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Data-driven characterization of distinct cognitive subtypes in Parkinson's disease dementia

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Individual cognitive profiles of patients with Parkinson's disease dementia (PDD) are highly heterogeneous, suggesting possible biological subtypes. We studied 75 PD patients who developed dementia in the course of the Parkinson's Progression Markers Initiative study to investigate data-driven evidence for the existence of distinct cognitive subtypes of PDD. Using Ward's hierarchical clustering on neuropsychological test data, we identified two distinct cognitive subtypes. Despite similar dementia severity (MoCA: 20.6 vs 20.0), cluster-A exhibited more pronounced memory deficits ($n = 50$), whereas cluster-B showed greater visuospatial impairments ($n = 25$). The subtypes did not differ in demographic, motor, or MRI-based neurodegeneration measures. However, the visuospatial-predominant cluster-B had a higher prevalence of GBA mutations ($p = 0.003$) and hallucinations ($p = 0.009$). No differences were found in APOE-ε4 prevalence or cerebrospinal fluid biomarkers of Alzheimer's pathology. These findings reveal distinct memory-predominant and visuospatial-predominant PDD subtypes, which associate with different clinical and genetic features but are independent of comorbid Alzheimer's pathology.

Although Parkinson's disease (PD) is primarily perceived as a movement disorder, cognitive decline is a very common non-motor complication and most patients will eventually develop a highly debilitating PD-associated dementia syndrome (PDD)[1–3]. Early epidemiological studies estimated that the point-prevalence of dementia in PD is approximately 30%, with an incidence rate 4–6 times higher than in healthy individuals and a very high cumulative prevalence, indicating that the large majority (75–85%) of PD patients who survive for more than 10–20 years will develop dementia[2,4]. While incidence rates and cumulative prevalences may vary in younger and less impaired PD cohorts, particularly during the first years after disease onset, a recent meta-analysis estimated the dementia risk in PD to be on average 3.25 times higher than in healthy controls, with a pooled incidence rate of 4.45 per 100 person-years[5].

In contrast to the characteristic amnestic dementia syndrome associated with Alzheimer's disease (AD), the typical clinical presentation of PDD more commonly involves cognitive impairments in attention, executive, and visuospatial functions, and these are frequently accompanied by distinct neuropsychiatric symptoms, such as hallucinations, delusions, and mood disturbances[1,6]. However, individual presentations within this dementia syndrome largely differ among patients, and systematic data-driven approaches applying clustering methods to cognitive and neuropsychiatric symptom scales could provide evidence for the existence of distinct PDD patient subgroups with different cognitive/neuropsychiatric profiles[7–9]. For example, a hierarchical cluster analysis of domain-specific cognitive test scores from a mixed group of dementia patients found that approximately half of the PDD patients in this sample had a typical attention/executive-predominant profile characterized by prominent impairments in attention, executive, and visuospatial subtests with relative preservation of memory scores, while a relatively sizeable subset of almost 30% of PDD patients was classified into a memory-predominant profile, which was the cognitive profile most often observed in AD dementia patients[7].

The neurobiological factors underlying such differences in clinical presentation among PDD patients remain largely unknown, and elucidating these factors may yield critical insights into the heterogeneity of pathophysiological processes leading to dementia in PD. Clinical research has

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identified several genetic, molecular biomarker, and neuroimaging markers associated with PDD, and these correspond to diverse and partially independent pathophysiological processes[10,11]. For example, specific genetic risk factors for PDD (e.g. MAPT, APOE, GBA) were found to be differentially linked to system-specific cortical neurodegeneration and –dysfunction[12–15]. Moreover, the presence of comorbid AD pathology may modify the neurodegenerative and clinical course in a subset of PDD patients[16–22]. A better understanding of whether and how these distinct pathophysiological markers are implicated in the differential clinical presentations of PDD is of key importance for improving diagnostic and prognostic biomarker accuracy and may eventually also foster the development of specific treatment guidelines and the selective use of drugs.

In the present study, we aimed to replicate and extend previous findings on different cognitive subtypes of PDD[7] by applying a data-driven clustering approach to detailed neuropsychological test data of incident PDD patients included in the longitudinal observational cohort study of the Parkinson's Progression Markers Initiative (PPMI). We then further characterized the identified PDD subtypes with respect to a wider set of clinical, molecular biomarker, genetic, and neuroimaging variables to gain a better understanding of the possible clinico-pathologic features that may underlie cognitive heterogeneity in PDD.

Results

Sample characteristics

Patient characteristics are summarized in Table 1. At the time of initial dementia diagnosis, PDD patients had an average age of 69.4 ± 9.8 years and an average disease duration (from diagnosis) of 5.0 ± 2.4 years. The average MoCA score was 20.0 ± 4.6 indicating relatively mild dementia on average. Cognitive performance was significantly lower compared to healthy controls across all neuropsychologic tests (p's <0.001), and group differences were highest for the symbol digit modalities test, as well as immediate and delayed recall scores.

Data-driven identification of distinct cognitive PDD subtypes

Objective clustering criteria of the Davies-Bouldin and the silhouette indices both indicated an optimal clustering solution with two distinct PDD clusters (see Supplementary Fig. 1). Compared to the healthy control reference, both PDD subgroups were significantly impaired in all cognitive tests. However, this impairment was not equally distributed across the different cognitive domains, such that patients in a "memory-predominant" cluster-A ($n = 50$, 67%) showed most pronounced impairment in memory (delayed and immediate recall) and least pronounced impairment in visuospatial function (judgement of line orientation), whereas patients in a "visuospatial-predominant" cluster-B ($n = 25$, 33%) showed the opposite pattern of most pronounced impairment in judgement of line orientation and relatively spared memory performance (Fig. 1, Table 2; also see Supplementary Table 1 for an alternative approach assessing differential cognitive profiles based on dichotomized cognitive test scores). Impairment in attention and executive function tests was not markedly different between the two PDD subgroups, though there were statistical trends towards worse semantic fluency performance in the memory-predominant cluster-A and worse performance in letter number sequencing and symbol digit modalities test in the visuospatial-predominant cluster-B.

