Uncovering the Neuroanatomical Signature of the Transition from Normal Cognition to Mild Cognitive Impairment in Parkinson's Disease: A VBM and Brain Age Estimation Study

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Article

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Abstract

The progression of Parkinson's disease (PD) is often accompanied by cognitive decline. This study aims to uncover neuroanatomical indicators of the transition from healthful cognition to mild cognitive impairment (MCI) in PD using brain age estimation methodologies and structural neuroimaging data. Structural MRI data for 244 subjects from the Parkinson Progression Markers Initiative (PPMI) was acquired. 192 of these were PD patients with stable healthy cognitive function from baseline out to 5 years (PD-SHC), and as the remaining 52 were PD patients who had unstable healthy cognition and developed MCI within 5 years (PD-UHC). We conducted voxel-based morphometry (VBM), deformation-based morphometry, and cortical thickness analyses to measure structural brain differences between these groups at baseline and to assess any differences in brain aging. The VBM analysis revealed that PD-SHC patients have larger grey matter volumes compared to PD-UHC subjects at baseline. This difference was located entirely within the cerebellum with significant clusters found within the posterior and anterior lobes and on the declive and culmen regions of the vermis. No differences were observed in the white matter, local brain tissue volumetry or cortical thickness measurements between the two groups. At baseline, PD-UHC patients exhibited significantly greater brain aging than PD-SHC patients (mean difference = 3.24 years, Cohen's d = 0.43; t(242) = 2.78, p = 0.005). Our analysis provides an in-depth understanding of the neuroanatomical signatures of cognitive decline in PD by demonstrating the role of the cerebellum as a site of early anatomical change that accompanies the transition from healthy cognition to MCI. This could aid in elucidating further changes along the structural-functional continuum which accompany this cognitive transition, serve as a biomarker of the earliest form of cognitive decline in patients with PD and enrich trials of cognitive intervention in this patient population.

Introduction

Parkinson's disease (PD) is a complex neurodegenerative disorder that affects around 10 millions of people worldwide in 2023. It is characterized by the progressive loss of dopaminergic neurons in the substantia nigra, which leads to the characteristic motor symptoms of tremors, rigidity, and bradykinesia. However, PD is also associated with a range of non-motor symptoms, including cognitive impairment, which can significantly impact the quality of life of patients and their caregivers. Approximately 50–80% of patients develop cognitive impairment after PD diagnosis. Cognitive decline in individuals with PD is generally marked by a decrease in cognitive processing speed, challenges in executive function (such as planning, organizing, and prioritizing tasks), attention deficits, impairment of working memory and compromised visuospatial abilities. This cognitive decline may also eventually progress to dementia, known as Parkinson's disease dementia (PDD), affecting approximately 25% of people with PD.

Even though the cause of cognitive decline in PD is not rigorously understood, it is established that the degeneration of neurons responsible for dopamine production in the basal ganglia and the consequent disturbance of dopamine-related signaling pathways in the brain likely exert a significant impact.
Additional factors that could potentially lead to a decrease in cognitive function in individuals with PD involve anomalies in diverse neurotransmitter systems, such as acetylcholine and serotonin, as well as pathological protein deposits such as α-synuclein, and the effects of cerebrovascular ailments. Addressing cognitive decline in individuals with PD involves the use of medications that increase the activity of neurotransmitter systems, most notably dopamine as well as non-pharmacological interventions such as cognitive training, speech therapy and physical therapy.

Neuroimaging techniques have significantly improved our comprehension of the impacts of cognitive decline and its underlying mechanism in the brain of those with PD. Several neuroimaging studies have reported that PD patients with cognitive decline have reduced gray matter volume in both cortical and subcortical regions compared to PD patients with intact cognition. A caveat of these studies is that they examined the anatomical dissimilarities between PD patients with stable cognitive functioning (PD-SHC) and those who had already been diagnosed with mild cognitive impairment (MCI) at baseline (PD-MCI).

