and normalization algorithm [Ashbumer & Friston, 2005; Ashbumer, 2007], utilizing the default IXI-549 tissue probability map template. Finally, functional data underwent smoothing through spatial convolution with a Gaussian kernel of 8 mm full width at half maximum.

Functional data were subsequently denoised using a standard denoising pipeline [Nieto-Castanon, 2020]. This process involved the regression of potential confounding effects, characterized by WM timeseries (5 CompCor noise components), CSF timeseries (5 CompCor noise components), motion parameters, and their first-order derivatives (12 factors) [Friston et al., 1996], outlier scans (below 10 factors) [Power et al., 2014],

session effects, and their first-order derivatives (2 factors), as well as linear trends (2 factors) within each functional run. This was followed by bandpass frequency filtering of the BOLD timeseries [Hallquist et al., 2013], restricting it between 0.008 Hz and 0.09 Hz. CompCor [Behzadi et al., 2007; Chai et al., 2012] noise components within WM and CSF were estimated by computing the average BOLD signal, as well as the largest principal components orthogonal to the BOLD average, motion parameters, and outlier scans within each subject's eroded segmentation masks. Taking into account the number of noise terms included in this denoising strategy, the effective degrees of freedom of the BOLD signal after denoising were estimated to range from 66.4 to 70.5 (average 70) across all subjects.

Finally, for each subject, seed-based connectivity maps were estimated to characterize patterns of functional connectivity. The CONN's default atlas, i.e. the Harvard-Oxford Atlas [Desikan et al., 2006] for cortical and subcortical regions, and the Automated Anatomical Labeling atlas [Tzourio-Mazoyer et al., 2002] for cerebellar regions (Supplemental Table 1), was utilized to identify cerebral regions of interest (ROI). Functional connectivity strength was represented by Fisher-transformed bivariate correlation coefficients derived from a weighted general linear model (GLM), defined separately for each pair of seed and target areas, modeling the association between their BOLD signal timeseries [Nieto-Castanon, 2020]. Individual scans were weighted by a step function convolved with an SPM canonical hemodynamic response function and rectified to compensate for possible transient magnetization effects at the beginning of each run.

2.6. Statistical analysis

2.6.1. Hippocampal volumetry: relationships with olfaction performances and differences among groups/subgroups

The correlation (ρ) between rTHV and OSIT-J scores in the entire study population, HC group, PD group, PD-N/MH, and PD-SH subgroups, was analyzed using non-parametric Spearman's partial correlations, with age and gender as control variables. The null hypothesis was rejected for p-value (p) < 0.05.

Additionally, differences in rTHV between the HC and PD group, as well as between the HC and PD-N/MH subgroups, HC and PD-SH subgroups, and PD-N/MH and PD-SH subgroups, were examined using a non-parametric Mann Whitney U test. Once again, the null hypothesis was rejected for $p < 0.05$.

The aforementioned statistical analyses were performed using JASP version 0.18.1 (JASP Team - 2023).

2.6.2. *Seed-to-voxel group rs-fMRI analysis*

The second-level seed-to-voxel group analysis was conducted using the GLM with the CONN toolbox release 22.a [Nieto-Castanon, 2020]. For each individual voxel, a separate GLM was estimated, with first-level connectivity measures at this voxel serving as dependent variables (one independent sample per subject) and groups or other subject-level identifiers as independent variables. Voxel-level hypotheses were assessed using multivariate parametric statistics with random effects across subjects and sample covariance estimation across multiple measurements.

Specifically, we compared the differences (increased or reduced) in seed-to-voxel connectivity between both the left and right hippocampus ("Hippocampus l" and "Hippocampus r" according to the Harvard-Oxford Atlas [Desikan et al., 2006]) and the rest of the brain using a one-way ANCOVA covariate model. The model was controlled for the variables "age" and "gender", and was applied in four different scenarios: HC group versus PD group (Analysis 1), PD-N/MH subgroup versus HC group (Analysis 2), PD-N/MH subgroup versus PD-SH subgroup (Analysis 3), and PD-SH subgroup versus HC group (Analysis 4).