Clinical and biological characterization of the identified memory-predominant and visuospatial-predominant PDD subtypes

Demographic, clinical, neuroimaging, molecular biomarker, and genetic characteristics of the two PDD subtypes are listed in Tables 2 and 3. The clusters did not differ significantly in any demographic characteristics, age at disease onset, disease duration, UPDRS-III total scores, prevalence of postural instability/gait difficulty (PIGD) motor phenotype, or severity of nigrostriatal dopaminergic degeneration as measured by [^{123}I]FP-CIT SPECT. Notably, MoCA scores were not significantly different between the two clusters either, indicating that these subgroups do not merely reflect differences in overall disease or dementia severity.

The visuospatial-predominant cluster-B had a significantly higher prevalence of delusions/hallucinations (56% vs 24%, $p = 0.009$), but prevalence of depression, apathy, REM sleep behavior disorder (RBD), excessive daytime sleepiness, severity of anxiety (STAI scores) or autonomic dysfunction (SCOPA-AUT) did not differ between the two clusters.

Interestingly, the visuospatial-predominant cluster-B was also significantly enriched for *GBA* mutation carriers (40% vs 8%, $p = 0.003$), but APOE-ε4 prevalence or other genetic factors did not differ between the clusters. Moreover, we did not observe any significant differences in

Table 1 | Cohort characteristics

	Healthy controls ($N = 132$)	PD Dementia ($N = 75$)	Statistical value (P value)	Effect size
Sex, *n* (%) female	54 (41%)	23 (31%)	$p = 0.178$	OR = 0.64
Age, years	60.3 (11.5)	69.4 (9.8)	$t = -6.03$ ($p < 0.001$)	$d = -0.85$
Education, years	16.1 (3.0)	14.7 (4.1)	$t = 2.58$ ($p = 0.011$)	$d = 0.39$
Age at onset, years		64.4 (10.1)		
Disease duration, years		5.0 (2.4)		
UPDRS-III score ("Off")		37.2 (15.1)		
Hoehn & Yahr stage ("Off")		2 (2–3)		
PIGD phenotype ("Off"), *n* (%)		36 (48%)		
MoCA score	28.4 (1.1)	20.4 (4.7)	$t = 14.60$ ($p < 0.001$)	$d = 2.36$
Delayed recall	9.8 (2.0)	4.0 (2.9)	$t = 15.52$ ($p < 0.001$)	$d = 2.34$
Immediate recall	26.8 (4.3)	15.4 (4.6)	$t = 17.50$ ($p < 0.001$)	$d = 2.55$
Judgment of line orientation	13.4 (1.7)	9.2 (3.3)	$t = 10.13$ ($p < 0.001$)	$d = 1.58$
Letter number sequencing	11.1 (2.3)	6.2 (3.0)	$t = 12.37$ ($p < 0.001$)	$d = 1.85$
Symbol digit modalities	48.9 (9.9)	19.0 (10.3)	$t = 20.08$ ($p < 0.001$)	$d = 2.95$
Semantic fluency	53.7 (11.4)	28.2 (11.8)	$t = 15.10$ ($p < 0.001$)	$d = 2.20$

The descriptive values presented are: number (percentage) for categorical variables; median (IQR) for Hoehn & Yahr stage; and mean (standard deviation) for all other continuous variables. Statistical values correspond to Fisher's exact test for categorical variables and t test for continuous variables. Effect size values correspond to odds ratios for categorical variables and Cohen's d for continuous variables.
PIGD Postural instability and gait disorders, *UPDRS-III* Unified Parkinson's Disease Rating Scale-Part III, *MoCA* Montreal Cognitive Assessment, *OR* Odds ratio.