The amalgamation of neuroimaging methodologies with machine learning algorithms has proven to be an effective approach in brain studies. One of these techniques is brain age estimation. This method predicts an individual's "brain age" based on their brain's anatomical or metabolism features and a supervised machine learning algorithm. This technique would allow us to evaluate overall brain health and understand the effects of different factors (such as genetics, environmental factors, lifestyle, and neurological diseases) on the rate of aging of the brain in a data-driven fashion. Furthermore, the application of brain age estimation can assist in the recognition of individuals who might be prone to age-related cognitive impairment or neurological disorders (e.g. Alzheimer's disease) prior to the onset of any clinical symptoms.

This technique has been widely applied to various neuroimaging modalities, such as magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography (FDG-PET), and has been shown to be a sensitive tool for detecting age-related changes in brain structure and function in a very wide variety of neurological disorders and neurodegenerative diseases. There exists a notable correlation between Brain-PAD (chronological age subtracted from model-estimated age) and the degree of cognitive decline observed in patients with Alzheimer's disease. Specifically, individuals who exhibit greater cognitive decline tend to display higher levels of Brain-PAD. Furthermore, brain age estimations are a demonstrably meaningful predictive marker for identifying patients with MCI who transitioned to AD from those who remained stable during a three-year period with 81% accuracy. Brain age estimation technique may therefore be a useful tool for identifying PD patients at risk of cognitive decline and progression to dementia, which could allow personalized treatment plans. To date, a limited number of studies have explored brain age in the context of PD. For example, Brain-PAD has previously shown to be correlated with both the Unified Parkinson's Disease Rating Scale (UPDRS) III (motor symptom severity) and the Montreal Cognitive Assessment (MoCA; cognitive symptom severity) in PD patients cross-sectionally.
Brain age estimation remains a relatively new biomarker within the computational neuroimaging community, and so there still exists a knowledge gap in understanding the association between Brain-PAD in PD patients and their cognitive status, which the present work aims to address. The purpose of the present work is to uncover the neuroanatomical signature of cognitive impairment in PD through the use of multiple biomarkers based upon MRI studies of the brain. The measures used in this study included voxel-based morphometry (VBM), deformation-based morphometry (DBM) and cortical thickness measurements on a large dataset of patients with PD from the PPMI database. We particularly focused on PD patients who underwent cognitive decline from healthy cognition to MCI over five years interval. We also employed the brain age estimation paradigm to measure Brain-PAD in all subjects and to examine associated morphological changes between the two groups that are associated with Brain-PAD. We hypothesize that PD patients who are in transition from normal cognitive function to MCI will have greater Brain-PAD than those without cognitive impairment at the baseline, indicating accelerated brain aging among this population. By examining the relationship between Brain-PAD and cognitive impairment in PD patients who are in transition from normal cognition to MCI using PPMI data, this and future research may contribute to our understanding of the mechanisms underlying cognitive decline in PD and the identification of potential neuroimaging-derived biomarkers for PD progression.

Results

Clinical and demographical characteristics

The educational level and duration of disease were similar between PD-UHC and PD-SHC ($q > 0.10$, FDR-corrected). The PD-UHC group had significantly greater age and age of onset age than PD-SHC subjects ($q < 0.001$, FDR-corrected). The measures related to disease severity, including UPDRS-III (total), UPDRS-III (total rigidity), and UPDRS-III (total tremor), as well as cognitive symptoms, such as MoCA, and mood symptoms, including anxiety and GDS, were not significantly different between the two groups in our sample ($q > 0.07$, FDR-corrected; Table 1).

Brain structural analysis: VBM and DBM

There was an enlargement of the GM observed in the cerebellum posterior and anterior lobes, and also on the declive and culmen regions of the vermis for PD-UHC patients compared to PD-SHC patients (Figure 1 and Table 2). In contrast, no significant GM reduction was seen in PD-UHC patients when compared to PD-SHC. The VBM and DBM analyses revealed no significant differences between PD-UHC and PD-SHC in terms of WM or deep brain structures.