Inferences were made at the level of individual clusters (groups of contiguous voxels). Cluster-level inferences relied on nonparametric statistics from randomization/permutation analyses [Bullmore et al., 1999; Nieto-Castanon, 2020], with 1000 residual-randomization iterations. Results were thresholded using a combination of a cluster-forming $p < 0.01$ voxel-level threshold and a p-FDR < 0.05 cluster-mass threshold [Chumbley et al., 2010].

3. **Results**

3.1. Demographics, olfaction assessment and hippocampal volumetric analysis

As mentioned earlier, the entire study population comprised 45 subjects (male = 25; female = 20; mean age = 66.1). The HC group consisted of 15 subjects (male = 7; female = 8; mean age = 63.3), and the PD group comprised 30 subjects (male = 13; female = 17; mean age = 67.6). Within the PD group, there were 15 PD-N/MH subjects (male = 6; female = 9; mean age = 64.4) and 15 PD-SH subjects (male = 7; female = 8; mean age = 70.7). For complete demographic details, please refer to the original publication by *Yoneyama et al.* [Yoneyama et al., 2018].

The mean OSIT-J score (utilized for olfaction assessment) and rTHV values (extracted from the voxel-based automated hippocampal volumetric analysis) were as follows: 6.533 and 0.509% for the entire study population; 10.400 and 0.521% for the HC group; 4.600 and 0.503% for the PD group; 7.467 and 0.522% for the PD-N/MH subgroup; 1.733 and 0.483% for the PD-SH subgroup. The details of olfaction assessment and hippocampal volumetric analysis are presented in Table 1, with individual subject data provided in Supplemental Table 2.

3.2. Hippocampal volumetry: relationships with olfaction performances and differences among groups/subgroups

The automated hippocampal segmentation was deemed correct for all subjects by the expert neuroradiologist, and therefore no subjects were excluded from the analysis.

The non-parametric Spearman's partial correlations analysis revealed a statistically significant moderate positive correlation between rTHV and OSIT-J in the entire study population ($\rho = 0.406$; $p = 0.007$), the PD group ($\rho = 0.493$; $p = 0.008$), and the PD-N/MH subgroup ($\rho = 0.617$; $p = 0.025$). No statistically significant findings were observed in the HC and PD-SH groups. The results are reported in Table 2, and the statistically significant correlation scatter plots are presented in Figure 2.

The non-parametric Mann-Whitney U test indicated that rTHV was significantly lower in the PD-SH subgroup compared to both the HC group ($p = 0.013$; mean rTHV HC group = 0.521%; mean rTHV PD-SH subgroup = 0.483%) and the PD-N/MH subgroup ($p = 0.029$; mean rTHV PD-N/MH subgroup = 0.522%; mean rTHV PD-SH subgroup = 0.483%). No statistically significant differences were found in the other

comparisons. The results are reported in Table 3, and the raincloud plots of statistically significant Mann-Whitney U test comparisons are illustrated in Figure 3.

3.3. Seed-to-voxel group rs-fMRI analysis

The seed-to-voxel analysis did not reveal any statistically significant findings in Analyses 1 (HC group versus PD group), 2 (PD-N/MH subgroup versus HC group), and 3 (PD-N/MH subgroup versus PD-SH subgroup).

In Analysis 4, the seed-to-voxel analysis showed reduced hippocampal connectivity with a single cluster of voxels in PD-SH subjects compared to HC subjects (cluster center coordinates according to the MNI space: +04 -44 -46 mm; cluster size = 1560; cluster-size p-FDR = 0.044367; mass = 20039.15; cluster mass p-FDR = 0.029409). This cluster encompassed several supra- and infratentorial areas, notably the anterior cerebellar lobes (vermis 1, 2, 3, 4, and 5, and cerebellar 3, 4, and 5 lobules of both hemispheres), the cerebellar 6 lobule (primarily the one located in the left hemisphere), the lingual gyrus, and the posterior division of the parahippocampal cortex in both cerebral hemispheres. No areas of increased connectivity were identified. The full results of Analysis 3 are reported in Table 4 and visually presented in Figure 4 (slice view) and Figure 5 (three-dimensional view).