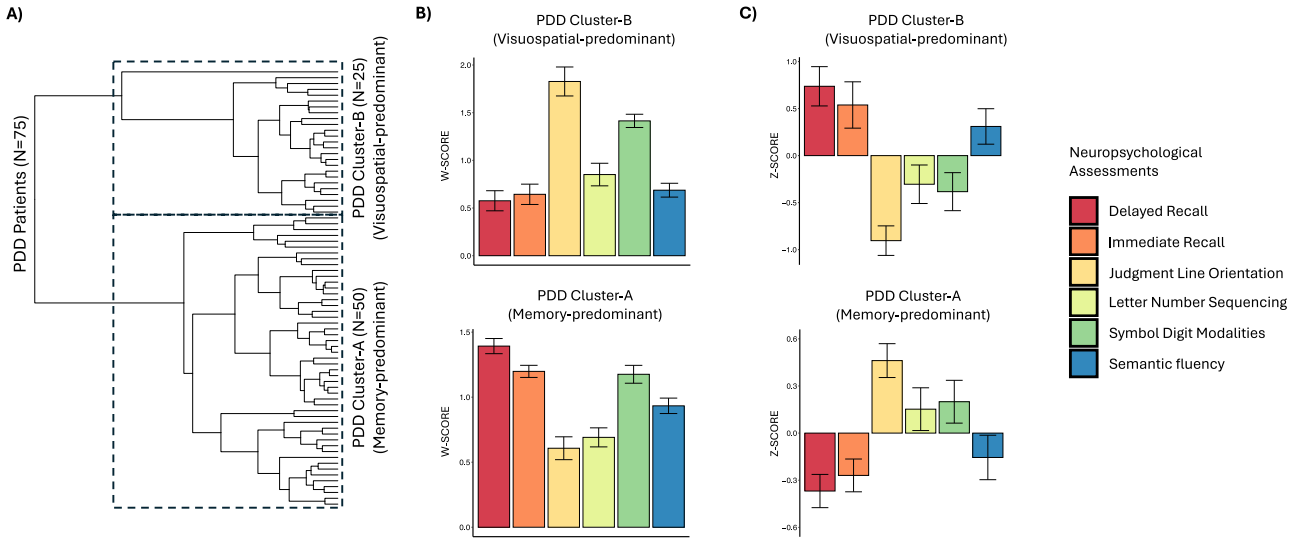

Fig. 1 | Hierarchical clustering dendrogram and cognitive profiles of identified PDD subtypes. Dendrogram resulting from Ward's hierarchical clustering analysis of individual cognitive profiles of PDD patients (**A**). Two distinct clusters of patients are identified that are characterized by memory-predominant (Cluster-A) and visuospatial-predominant (Cluster-B) cognitive profiles, respectively. Cluster-specific cognitive profiles are represented by average w-scores referenced to the control group (**B**), as well as by mean-centered scores with reference to the average performance of the whole PDD group (**C**).

Table 2 | Clinical characterization

	PDD Cluster-A (Memory-predominant)	PDD Cluster-B (Visuospatial-predominant)	Statistic value (*P* value)	Effect size
Number of patients	*N* = 50	*N* = 25		
Female, *n* (%)	13 (26%)	10 (40%)	$p = 0.288$	OR = 0.53
Age, years	69.7 (10.5)	68.6 (8.2)	$t = 0.51$ ($p = 0.609$)	$d = 0.12$
Education, years	15.1 (3.8)	13.9 (4.9)	$t = 1.08$ ($p = 0.288$)	$d = 0.28$
Age at onset, years	64.9 (10.5)	63.4 (9.3)	$t = 0.61$ ($p = 0.545$)	$d = 0.15$
Disease duration, years	4.9 (2.3)	5.2 (2.6)	$t = -0.49$ ($p = 0.628$)	$d = -0.12$
UPDRS-III score ("Off")	35.6 (14.7)	40.5 (15.5)	$t = -1.24$ ($p = 0.223$)	$d = -0.32$
Hoehn & Yahr stage ("Off")	2 (2–2)	2 (2–3)	U = 455 ($p = 0.354$)	r = 0.11
PIGD phenotype ("Off"), *n* (%)	24 (50%)	12 (55%)	$p = 0.799$	OR = 1.19
MoCA	20.6 (4.6)	20.0 (4.9)	$t = 0.46$ ($p = 0.650$)	$d = 0.11$
Delayed recall	2.9 (2.1)	6.1 (3)	$t = -4.72$ ($p = <0.001$)	$d = -1.22$
Immediate recall	14.2 (3.4)	17.9 (5.6)	$t = -3.02$ ($p = 0.005$)	$d = -0.80$
Judgment of line orientation	10.8 (2.5)	6.3 (2.6)	$t = 7.17$ ($p = <0.001$)	$d = 1.77$
Letter number sequencing	6.6 (2.9)	5.3 (3)	$t = 1.86$ ($p = 0.070$)	$d = 0.46$
Symbol digit modalities	21.1 (9.8)	15.1 (10.4)	$t = 2.39$ ($p = 0.021$)	$d = 0.60$
Semantic fluency	26.4 (11.8)	31.9 (11.2)	$t = -1.97$ ($p = 0.054$)	$d = -0.48$
Hallucinations (UPDRS-I), *n* (%)	12 (24%)	14 (56%)	$p = 0.009$	OR = 3.95
Apathy (UPDRS-I), *n* (%)	23 (46%)	14 (56%)	$p = 0.469$	OR = 1.49
GDS score ≥5, *n* (%)	44 (88%)	22 (88%)	$p = 0.99$	OR = 1.00
STAI index	119.1 (22.3)	113.8 (20.1)	$t = 1.03$ ($p = 0.308$)	$d = 0.25$
TRAIT index	59.2 (10.9)	57.4 (10.3)	$t = 0.71$ ($p = 0.483$)	$d = 0.17$
STATE index	59.9 (12)	56.4 (10.6)	$t = 1.26$ ($p = 0.212$)	$d = 0.30$
RBD score ≥5, *n* (%)	30 (60%)	20 (80%)	$p = 0.119$	OR = 2.63
ESS score ≥10, *n* (%)	22 (44%)	15 (60%)	$p = 0.226$	OR = 1.89
SCOPA-AUT	26.2 (10)	29.6 (9.8)	$t = -1.39$ ($p = 0.17$)	$d = -0.34$

The descriptive values presented are: number (percentage) for categorical variables; median (IQR) for Hoehn & Yahr stage; and mean (standard deviation) for all other continuous variables. Statistical values correspond to Fisher's exact test for categorical variables, Mann–Whitney U test for Hoehn & Yahr stage, and t test for continuous variables. Effect size values correspond to odds ratios for categorical variables, Mann–Whitney U Test effect size (r value) for Hoehn & Yahr stage, and Cohen's d for continuous variables.