In order to confirm that the VBM/DBM results were not influenced by differences (although not significant) in baseline clinical symptom severity (MoCA and UPDRS-III) between the two groups, the VBM/DBM analyses were repeated with these items as covariates, along with age, sex, and TIV. All repeated VBM/DBM results yielded similar significant results.
To test the direction of GM volume differences compared to HC, the mean GM volumes were extracted from the same cluster (Figure 1) in all three groups (HC, PD-SHC, and PD-UHC). To ensure a fair and unbiased comparison, we regressed out the effects of age, sex and differences in TIV by using our independent group of healthy controls as a reference. An ANOVA test among three groups revealed a statistically significant difference ($F (2,346) = 6.65, p < 0.001$; Figure 2). The post-hoc analyses did not reveal significant differences between the HC and PD-SHC (mean difference = 0.07, $p = 0.17$, post-hoc Bonferroni test), nor between the HC group and PD-UHC (mean difference = 0.09, $p = 0.18$, post-hoc Bonferroni). As expected, there was a significant difference between PD-SHC and PD-UHC groups (mean difference = 0.16, $p = 0.003$, Bonferroni -corrected), highlighting a notable distinction between these groups.

**Brain structural analysis: cortical thickness**

No significant difference was observed between the two groups in terms of cortical thickness after controlling for age and sex ($q > 0.20$, FDR-corrected).

**Brain-PAD analysis**

Our prediction model achieved a desirable level of performance on the training (MAE = 4.72 years, RMSE = 6.07 years, $R^2 = 0.91$, mean Brain-PAD = $0 \pm 4.80$ years) and hold-out HC sets (MAE = 4.63 years, RMSE = 5.88 years, $R^2 = 0.91$, mean brain-PAD = -0.08 $\pm 5.90$ years) in line with standards common within brain age prediction literature $^{27,28}$. Our prediction model did not show any bias between females and males in the training set ($t(947) = 0.52, p = 0.60$) or as the hold-out HC set ($t(103) = 0.56, p = 0.57$) with regard to brain-PAD. The mean Brain-PAD for all PD patients ($N_{total} = 244$) used in this study was $+3.11 \pm 7.54$ years, which was statistically higher than the hold-out HC group ($t(347) = 3.86, p < 0.001$). The mean Brain-PAD of $+3.11$ years for PD patients that we observed agrees with the literature $^{24,26}$.

Figure 3 shows the grouped data plots displacing the Brain-PAD in hold-out and PD sets. We conducted an ANCOVA test to investigate whether there were differences in the mean brain-PAD values among PD groups that had healthy cognitive function at baseline as well as hold-out HC group. The ANCOVA test revealed a significant difference in Brain-PAD among groups after accounting for sex and chronological age ($F (2,344) = 9.33, p < 0.001$). Real age did not show a significant effect on Brain-PAD ($F (1,344) = 0.12, p = 0.72$), indicating that the variation in Brain-PAD is not explained by differences in chronological age. The effect of sex on brain-PAD was marginally significant ($F (1,344) = 3.88, p = 0.049$), suggesting that there may be some differences in Brain-PAD based on sex.

Both PD groups showed a significantly higher mean Brain-PAD ($p < 0.02$) compared to the HC group (Figure 3). The PD-UHC group showed the highest Brain-PAD, with a value of $+5.66 \pm 7.40$ years. The mean Brain-PAD in PD-SHC was $+2.42 \pm 7.45$ years. The Brain-PAD of HC group was significantly different from both PD-SHC (mean difference = 2.50, $p = 0.009$, post-hoc Bonferroni) and PD-UHC group.
(mean difference = 5.75, \( p < 0.001 \), post-hoc Bonferroni). The Brain-PAD was also significantly different between PD-SHC and PD-UHC (mean difference = 3.24, \( p = 0.009 \), post-hoc Bonferroni).