4. Discussion

The main clinical manifestations of PD are characterized by motor symptoms, attributed to the progressive degeneration of dopaminergic cells in the substantia nigra and the consequent involvement of the extrapyramidal motor pathway [Bae et al., 2021]. However, PD patients may also present a broad spectrum of non-motor symptoms. Some, like sleep disorders, dysautonomia, and olfactory dysfunction (OD), tend to manifest earlier than non-motor symptoms [Torres-Pasillas et al., 2023], while others, such as cognitive impairments, typically appear after the onset of motor symptoms [Meireles et al., 2012].

As mentioned in the introduction, OD is observed in up to 90% of symptomatic PD patients and is often noted in the preclinical stage of the disease [Doty, 2012; Ercoli et al., 2022]. Its presence has been identified as a risk factor for the development of dementia, as demonstrated, for example, by *Baba et al.* [Baba et al., 2012]. Consequently, OD in PD has garnered attention from researchers for its potential role in enhancing

early diagnosis and optimizing therapy [Torres-Pasillas et al., 2023]. Although the precise pathological mechanisms underlying PD are still under investigation, the abnormal and progressive deposition of α-synuclein aggregates appears to play a central role, leading to inflammation, selective neural dysfunction, and ultimately, neural death [Iemolo et al., 2023; Calabresi et al., 2023]. Similar to other neurodegenerative disorders, this process results in progressive brain atrophy [Filippi et al., 2020]. The phenomenon of atrophy also impacts the hippocampus [Camicioli et al., 2003], influenced by both dopamine denervation [Bohnen et al., 2008] and neuronal death due to α-synuclein aggregate deposition [Giráldez-Pérez et al., 2014]. The hippocampus, a complex brain region involved in various higher neurological functions such as spatial navigation, emotional behavior, regulation of hypothalamic functions, and olfaction processing [Anand & Dhikav, 2012; Calabresi et al., 2013], undergoes a progressive atrophy development in PD. This process is associated with the onset of cognitive deficits in the later stages of the disease [Camicioli et al., 2003; Yildiz et al., 2015; Uribe et al., 2018]. Similar associations have also been identified for OD [Torres-Pasillas et al., 2023].

In this study, our focus was on analyzing volumetric and fMRI differences in the hippocampus among HC, cognitively normal PD-N/MH subjects, and cognitively normal PD-SH patients.

The volumetric analysis revealed a moderate positive correlation between hippocampal volumetry, calculated in terms of rTHV, and olfactory performance measured with the OSIT-J score in the entire study population, the PD group, and the PD-N/MH subgroup. However, no statistically significant correlations were found in the HC group and the PD-SH subgroup. All these correlations included age and gender as control variables to mitigate potential biases. Furthermore, the comparison of rTHV between the population groups and subgroups indicated that rTHV was greater in both the HC group and PD-N/MH group compared to the PD-SH group. However, no statistically significant differences were found in the comparison between the HC group and PD-N/MH group.

On the other hand, the seed-based fMRI analysis, which compared connectivity differences between the hippocampi and the rest of the brain in different subgroups, revealed a statistically significant difference in terms of reduced connectivity between the hippocampi and both the cerebellum and supratentorial areas of both cerebral hemispheres (especially the lingual gyrus and posterior division of the parahippocampal cortex) only in the PD-SH subgroup when compared to the HC group. No statistically significant differences were

found in other comparisons (HC group versus PD group, PD-N/MH subgroup versus HC group, and PD-N/MH subgroup versus PD-SH subgroup).