PIGD Postural instability and gait disorders, *UPDRS* Unified Parkinson's Disease Rating Scale, *MoCA* Montreal Cognitive Assessment, *GDS* Geriatric Depression Scale, *STAI* State-Trait Anxiety Inventory, *RBD* Rapid eye movement (REM) sleep behavior disorder, *ESS* Epworth Sleepiness Scale, *SCOPA-AUT* Scales for outcomes in Parkinson's disease – Autonomy dysfunction part, *OR* Odds Ratio.

Table 3 | Biomarkers

	HC	PDD cluster-A (memory-predominant)	PDD cluster-B (visuospatial-predominant)	HC vs A	HC vs B	A vs B
Structural MRI	$N = 121$	$N = 41$	$N = 17$			
Anterior cBF, mm^3	954 (83)	911 (72)	908 (58)	$d = 0.10$, $t = 0.55$ ($p = 0.59$)	$d = 0.17$, $t = 0.67$ ($p = 0.50$)	$d = 0.06$, $t = 0.22$ ($p = 0.83$)
Posterior cBF, mm^3	651 (59)	596 (46)	598 (74)	$d = 0.62$, $t = 3.42$ ($p < 0.001$)	$d = 0.78$, $t = 3.01$ ($p = 0.003$)	$d = -0.03$, $t = -0.11$ ($p = 0.911$)
Hippocampal volume, mm^3	4859 (489)	4530 (532)	4475 (406)	$d = 0.39$. $t = 2.18$ ($p = 0.031$)	$d = 0.59$, $t = 2.28$ ($p = 0.024$)	$d = 0.12$, $t = 0.45$ ($p = 0.656$)
[^{123}I]FP-CIT SPECT	$N = 111$	$N = 44$	$N = 21$			
Caudate, SBR	3.02 (0.58)	1.36 (0.62)	1.43 (0.82)	$d = 1.92$, $t = 10.77$ ($p < 0.001$)	$d = 2.13$, $t = 8.95$ ($p < 0.001$)	$d = -0.05$, $t = -0.17$ ($p = 0.861$)
Putamen, SBR	2.19 (0.54)	0.61 (0.42)	0.68 (0.55)	$d = 2.22$, $t = 12.46$ ($p < 0.001$)	$d = 2.46$, $t = 10.34$ ($p < 0.001$)	$d = -0.06$, $t = -0.21$ ($p = 0.828$)
CSF biomarkers	$N = 129$	$N = 42$	$N = 21$			
$A\beta_{42}$ levels, pg/mL	1078 (474)	803 (471)	750 (237)	$d = 0.54$, $t = 3.06$ ($p = 0.002$)	$d = 0.67$, $t = 2.86$ ($p = 0.004$)	$d = 0.09$, $t = 0.33$ ($p = 0.742$)
p-Tau levels, pg/mL	16.5 (8.0)	16.7 (7.4)	15.2 (5.6)	$d = -0.11$, $t = 0.61$ ($p = 0.542$)	$d = 0.25$, $t = 1.08$ ($p = 0.282$)	$d = 0.14$, $t = 0.51$ ($p = 0.611$)
Genetics						
GBA, +/− (+%)		4/45 (8%)	10/15 (40%)			OR = 7.26 ($p = 0.003$)
LRRK2, +/− (+%)		3/45 (6%)	3/22 (12%)			OR = 2.02 ($p = 0.405$)
SNCA, +/− (+%)		7/42 (14%)	2/23 (8%)			OR = 0.53 ($p = 0.709$)
APOE-ε4, +/− (+%)	31/101 (23%)	13/37 (26%)	6/19 (24%)	OR = 1.14 ($p = 0.703$)	OR = 1.03 ($p = 0.99$)	OR = 0.90 ($p = 0.99$)

The descriptive values presented are: mean (standard deviation) for all continuous variables, and number (percentage) for categorical variables. MRI-based measurements of ROI volumes are mean TIV-normalized GM volumes in mm^3. Statistical values correspond to ANCOVA for continuous variables and Fisher's exact test for categorical variables. Effect size values correspond to odds ratios for categorical variables and Cohen's d for continuous variables.

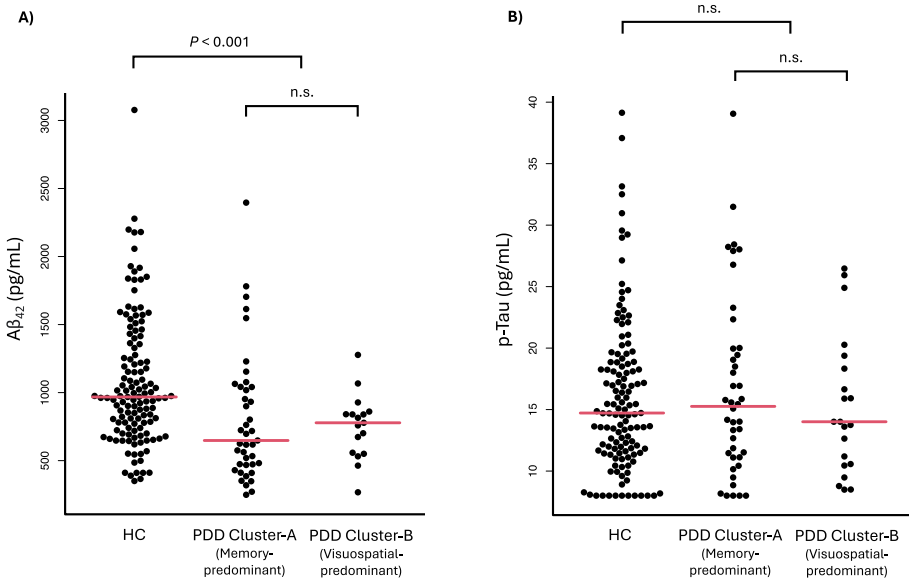

Fig. 2 | Molecular biomarker levels of PDD subtypes in comparison to healthy controls. Beeswarm plots for CSF biomarker values of $A\beta_{42}$ (**A**), and p-tau (**B**) levels across healthy controls (HC) and the two PDD clusters. HC Healthy controls, Cluster-A memory-predominant PDD subtype, Cluster-B visuospatial-predominant PDD subtype, n.s. not significant.

cerebrospinal fluid (CSF) AD biomarker levels between the clusters (Fig. 2). As expected, $A\beta_{42}$ levels were significantly lower in the PDD group as compared to healthy controls ($d = 0.54$, $p < 0.001$), but there were no significant differences between the PDD subgroups. CSF p-tau181 levels did not differ between any of the groups.