**The relationship between GM of ROI and Brain-PAD**

Figure 4 displays the relationship between adjusted GM volumes in the cluster identified contrasting PD-SHC vs. PD-UHC (Figure 1) and Brain-PAD within each group. The HC group revealed a strong negative correlation between this regional GM volumes and Brain-PAD \( (r = -0.32, p < 0.001) \), demonstrating that a decreased GM volume in this region is significantly associated with an accelerated brain aging among HC. A similar pattern was observed in the PD-SHC group \( (r = -0.31, p < 0.001) \), further supporting the relationship between GM volume of this region and Brain-PAD, however, the patients with PD-UHC did not demonstrate this pattern \( (r = -0.16, p = 0.27) \), suggesting a potential disturbance on the role of cerebellum in brain aging in PD patients who later experience cognitive decline.

**Discussion**

In this study our goal was to uncover the early neuroanatomical signature of the progression from normal cognition to MCI in patients with PD using VBM and brain age estimation techniques. Our VBM analysis additionally revealed for the first time that PD-UHC patients had a greater GM volumes in the cerebellar posterior and anterior lobes, and also the declive and culmen regions of the vermis when compared to PD-SHC patients at baseline (Fig 1 and 2). Interestingly, GM volumes extracted from the same cluster of HC group was placed in between the mean of PD-SHC (lower than HC) and PD-UHC (higher than HC). This result potentially suggests that the regional cerebellar GM volume differences found in PD patients (both SHC and UHC) were not significantly deviated from the normal ranges of variation.

Decreased GM volumes are typically associated with atrophy, while the etiology of increased GM volume in neurodegenerative disorders are not well understood. Nevertheless, increased cerebellar glucose metabolism has consistently been observed in the literature in cognitively impaired PD patients\(^29,30\), which has often been hypothesized to be related with compensatory mechanisms. Previous VBM studies have revealed that PD-MCI patients had a drastic GM decrease in the right insula, right inferior frontal gyrus middle frontal gyrus), and right cerebellum regions in comparison to PD patients who were cognitively healthy\(^31\). In this study, we observed an increase in GM within the cerebellum of PD-UHC patients compared to PD-SHC, even before they exhibited noticeable cognitive symptoms. This finding suggests that GM abnormalities in the cerebellum may be a distinctive feature in the very early stages of cognitive decline in PD.

The role of cerebellum has traditionally been viewed in controlling and harmonizing voluntary movement, balance, posture, and motor learning. In PD, cerebellar abnormalities have traditionally been implicated in the tremor\(^32\) and gait disturbances\(^33\). More recently, it has been hypothesized that cerebellum is also involved in cognitive decline shown in PD\(^33\). Previously, increased cerebellar glucose metabolism has reported to be related with cognitive decline in PD\(^30\). On the contrary, cerebellar atrophy has been
associated with patients’ impaired performance on semantic fluency tests \(^\text{34}\) and executive function \(^\text{35}\), potentially suggesting the increased cerebellar metabolism may reflect compensatory mechanism, although our previous graph theory analysis suggested denser connections within the hyper-metabolic regions including limbic-pontine-cerebellar network in PD is the key contributor for the formation of the overall PD-related metabolic pattern that characterizes PD brain’s hyper-smallworldness \(^\text{36}\).

Morphological changes in the brain's white matter have been linked to MCI in PD. For example, reduced white matter density in the midbrain, occipital lobe, inferior frontal gyrus, and lingual gyrus has been noted in PD-MCI patients compared to PD patients with healthy cognition \(^\text{37}\). Our VBM analysis on WM did not identify any significant differences between the PD-SHC and PD-UHC groups, suggesting that both groups had only comparable WM changes even if there was any.

The results of the DBM analysis also did not indicate any considerable variation in deep brain structures between the PD-SHC and PD-UHC groups. Recall that DBM is a sophisticated MRI analysis technique that is more sensitive in detecting brain atrophy in subcortical regions than VBM, and it has been recently used to detect the brain abnormalities in PD \(^\text{38,39}\). We also performed a cortical thickness analysis, as it may be more sensitive than VBM in detecting regional gray matter changes associated with the disease \(^\text{40,41}\). Compared to PD patients without MCI, PD-MCI patients showed reduced cortical thickness in the medial temporal, superior frontal, inferior parietal, and supramarginal gyri, the precentral gyrus, the precuneus, the insula, and the occipital cortex regions \(^\text{31,42,43}\). In our analysis, we did not observe any distinctions between the PD-SHC and PD-UHC groups in terms of cortical thickness, implying that both groups experience a similar rate of cortical thinning at baseline.