The results of the volumetric analysis are consistent with those reported in the literature. Notably, *Xu et al.* [Xu et al., 2020] found that the bilateral hippocampal volume in non-demented PD patients was smaller compared to HC. Additionally, a recent study by *Roh et al.* [Roh et al., 2021] demonstrated that cognitively normal PD patients with severe hyposmia exhibited significantly smaller bilateral hippocampal volume, particularly in the hippocampal body. This study also found a positive correlation between hippocampal volume and olfactory performance measured with the cross-cultural smell identification test. Regarding the correlations between hippocampal volume and olfactory performance, a moderate positive correlation between rTHV and OSIT-J score was found in the PD group, similar to what was observed by *Roh et al.* [Roh et al., 2021]. This finding suggests a decline in odor function in correlation with the reduction of hippocampal volume. However, it is noteworthy that when the analysis focused on specific PD subgroups, the same positive correlation was observed only in the PD-N/MH subgroup and not in the PD-SH subgroup. This observation could be better interpreted in light of the seed-based rs-fMRI connectivity.

The functional analysis revealed statistically significant findings only in Analysis 4, which compared the HC group and the PD-SH subgroup. Specifically, it showed reduced hippocampal connectivity with both supratentorial areas (mainly the lingual gyrus and posterior division of the parahippocampal cortex) and the cerebellum (mainly the anterior lobe and lobule 6 of both hemispheres). Indeed, a substantial input to the superficial layers of the enthorinal cortex originates from olfactory structures such as the olfactory bulb, the anterior olfactory nucleus, and the piriform cortex. These olfactory projections terminate throughout most of the rostrocaudal extent of the entorhinal cortex. Moreover, the infralimbic cortex extends their projections to the medial portion of the olfactory bulb subicular fibers [Burwell, 2001]. In addition, it is of mention the fact that only olfactory input originating from all levels of the olfactory system has direct access to hippocampal structures although in primates this access is restricted to about 10% of the surface area of the enthorinal cortex. In an extreme synthesis the hippocampal formation can be viewed as the final stage in a cascade of neocortical sensory processing from unimodal association cortices to few polysensory cortical regions which in turn project on the enthorinal cortex [Lavenex & Amaral, 2000]. Obviously, this pathway is extremely important in the functional performance of the olfaction end its correlated activities as enthorinal lesions cause rapid

forgetting of olfactory information [Stäubli et al., 1984]. However, it is important to note that the hippocampus is also implicated in the control of the odor habituation process, as demonstrated by Poellinger et al. (2001) in their task-based fMRI study. Furthermore, recent research by Georgiopoulos et al. (2024) suggests that this mechanism is preserved in PD patients. Initially, these findings may appear somewhat contradictory to ours; however, it is important to underline that our fMRI study was conducted under resting conditions and, to the best of our knowledge, no rs-fMRI studies have examined the odor habituation phenomenon to date. Therefore, we believe that our findings do not contradict those previously reported in the literature, although further studies are required to clarify this aspect.

While the reduced connectivity with the lingual gyrus and posterior division of the parahippocampal cortex is more easily understandable due to the widely demonstrated involvement of these structures in odor processing and memory [Han et al., 2019], the reduced connectivity with the cerebellum might seem less intuitive. However, the cerebellar contribution to motor and non-motor functions in PD is well known [Solstrand Dahlberg, Lungu & Doyon, 2020]; further, although the cerebellum is traditionally not considered part of the olfactory processing system [Wu & Hallett, 2013], some studies in healthy subjects have demonstrated its involvement..