Finally, in the MRI analyses, PDD patients showed significantly reduced hippocampus ($d = 0.41$, $p < 0.001$) and posterior cholinergic basal forebrain (cBF) ($d = 0.61$, $p < 0.001$) volumes compared to healthy controls, but atrophy of these regions did not differ between the two PDD clusters (Table 3). In the complementary brain-wide voxel-wise analyses, both clusters showed similar patterns of temporo-parietal and frontal atrophy compared to healthy controls (Supplementary Fig. 2), and a direct comparison between the two PDD clusters did not reveal any significant differences (Supplementary Fig. 3).

Discussion

In the present study we used a data-driven approach to explore heterogeneity in dementia presentations among incident PDD patients and identified distinct memory-predominant and visuospatial-predominant subtypes of PDD. The visuospatial-predominant profile was associated with a higher frequency of hallucinations and was enriched for *GBA* mutation carriers. Interestingly, the memory-predominant profile did not appear to be significantly enriched for features of comorbid AD pathology.

Similar to our study, an earlier study by Janvin et al.[7] used clustering analysis of domain-specific subscores from the Dementia Rating Scale (DRS) to characterize the heterogeneity in cognitive profiles in a sample of 50 PDD patients. In addition to a typical "subcortical" profile characterized by impaired performance in attention, initiation/perseveration, and construction DRS subtests with relatively preserved memory performance, they also identified a sizeable subgroup of 15 PDD patients (30%) who presented a memory-predominant cognitive impairment that resembled the profile typically observed among AD dementia patients. While notable differences in the employed neuropsychological test batteries prevent a direct comparison of the distinct cognitive profiles identified in our study with those previously identified by Janvin et al.[7] both studies agree in the identification of a subgroup of PDD patients with prominent memory impairment. In fact, in our study the memory-predominant PDD subgroup (cluster-A) represented the majority (67%) of our PDD cohort. While this may seem surprising at first sight, it may relate to the high sensitivity of the employed memory tests (i.e., the Hopkins Verbal Learning Test) for even subtle memory impairments and the overall less severe dementia severity of the incident PDD cases in our study. Moreover, it should be noted that the "memory predominance" of the identified profile mainly refers to the contrast with relatively spared visuospatial function. Thus, in contrast to the study by Janvin et al.[7] the "memory-predominant" profile identified in our study may not clinically resemble a typical amnestic dementia profile as commonly associated with AD. Given that visuospatial impairments are usually considered a relatively late event in the progression towards dementia in PD[23–25], the question arises whether the relative sparing of this domain may reflect an earlier disease stage rather than a distinct disease subtype. However, comparable degrees of overall dementia severity (as measured by the MoCA), motor severity, years of disease duration, as well as severity of nigrostriatal dopaminergic degeneration all argue against this possibility.

While the neurobiological underpinnings of the observed differences in clinical presentation among PDD patients remain largely unknown, the prominent memory impairments in cluster-A may suggest a possible influence of comorbid AD pathology[22]. Indeed, comorbid AD pathology is a very frequent finding in autopsy studies of PDD, affecting approximately 50% of patients[21,26]. AD co-pathology has also been estimated to be a major pathologic driver of clinical heterogeneity in PD[18,22,27], and some neuropathological studies have suggested that PD patients with AD co-pathology have more pronounced memory and naming deficits[28,29]. However, other biomarker studies could not confirm this specificity for the memory domain over and above the well-established negative effect of AD co-pathology on general cognition in PD[18,30]. In line with the high degree of AD co-pathology in PDD, in our study we found significantly lower (i.e., more abnormal) CSF $A\beta_{42}$ levels in the PDD sample compared to healthy controls. However, CSF ptau181 levels were not significantly different between groups, calling into question the overall contribution of AD co-pathology to the clinical phenotype in this sample. Most importantly, none of the AD biomarkers were more abnormal in the memory-predominant PDD subgroup compared to the visuospatial-predominant subgroup, indicating that prominent memory impairments are not generally reflective of AD co-pathology but may result from pathophysiologic processes intrinsic to PD itself. In this context, differences in the regional distribution of Lewy body pathology and associated neurodegenerative processes may represent likely pathological substrates of the cognitive differences among the PDD subgroups[19,20,31–33]. Surprisingly, however, analysis of available MRI data did not reveal any statistically significant differences in subcortical or cortical neurodegeneration patterns between the visuospatial- and memory-predominant PDD subgroups. Moreover, both PDD subgroups showed comparable degrees of hippocampal atrophy, which would be expected to be more severe in patients with prominent memory impairment[34,35]. While this negative finding may have been affected by the limited sample size of PDD patients for whom MRI scans were available, it may also relate to the reportedly low sensitivity of structural MRI for the neurodegenerative processes underlying cognitive impairment in PD[36–38]. This is also reflected in the comparably low effect sizes of volumetric differences between the PDD subgroups and healthy controls in our study (see Table 3 and Supplementary Figs. 2 and 3). Functional neuroimaging modalities such as FDG-PET may be better suited to map cortical patterns underlying phenotypic differences among PDD patients[36–38], but these images were not available for the analyzed PPMI cohort in the current study.