Using our brain age estimation model, we replicated the overall increase of Brain-PAD in our PD patients compared to HC (Figure 3) \(^\text{24,26}\). In the PD group, increased Brain-PAD has been associated with a decrease in GM volume in the limbic, occipital, temporal, parietal and primary frontal lobes, as well as a decrease in WM volume in the frontal lobe, cerebellum, midbrain, lentiform nucleus, and medulla [Our last paper]. Interestingly within PD patient groups, we found that the Brain-PAD was significantly higher in PD-UHC patients than PD-SHC patients (Figure 3). This result support our hypothesis that PD patients undergoing the shift from normal cognitive functioning to MCI would exhibit higher Brain-PAD values compared to those with stable healthy cognitive functioning, which suggests that patients with PD who are progressing from normal cognitive function to MCI experience an accelerated brain atrophy linked to aging at baseline compared to PD patients who maintain a healthy cognitive state. This result is in line with previous VBM studies contrasting PD patients with and without MCI \(^\text{15,44}\), while highlighting that overall brain atrophy associated with normal aging process was more accelerated in PD-UHC patients even at baseline when they still showed healthy normal cognition.

Significant inverse correlations were observed between Brain-PAD and cerebellar GM volumes in both HC and PD-SHC groups, suggesting the observed cerebellar atrophy is associated with accelerated brain aging process. Interestingly, the PD-UHC patients did not exhibit the same pattern (Fig 4). One potential explanation for this discrepancy is that the enlarged GM volumes (and/or hypermetabolism as previously
reported \(^{33}\)) in the cerebellum represents a compensatory mechanism against overall accelerated brain aging and associated atrophy found in PD-UHC as depicted by elevated Brain-PAD. These findings not only provide valuable insights into the origins of cognitive impairment in the earliest stages of PD but also offer prospects for future interventions targeting PD patients who are at risk of cognitive decline by elucidating a data-driven biomarker that may enrich future trials targeting preventive medicine, e.g., screening out individuals who will not develop cognitive symptoms may not need to be included in the trials that tests preventive medicine targeting cognition.

An important limitation to the presented study is the limited sample size in the PD-UHC group and not counting the longitudinally acquired MRI scans. It is expected that PPMI data collection be completed in near future, which will provide larger dataset which may even include sizable patients who progress to dementia. This prospective data will allow one to develop more comprehensive model that predicts cognitive decline in PD.

In summary, this study provides the first empirical evidence that there are distinct structural brain differences between PD-SHC and PD-UHC at baseline. Using VBM, we identified an increased GM volume in the cerebellar regions of PD-UHC patients compared to PD-SHC patients. This intriguing finding suggests that the cerebellum may play a compensatory role in the very early stage of cognitive decline in PD patients, even years before the symptoms become visible. We also provided evidence that patients with PD will transition from normal cognitive function to MCI have a higher Brain-PAD than those with stable cognition. These findings not only provide valuable insights into the origins of cognitive impairment in the earliest stages of PD but also offer prospects for future interventions targeting PD patients who are at risk of cognitive decline by elucidating a data-driven biomarker that may enrich future trials targeting preventive medicine, e.g., screening out individuals who will not develop cognitive symptoms may not need to be included in the trials that tests preventive medicine targeting cognition.