Among the first studies demonstrating the cerebellum's role in olfactory function in healthy subjects is the research by *Ferdon et al.* [Ferdon & Murphy, 2003], which established an association between decreased cerebellar activation and a reduction in olfactory abilities during healthy aging. Another study by *Mainland et al.* [Mainland et al., 2005] detected olfactory dysfunction in patients with cerebellar lesions. Furthermore, the task fMRI study by *Sobel et al.* [Sobel et al., 1998] demonstrated the activation of the cerebellar cortex in response to odor stimuli, particularly the activation of the anterior central portion of the cerebellum in response to sniffing. The same areas were found to be metabolically more active in response to olfactory stimuli in the ^{18}F-fluorodeoxyglucose-positron emission tomography/computer tomography conducted by *Alessandrini et al.* [Alessandrini et al., 2014]. More recently, a voxel-based morphometry analysis revealed a positive association between gray matter volume in lobule 6 of the left cerebellar hemisphere and olfactory identification performances [Wabnegger & Schienle, 2019]. Additionally, a task-based fMRI study by *Zhang et al.* [Zhang et al., 2021] demonstrated the activation of lobule 6 of the right cerebellar hemisphere in response to unpleasant odors, suggesting that the cerebellum is likely involved in olfactory-related responses to unpleasant odors. In

a relatively recent review [Wu & Hallet, 2013] suggested that these findings trace a correlation between cerebellar WM damage and olfactory dysfunction in PD subjects. Moreover, cerebellar pathologies such as ataxia seem to correlate with olfactory impairment [Mainland et al., 2005; Moscovich et al., 2012].

While, to the best of our knowledge, no studies specifically analyzing the role of the cerebellum in OD in PD patients have been conducted, the evidence presented above from studies on healthy subjects seems to support the hypothesis that dysfunction in the anterior lobes and lobule 6 of the cerebellum plays a crucial role in the OD process in PD patients as well. This hypothesis is further supported by a diffusion tensor imaging study conducted by *Zhang et al.* [Zhang et al., 2011], which revealed reduced white matter integrity in terms of decreased Fractional Anisotropy (FA) and increased Mean Diffusivity (MD) in the bilateral orbitofrontal cortex and both cerebellar hemispheres in PD subjects with OD compared to HC. The authors also found a positive correlation between olfactory identification thresholds and FA values in the white matter of the left cerebellar hemisphere in the PD population, along with a negative correlation with MD values in the white matter of the right cerebellar hemispheres. It is reasonable to speculate that a similar mechanism could at least partly explain the reduced patterns of connectivity observed in our analysis, although this aspect has not been investigated in this study. Some concerns about this hypothesis could arise from the results of the task-fMRI study conducted by *Westermann et al.* [Westermann et al., 2008], which observed an activation of both cerebellar lobes in response to odor stimuli in both HC and hyposmic PD patients, suggesting that this activation might be related to the arousal elicited by the olfactory condition. The results of this study might seem somewhat contradictory to our hypothesis, but it is important to underline that our study was conducted on a population analyzed in a resting state, and it is methodologically different because it focused solely on the analysis of hippocampal connectivity. Similar considerations can be made when looking at the results of the task-fMRI study conducted by *Takeda et al.* [Takeda et al., 2010], which evidenced a reduced activation of the right cerebellar tonsil in response to olfactory stimulation in PD patients compared to HC.

Summarizing the structural and functional results of our study, the evidence from the literature, and the findings of some longitudinal studies demonstrating the progression of OD during the course of PD [Herting et al., 2008; Meusel et al., 2010; Campabadal et al., 2017], it is reasonable to comprehensively speculate that the progressive involvement of the hippocampus in PD leads to the progression of OD in PD patients, resulting in volumetric reduction and functional dysfunction. The absence of statistically significant

findings in the seed-based rs-fMRI analysis of the PD-N/MH group could reflect what happens in the early stages of OD, where the impact on hippocampal activity would be negligible. In the later stages of OD, however, the progression of hippocampal atrophy would significantly affect hippocampal activity with the aforementioned supratentorial and infratentorial areas, as observed in the PD-SH subgroup where the correlation between hippocampal volume and olfactory performances was no longer demonstrable. This hypothesis might seem somewhat contradictory given the results reported in the original paper by Yoneyama et al. (2018), where the authors reported no statistically significant differences in terms of duration and severity of disease between the PD-N/MH and the PD-SH subgroups. However, the absence of specific data regarding the duration and severity of the disease for each participant in the dataset stored in the OpenfMRI database (https://openfmri.org/dataset/ds000245), as well as data regarding the treatment received and the onset of symptoms, did not allow us to analyze in greater detail the relationship between OD, PD features of the disease, and hippocampal dysfunctions. Considering the aforementioned points and the cross-sectional design of the study, it is important to emphasize that our theory remains purely speculative, and further longitudinal studies with larger cohorts of patients are required to confirm or refute this hypothesis.