Finally, given the known effect of specific genetic factors on phenotypic differences in PD[12], we studied possible differences in the prevalence of common genetic mutations and risk alleles among the identified PDD subtypes. Particularly, the APOE-ε4 allele has been previously linked to cognitive impairment in PD and suggested to be a phenotypic modifier among PDD patients through its association with comorbid AD pathology[22,39,40], However, in our study the memory-predominant subgroup was not significantly enriched for APOE-ε4, reinforcing the notion that AD co-pathology does not seem to be a major driver of the memory deficits defining this subgroup. By contrast, the visuospatial-predominant PDD subgroup was found to have a significantly higher proportion of GBA variant carriers. This finding is in line with previous research showing that PD patients carrying GBA variants exhibit a distinct cognitive profile characterized by relatively greater impairments in visuospatial abilities[41–43]. Interestingly, PD patients that carry GBA variants were also found to show higher frequencies of visual hallucinations[44–46], which were also elevated in the visuospatial-predominant PDD subgroup identified here. Growing evidence also suggests that GBA mutations may affect cognitive decline by modifying the beneficial effect of cognitive reserve on domain-specific cognitive functions[47–49]. However, GBA carriers represented less than 50% of the visuospatial-predominant PDD subgroup, indicating that this phenotype cluster is not specific to GBA mutations but also occurs in idiopathic PD[50]. Accordingly, a complementary analysis comparing GBA mutation carriers and noncarriers within the visuospatial-predominant PDD subgroup did not reveal major differences in their cognitive profile or the prevalence of hallucinations (Supplementary Table 2). A possible common mechanism is abnormal glucocerebrosidase activity, which is strongly linked to GBA mutations, but also occurs in idiopathic PD and is linked to a more aggressive disease course with a higher incidence of non-motor symptoms regardless of the genetic background[51–53]. In addition, the cognitive phenotype in PD may also be affected by other genetic variants that have not been tested in our study, such as those of the WWOX/MAF locus[54,55].

Our findings of a genetic influence on the cognitive phenotype in PDD should be interpreted within the context of a potential race-specificity of genetic factors and the possible role of gene-environment interactions. Thus, growing evidence demonstrates that the interplay between environmental influences and genetic factors is a key determinant in PD progression[56,57]. Toxicants commonly used to model PD, such as pesticides and herbicides like rotenone and paraquat, have been shown to interact with several PD-related genes, including GBA mutations[56,58]. Considering the potential interactions of race and environmental factors with genetic influences on PD-related cognitive and neuropsychiatric symptoms, further research should explore how these characteristics may influence heterogeneous clinical trajectories in PD and their potential effect on the cognitive PDD subtypes identified in the current study. Further elucidating these interactions may have important implications for patient stratification in biomarker-driven clinical trials and personalized medicine approaches[59].

An interesting question is whether and how the identified cognitive subtypes of PDD may influence social and daily functioning, which are increasingly recognized as critical aspects of cognitive decline in PD that

significantly impact patient quality of life and care strategies[60–62]. Social functioning in PD reflects complex interactions between cognitive, neuropsychiatric, and daily activity-related factors[61,62]. To our knowledge, there is little data available on whether any particular cognitive profile or type of cognitive impairment may have a bigger impact on social and daily functioning in PD. However, the visuospatial-predominant PDD phenotype identified in our study also exhibited a higher prevalence of hallucinations, which may be particularly relevant in this context[61]. Whether and how this interaction between specific cognitive and neuropsychiatric features may affect social-daily functioning in PDD is an interesting venue for further research.

Our study also presents a series of important limitations that should be considered when interpreting our results. First, while we present data from a relatively large sample of well-characterized PD patients with incident dementia, this sample is still relatively small for a data-driven clustering approach. Future clustering studies including larger samples may reveal more diverse cognitive profiles than the two broad subgroups identified here, as the ability of these approaches to resolve distinct subgroups directly scales with the available observations. Thus, a larger sample would enhance the ability of the clustering algorithm to distinguish more nuanced subgroups and reduce the risk of unstable classifications. Second, clustering results may depend on the employed neuropsychological instruments (i.e., the specific tests used for clustering). While the use of the PPMI data allowed us to employ a very comprehensive test battery, the included tests may not cover all cognitive domains to the same degree and may also differ in test difficulty, and thus, the sensitivity to detect impairments may differ across cognitive domains. Moreover, one has to keep in mind that certain neuropsychological and psychiatric factors have been shown to be influenced by cultural differences, and thus, cognitive PDD subtypes and their associated neuropsychiatric characteristics may differ in other socio-cultural contexts[63,64]. Finally, our analyses were based on a convenience sample of incident PDD patients from the PPMI cohort, limiting the phenotypic and neuroimaging variables to the data that is being collected in this study. Future studies may include more comprehensive assessments of neuropsychiatric symptoms (e.g., type and severity of hallucinations) and other non-motor symptoms (e.g., polysomnography of RBD, social functioning,…), as well as other neuroimaging modalities that are potentially more sensitive for mapping differences in cortical neurodegeneration patterns among PDD subtypes[36–38].