**Material and methods**

**Participants and MRI acquisition**

Data for this study was provided by the Parkinson's Progression Markers Initiative (PPMI) dataset. 373 total subjects with PD were available who underwent \(T_1\)-weighted MRI studies. Baseline MRI scans, demographic characteristics (i.e., age, education, onset age and disease duration) and clinical measurements related to the PD group were downloaded from the PPMI website in September 2022 (Table 1). The cognitive condition of the individuals with PD was assessed by analyzing the "cogstate" and "MCI test score" variables as documented in the PPMI dataset. The "cogstate" variable for each subject was tracked over the course of the five-year follow-up, and any missing time points were interpolated for each subject. We identified 244 patients with PD appropriate to our study which we divided into 2 groups based on their cognitive statues:
• PD-SHC subjects (N = 192): PD patients with stable healthy cognition (SHC) at baseline who maintained this status during the five-year follow-up.

• PD-UHC subjects (N = 52): PD patients with unstable healthy cognition (UHC) who had healthy cognition at baseline but developed MCI within the five-year follow-up.

**MRI preprocessing**

The T1-weighted MRI scans were preprocessed using the CAT12 toolbox (http://www.neuro.uni-jena.de/cat/), which is an extension of the Statistical Parametric Mapping (SPM12, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) software package. The pre-processing parameters were considered with the default settings. The technical details of VBM-based preprocessing have been described in [45]. Briefly, the T1-weighted MRI scans were corrected for bias-field distortions, non-brain tissues were removed, and the images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) images. Jacobian determinant (JD) images were also generated. The images were then normalized to MNI-space using the diffeomorphic anatomical registration through exponentiated Lie algebra (DARTEL) algorithm. The normalized GM, WM, CSF and JD images were smoothed using an isotropic Gaussian smoothing kernel with a full-width at half maximum (FWHM) of 8x8x8 mm³. GM and WM density images were used in subsequent VBM analysis, and the JD images were used for DBM analysis. The quality of the images was evaluated using the "Check Homogeneity" feature within the CAT12 toolbox, in addition to visual evaluation. Total intracranial volume (TIV) and total GM, WM, CSF volumes per subject were also computed with the CAT12 toolbox. Cortical thickness (CT) measurements were obtained using the CAT12 toolbox by employing the Desikan-Killiany-Tourville (DKT) atlas. This atlas is composed of 34 pre-defined regions of interest (ROIs) in each cerebral hemisphere that were utilized to assess cortical thickness [46]. For brain age estimation, GM, WM and CSF images were smoothed using an isotropic Gaussian smoothing kernel with a FWHM of 4x4x4 mm³, as suggested in [47], and then resampled to an 8-mm isotropic spatial resolution, which resulted in 3,747 voxels per volume.

**Brain-age prediction model**

To build our brain age prediction model, we used data from three datasets of healthy individuals: the Information eXtraction from Images (IXI) dataset (http://brain-development.org/ixi-dataset/), the Open Access Series of Imaging Studies (OASIS; https://www.oasis-brains.org/), and the Parkinson's Progression Markers Initiative (PPMI; www.ppmi-info.org). The IXI dataset includes 563 healthy control (HC) participants. The OASIS 1 dataset includes 313 HC participants and 120 participants diagnosed with Alzheimer's disease (AD). The PPMI database is composed of a group of participants who were diagnosed with PD (N = 373, at baseline) and a control group of HC participants (N = 198, at baseline). In total, 1,054 T1-weighted (T1w) MRI scans from HCs were included in this study and all other subjects were not included. These HC subjects were then randomly divided into two main cohorts: a training set (90% of HCs; \(N_{\text{train}} = 949\), mean age ± SD: 49.75 ± 18.96, age range: 18-94, 54% female) and a validation
set (i.e., 10% of HC; $N_{test} = 105$, mean age ± SD: 48.62 ± 19.14, age range: 18–93, 53% female). All HC were free from any signs of cognitive impairment or neurological disorder according to database criteria.