Certainly, we identified at least two major limitations in this study. The first one is the small study population. In analogy to previous studies [Porcu et al., 2020; Porcu et al., 2024], we decided not to apply any multiple test corrections for both the hippocampal and functional analyses to minimize type II statistical errors in [Bender et al., 2001] due to the exploratory design of the research. For this reason, and also considering the intrinsic variability demonstrated in fMRI studies [Botvinik-Nezer et al., 2020], the results of this research must be approached with care, and more studies (prospective longitudinal studies in particular) with bigger study populations (included HC with OD) are needed to confirm these findings.

The second limitation relates to the use of an automated system for rTHV calculation. It is known from the literature that there is a certain degree of variability in results among different tools used for automated segmentation of brain structures [Singh MK & Singh KK, 2021]. However, the HIPS tool was specifically designed for hippocampal analysis [Romero et al., 2017], and the use of an automated tool ensured a standardized and bias-free rTHV calculation. Furthermore, all results were meticulously reviewed in blind by an expert neuroradiologist.

5. Conclusion

In this study, we examined the role of hippocampal volumetric differences and functional properties in PD patients with and without OD. Although the study was cross-sectional and not designed longitudinally, the comparison of structural and functional data among HC, PD-N/MH, and PD-SH subjects allows us to speculate that the progressive involvement of the hippocampus in PD patients is associated with the progression of OD. This association leads to volumetric reduction already visible in the early stages and, in the later stages, a decrease in connectivity between the hippocampus and both supratentorial areas (especially the lingual gyrus and posterior division of the parahippocampal cortex in both cerebral hemispheres) and infratentorial areas (particularly the anterior lobe and lobule 6 of both cerebellar hemispheres). However, future longitudinal studies are necessary to test this hypothesis. Finally, the involvement of several structures other than the motor circuitries highlight once more the pervasive involvement of the entire brain, prompting further investigation of PD within a broader context.

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Declaration of Interests

The authors declare no conflict of interests.

Ethical approval

The present study was conducted by exploiting the freely available public-dataset used for the research study "*Severe hyposmia and aberrant functional connectivity in cognitively normal Parkinson's disease*" by *Yoneyama et al.* [Yoneyama et al., 2018]. This dataset is freely publicly available (License: CC0), and it was obtained from the OpenfMRI database. Its accession number is ds000245 (https://openfmri.org/dataset/ds000245). The dataset was collected in accordance with the World Medical Association Declaration of Helsinki revised in 1989 and approved by the Ethical Committee of the Nagoya University Graduate School of Medicine.

Data availability statement

All data generated specifically for the analyses of this study are included in this published article (and its supplemental information file).

Figure legends

- **Figure 1**: Example of bilateral hippocampal voxel-based segmentation (red areas) with the automated HIPS tool [Romero et al., 2017]. A) axial view; B) coronal view; C) sagittal view.

- **Figure 2**: Scatter plots of statistically significant Spearman's correlations. From left to right: Study population ($\rho = 0.406$; $p = 0.007$), PD group ($\rho = 0.493$; $p = 0.008$) and PD-N/MH group ($\rho = 0.617$; $p = 0.025$). PD = Parkinson's Disease; PD-N/MH = Parkinson's Disease patients with No/Mild Hyposmia.

- **Figure 3**: Raincloud plots of statistically significant Mann-Whitney U test comparisons. From left to right: HC group vs PD-SH subgroup ($p = 0.013$; mean rTHV HC group = 0.521%; mean rTHV PD-SH subgroup = 0.483%), and PD-N/MH vs PD-SH ($p = 0.029$; mean rTHV PD-N/MH subgroup = 0.522%; mean rTHV PD-SH subgroup = 0.483%). HC = Healthy Controls; PD = Parkinson's Disease; PD-SH = Parkinson's Disease patients with Severe Hyposmia; PD-N/MH = Parkinson's Disease patients with No/Mild Hyposmia.