In conclusion, our data-driven approach has identified distinct memory-predominant and visuospatial-predominant cognitive profiles among incident PDD patients, which also showed differential associations with other non-motor features (i.e., hallucinations) and genetic risk factors (i.e., GBA mutations). These findings point to differential pathophysiologic processes underlying domain-specific cognitive impairment in PD and may have important implications for accurate diagnosis, personalized prognosis, and potentially also therapeutic decision making for patients with PDD.

Methods

Study participants

Participants included in this study were selected from the PPMI cohort[65]. The PPMI is a longitudinal, multicentre study investigating the progression of clinical features, imaging, and biological markers in patients with PD. It is a public-private partnership funded by the Michael J. Fox Foundation for Parkinson's research and funding partners, which can be found at https://www.ppmi-info.org/about-ppmi/who-we-are/study-sponsor. The inclusion/exclusion criteria for the PPMI cohort are described in detail in the PPMI study documents available at https://www.ppmi-info.org/study-design. The PPMI study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice (GCP) guidelines after approval of the local ethics committees of the participating sites (https://www.ppmi-info.org/about-ppmi/ppmi-clinical-sites)[66], including Banner Sun Health Research Institute, Barrow Neurological Institute, Baylor College of Medicine, Boston University Medical Center, Cleveland Clinic Lou Ruvo Center for Brain Health, Clinical Ageing Research Unit, Newcastle University, Columbia University Medical Center, Emory University School of Medicine, Hospital Clinic de Barcelona, Hospital Universitario Donostia, Imperial College London, Institute for Neurodegenerative Disorders/XingImaging, John Radcliffe Hospital Oxford and Oxford University, Johns Hopkins University, Keck School of Medicine of USC, Lagos College of Medicine, University of Lagos, Massachusetts General Hospital, Mayo Clinic of Arizona, Medical University Innsbruck, Montreal Neurological Institute-Hospital, Mount Sinai Beth Israel, National and Kapodistrian University of Athens, Northwestern University, NYU Langone Health, Oregon Health and Science University, Paracelsus-Elena Klinik Kassel, Parkinson's Disease and Movement Disorders Center of Boca Raton, Philipps-University of Marburg, Radboud University, Tel Aviv Medical Center, Tel Aviv Sourasky Medical Center, The Cleveland Clinic, The Ottawa Hospital, Toronto Western Hospital, University of Alabama at Birmingham, University of California, San Diego, University of California, San Francisco, University of Cincinnati, University of Colorado Denver, University of Florida, University of Kansas Medical Center, University of Luebeck, University of Luxembourg, University of Michigan, University of Pennsylvania, University of Pittsburgh, University of Rochester, University of Salerno, University of South Florida, University of Tuebingen, VA Puget Sound Health Care System, and Wolfson Institute of Population Health. Written informed consent was obtained from all participants before undergoing any study evaluations.

In the current study, we studied all PD patients from the PPMI cohort who developed dementia over clinical follow-up. At the date of database retrieval (May, 2024), this was the case for 75 incident PDD patients (see detailed flow chart of patient selection in Supplementary Fig. 4). Considering a total baseline sample of 702 PD patients and an average follow-up of 4.6 ± 2.6, this mounts to an incidence rate of 2.3 per 100 person-years. We note that this relatively low incidence rate is consistent with recent meta-analytic estimates of dementia risk in PD[5], considering that most of the patients included in our study were enrolled as de novo PD patients and at a comparably young age (62.0 ± 10.0 years at baseline). Dementia status was determined by PPMI study clinicians and required evidence of (1) cognitive function being impaired in more than one cognitive domain, (2) decline from pre-morbid function, and (3) significant impact of cognitive impairment on daily function. Fifty (66.7%) of the PDD patients were diagnosed as idiopathic PD patients at study entry, while 25 (33.3%) had a confirmed pathogenic *LRRK2*, *GBA*, or *SNCA* genetic variant (see details below). For comparison, we included baseline assessments of a control group of 132 healthy individuals enrolled in PPMI.

Clinical assessments

All subjects underwent a comprehensive evaluation of motor and non-motor symptoms. Motor assessment was performed using the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III as well as Hoehn and Yahr staging. Motor phenotype was classified as tremor dominant (TD) or postural instability/gait difficulty (PIGD) subtype based on tremor- and gait-specific MDS-UPDRS scores according to established formulas[67].

Global cognitive performance was measured using the Montreal Cognitive Assessment (MoCA), while specific cognitive domains were assessed using the symbol digit modalities test (attention), letter-number sequencing (working memory), semantic (animals) fluency test (executive function/language), the Benton Judgment of Line Orientation test (visuospatial function), as well as the Hopkins Verbal Learning Test (HVLT) immediate and delayed recall tests (memory).

Presence of delusions/hallucinations and apathy were assessed using the corresponding items of the UPDRS part I. Depressive symptoms were assessed using the Geriatric Depression Scale (GDS, short version), where scores ≥5 are reflective of the presence of clinically relevant depression. Anxiety levels were measured using the State-Trait Anxiety Inventory (STAI).

Clinical features of rapid eye movement (REM) sleep behavior disorder (RBD) were assessed using the REM Sleep Behavior Disorder Questionnaire (RBDQ), and scores ≥5 were used to indicate presence of RBD. The presence of daytime sleepiness was ascertained by an Epworth Sleepiness Scale (ESS) score ≥10. The severity of autonomic symptoms was assessed using the SCOPA-AUT autonomic dysfunction scale.

All clinical assessments used in the current study were derived from the study visit where dementia was first diagnosed.

Genetic assessments, molecular biomarkers, and neuroimaging

Pathogenic variants in the *LRRK2* (p.G2019S), *SNCA* (A53T), and *GBA* (N409S, L483P, R159W, and L29Afs*18) genes were identified using consensus data across several genotyping projects in the PPMI study, including genome-wide genotyping arrays, whole-exome sequencing, whole-genome sequencing, Sanger sequencing, and RNA-sequencing[51,68].