The brain age estimation model consists of a support vector regression (SVR) algorithm with a linear kernel in MATLAB r2020b (The Mathworks, Natick, MA, USA). Structural brain features (i.e., GM, WM, and CSF voxel intensities, TIV and total GM, WM, and CSF brain volumes) were fed into the SVR along with scanner vendor, field strength and sex as independent variables. Chronological age was the dependent output variable of this model. To assess the accuracy of predictions in both the training and hold-out sets, the mean absolute error (MAE), root mean square error (RMSE), and coefficient of determination ($R^2$) were employed. The prediction accuracy of the training set was computed using a 10-fold cross-validation strategy. Brain-PAD was computed as a mean with a standard deviation (SD). Bias adjustment was implemented as described in 48. The entire training set ($N_{train} = 949$) was used to build the final prediction model, which was applied to independent test sets.

**Statistical analysis**

SPM12 was used to perform independent $t$-test analysis on the processed GM, WM and JD images to identify any morphological differences between the PD-SHC and PD-UHC groups. The peak-level $p$-value threshold was adjusted to $<0.001$ (uncorrected) and clusters with $q<0.05$ (cluster-level correction for false discovery rate, FDR) were considered significant. Sex, age and TIV of the subjects were considered as covariates in the VBM analysis, whereas only sex and age were considered for the DBM analysis.

Difference in cortical thickness measurements between the PD-SHC and PD-UHC groups were compared for each brain region via two-tailed general linear models (GLMs) with age and sex as covariates. All statistical analyses were performed in MATLAB. FDR was applied to correct for multiple comparisons. The mean Brain-PAD and ROI-based brain volumes among the test groups (i.e., HC, PD-SHC and PD-UHC) were examined using analysis of covariance (ANCOVA) with sex and age as covariates of interest, then followed by post-hoc Bonferroni tests if applicable to examine the direction of group differences. An independent $t$-test was used to investigate the mean Brain-PAD between PD-SHC vs. PD-UHC. A significance threshold of $q < 0.05$ was adopted a priori for all statistical tests.

**Declarations**

**Data Availability**

The raw MRI scans used in this study are publicly available at Open Access Series of Imaging Studies (OASIS; https://www.oasis-brains.org/), the IXI (https://brain-development.org/ixi-dataset/), and Parkinson's Progression Markers Initiative (PPMI) databases.

**Code Availability**
We performed brain age estimation and bias adjustment using our previously validated framework, which can be found on https://github.com/medicslab/Bias_Correction.

Acknowledgments

Data used in the preparation of this article were obtained from the Open Access Series of Imaging Studies (OASIS), the IXI, and Parkinson's Progression Markers Initiative (PPMI) databases. We wish to thank all investigators and participants of these projects who collected these valuable datasets and made them freely accessible.

The OASIS project is funded by grants P50 AG05681, P01 AG03991, P01 AG026276, R01 AG021910, P20 MH071616, U24 RR021382. Principal Investigators: D. Marcus, R, Buckner, J, Csernansky J. Morris. See http://www.oasis-brains.org/ for more details. The IXI data used in the preparation of this manuscript were supported by the U.K. Engineering and Physical Sciences Research Council (EPSRC) GR/S21533/02. The IXI Dataset is a collection of nearly 600 MR images from normal, healthy subjects. The MR image acquisition protocol for each subject includes T1, T2 and PD-weighted images, MRA images, and diffusion-weighted images (15 directions). The data was collected at three different hospitals in London using 1.5T and 3T scanners. See http://www.brain-development.org/ for more details. The PPMI database used in this study is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners, including AbbVie, Avid Radiopharmaceuticals, Biogen, Bristol-Myers Squibb, Covance, GE Healthcare, Genentech, GlaxoSmithKline (GSK), Eli Lilly and Company, Lundbeck, Merck, Meso Scale Discovery (MSD), Pfizer, Piramal Imaging, Roche, Sanofi Genzyme, Servier, Teva, and UCB. See www.ppmi-info.org/fundingpartners for more details.