- **Figure 4**: A) Slice view (neurological orientation) and B) three-dimensional view of the statistically significant cluster of reduced hippocampal connectivity (blueish area) revealed in Analysis 4 (PD-SH subgroup versus HC group). The details of the cluster composition are reported in Table 4, but it is noticeable that the cluster predominantly extends into the anterior lobe of both cerebellar hemispheres and the lingual and posterior division of the parahippocampal cortex in both cerebral hemispheres. PD-SH = Parkinson's Disease patients with Severe Hyposmia; HC = Healthy Controls.

Table legends

- **Table 1**: Results of olfaction assessment (in terms of OSIT-J score) and hippocampal volumetric analysis (in terms of rTHV, expressed in %) of the whole study population, HC group, PD group, PD-N/MH subgroup, and PD-SH subgroup. HC = Healthy Controls; PD = Parkinson's Disease; PD-N/MH = Parkinson Disease patients with No/Mild Hyposmia; PD-SH = Parkinson's Disease patients with Severe Hyposmia; OSIT-J = Odor Stick Identification Test for the Japanese; rTHV = relative Total Hippocampal Volume.

- **Table 2**: Results of the non-parametric Spearman's partial correlations analysis between rTHV and ODIT-J score (controlled for age and gender) for the entire study population, as well as according to different groups and subgroups. rTHV = relative Total Hippocampal Volume; n = number of subjects; ρ = correlation coefficient; OSIT-J = Odor Stick Identification Test for the Japanese; HC = Healthy Controls; PD = Parkinson's Disease; PD-N/MH = Parkinson's Disease patients with No/Mild Hyposmia; PD-SH = Parkinson's Disease patients with severe Hyposmia.

- **Table 3**: Results of the non-parametric Mann-Whitney U test for comparing rTHV between the different groups and subgroups. rTHV = relative Total Hippocampal Volume; W = W value; CI = Confidence Interval; HC = Healthy Controls; PD = Parkinson's Disease; PD-N/MH = Parkinson's Disease patients with No/Mild Hyposmia; PD-SH = Parkinson's Disease patients with Severe Hyposmia.

- **Table 4**: Results of the seed-to-voxel Analysis 4 (PD-SH subgroup versus HC group); a single statistically significant cluster of reduced hippocampal connectivity was found in PD-SH subgroup when compared to HC group (the cluster composition according to the CONN's default atlas is reported at the bottom of the table). No cluster of increased connectivity were found. PD-SH = Parkinson's Disease patients with Severe Hyposmia; HC = Healthy Controls; p-FWE = familywise corrected p-value; p-FDR = p-value corrected for False Discovery Rate; p-unc = uncorrected p-value.

Supplemental table legends

- **Supplemental table 1**: Atlas – Regions of interest (ROI) legend [Desikan et al., 2006; Tzourio-Mazoyer et al., 2002].

- **Supplemental table 2**: Full details of demographic data, olfactory assessment, and hippocampal volumetric analysis for each subject of the whole study population. HC = healthy control; PD = Parkinson Disease; PD-N/MH = Parkinson's Disease patients with No/Mild Hyposmia; PD-SH = Parkinson's Disease patients with Severe Hyposmia; OSIT-J = Odor Stick Identification Test for the Japanese; rTHV = relative Total Hippocampal Volume.

- **Supplemental table 3**: Full details of the preprocessing of fMRI data. HC = healthy control; PD = Parkinson Disease; PD-N/MH = Parkinson's Disease patients with No/Mild Hyposmia; PD-SH = Parkinson's Disease patients with Severe Hyposmia; BOLD = Blood Oxygen Level Dependent; std = standard deviation.

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