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References


**Tables**
Table 1: Clinical demographics and brain-PAD results of PD patients included in this study.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PD-SHC</th>
<th>PD-UHC</th>
<th>q*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (male %)</td>
<td>192 (61.954%)</td>
<td>52 (71.15%)</td>
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<tr>
<td><strong>Demographics</strong></td>
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<tr>
<td>Age, years</td>
<td>58.41</td>
<td>64.33</td>
<td>&lt;0.01</td>
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<td>Onset age</td>
<td>56.34</td>
<td>62.47</td>
<td>&lt;0.01</td>
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<tr>
<td>Education, years</td>
<td>15.80</td>
<td>15.06</td>
<td>0.10</td>
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<tr>
<td>Disease duration, months</td>
<td>6.67</td>
<td>6.18</td>
<td>0.75</td>
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<tr>
<td><strong>Motor symptoms</strong></td>
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<tr>
<td>UPDRS-III (total)</td>
<td>28.59</td>
<td>33.18</td>
<td>0.06</td>
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<td>UPDRS-III (total rigidity)</td>
<td>3.61</td>
<td>3.46</td>
<td>0.75</td>
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<tr>
<td>UPDRS-III (total tremor)</td>
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<td>5.10</td>
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<td><strong>Cognitive symptoms</strong></td>
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<td>MoCA</td>
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<td><strong>Mood</strong></td>
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<tr>
<td>GDS</td>
<td>1.87</td>
<td>2.52</td>
<td>0.07</td>
</tr>
</tbody>
</table>

PD, Parkinson diseases; UPDRS, Unified Parkinson Disease Rating Scale; MoCA, Montreal Cognitive Assessment; BJLO, Benton Judgement of Line Orientation Score; GDS, Geriatric Depression Scale, N, number of subjects; q*, p-value of t-test between two groups after FDR Correction for multiple comparisons.

Table 2. The brain regions with increased GM volume in 52 PD patients who transitioned from normal cognition to mild cognitive impairment compared to 192 PD patients who maintained normal cognitive status.

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Region</th>
<th>Cluster Size (No. of Voxels)</th>
<th>q (FDR)</th>
<th>Hemisphere</th>
<th>MNI Coordinates (x, y, z)</th>
<th>t-Value (Peak Voxel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right Cerebellum/ Cerebellum Posterior Lobe/ Declive/ Cerebellum Anterior Lobe/ Culmen</td>
<td>1136</td>
<td>0.02</td>
<td>R</td>
<td>25, -57, -21</td>
<td>4.41</td>
</tr>
</tbody>
</table>
R = right hemisphere = Montreal Neurological Institute; FDR = false discovery rate.

Figures

Figure 1

Gray matter volume comparison by VBM among 52 PD-UHC patients compared to 192 PD-SHC. PD-UHC patients exhibited a greater amount of GM in the cerebellar posterior and anterior lobes, as well as the declive and culmen regions of the vermis, when compared to PD-SHC. Notable changes are shown within the figure as coloured regions. The map of $t$-values was generated via uncorrected contrast with a $p<0.001$ and an extent threshold of greater than 1000 voxels. The scale of the $t$-statistic is given by the colour bar on the right-hand of the figure. Note that the vertical lines of the whole brain volume (bottom right) give the relative location of the visualized slices within the brain.
Figure 2

The brain region displaying a significant GM volume between the PD-SHC and PD-UHC groups using VBM analysis. (B): Box plots displaying the adjusted ROI volumes in different groups. Pairwise comparisons were conducted through an ANOVA test with *p*-value adjusted by Bonferroni correction.
Figure 3

Box plots displaying the Brain-PAD values in hold-out sets. The mean Brain-PAD values of each group were depicted by a solid black line while the reference line (y = 0) was indicated by a dashed black line. Pairwise comparisons were conducted through an ANCOVA test adjusted for age and sex, with the \( p \)-value adjusted by Bonferroni correction. * indicates \( p < 0.05 \) and ** indicates \( p < 0.001 \).

Figure 4

HC

\[ r = -0.32, p < 0.001 \]

PD-SHC

\[ r = -0.31, p < 0.001 \]

PD-UHC

\[ r = -0.16, p = 0.16 \]
The correlation between adjusted GM volumes in the region that was identified by VBM and Brain-PAD within each group, adjusting for sex, real age and TIV.