In addition, blood samples were analyzed for APOE genotype at the PPMI genetics core as previously described[69,70]. APOE genotype was determined by the rs429358 and rs7412 single nucleotide polymorphisms (SNPs) and was coded in our study as a binary variable indicating the presence or absence of the APOE-ε4 risk variant.

A subset of 63 PDD patients (84%) had serial cerebrospinal fluid (CSF) biomarker measurements available. CSF collection and biomarker measurements in the PPMI study have been described in detail previously[30,69]. In the present study, we included measurements of amyloid-beta 1-42 ($A\beta_{42}$) and tau phosphorylated at threonine 181 (p-tau181) measured using the fully automated Roche Elecsys® electrochemiluminescence immunoassays on a cobas e 601 instrument[30]. We used the CSF sample that was acquired closest in time to the study visit when dementia was diagnosed (average offset: 2.3 ± 2.0 years).

Dopamine transporter imaging with [^{123}I]FP-CIT SPECT was used to assess dopaminergic denervation. SPECT data acquisition in the PPMI cohort follows a unified protocol and standardized pre-processing steps are applied to the SPECT images to improve homogeneity across the multicentric image acquisitions[71]. The specific [^{123}I]FP-CIT binding ratio (SBR) was calculated according to the PPMI protocol for caudate and putamen striatal regions-of-interests (ROIs) using the occipital cortex as reference region (i.e., $SBR = (striatal\ ROI / occipital\ ROI) - 1$).

Volumetric 3D T1-weighted MRI scans suitable for automated volumetric analysis were available for a subset of 58 PDD patients (77%), and we used the MRI scan that was acquired closest in time to the study visit when dementia was diagnosed (average offset: 2.8 ± 2.5 years). Structural MRI images were used to assess volumes of the hippocampus and the cholinergic basal forebrain (cBF), two brain regions in which volume reductions (atrophy) have been consistently linked to cognitive decline and dementia in PD[72–76]. cBF and hippocampal gray matter (GM) volumes were measured using established automated volumetry approaches implemented in the Statistical Parametric Mapping software package (SPM12, Wellcome Trust Center for Neuroimaging) that have been described in detail previously[75,77,78]. The cBF region-of-interest (ROI) was separated into distinct anterior and posterior subdivisions, as defined by a previous methodological study characterizing functionally homogeneous subdivisions within the human cBF[79]. The posterior cBF subdivision primarily corresponds to the cytoarchitectonic subregion of the nucleus basalis of Meynert, while the anterior cBF subdivision corresponds to the medial septum and diagonal band of Broca. The total intracranial volume (TIV), calculated as the sum of the total volumes of the GM, white matter, and cerebrospinal fluid partitions, was used to account for differences in head size.

Clustering based on neuropsychological test data

For clustering of individual cognitive profiles, we first converted the different test scores, measured at very different scales, to w-scores with respect to healthy controls (corrected for age, sex, and education) so that they were comparable to each other. We then scaled each patient's test scores to the average w-score of this patient to account for possible differences in global cognitive impairment between patients. The pre-processed neuropsychological test data was then submitted to Ward's hierarchical clustering, which determines the similarity between all patients based on the Euclidean distance of their cognitive profiles (i.e., vector of globally scaled neuropsychologic w-scores). This similarity information is then used to successively pair patients into larger clusters such that the total within-cluster variance is minimized[80,81]. The output of this algorithm is a hierarchical dendrogram in which the level of branching indicates the degree of dissimilarity between clusters. We determined the optimal number of separable clusters in the data using standard clustering performance measures, including the Davies-Bouldin[82] and silhouette indices[83].

Statistical analysis

Demographic, clinical, and genetic characteristics were compared between the stratified patient groups using two-sample t-tests for continuous variables and Fisher's exact tests for dichotomous variables. Following recommendations described in the statistical literature[84], we did not apply a specific correction for multiple comparisons in this hypothesis-driven study with a limited number of planned comparisons.

CSF biomarker levels were compared between stratified patient groups using ANCOVA models controlled for offset between CSF sampling and dementia diagnosis. Neuroimaging variables were compared between groups using analogous ANCOVA models controlled for offset between image acquisition and dementia diagnosis, age, sex, and years of education, as well as TIV and the magnetic field strength (1.5 T, 3 T) in the case of MRI-derived volumes. In addition, we conducted brain-wide voxel-wise analyses across the whole-brain gray matter, following standard procedures described previously, and voxel-wise effects were corrected for multiple comparisons using the false discovery rate ($P_{FDR} < 0.05$)[85].

Group differences were assessed for each PDD cluster in comparison to healthy controls as well as using direct comparisons between the PDD clusters. Note that some neuroimaging, CSF biomarker, and genetic variables were not available for all individuals in this study and participants with missing data were excluded from the corresponding statistical analyses.

Statistical analyses were carried out using RStudio and R version 4.4.0, and the significance threshold was set at $p < 0.05$ (two-tailed).

Data availability

Data used in the preparation of this study were obtained from the Parkinson's Progression Markers Initiative database, which is publicly available to interested researchers (www.ppmi-info.org).

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Author contributions

M.J.G. and M.A.L.E. contributed to the conception and design of the study; M.J.G., M.A.L.E., J.S.R. - contributed to the acquisition, analysis, and interpretation of data; M.J.G. and M.A.L.E. – contributed to drafting the text and preparing the figures. M.J.G., M.A.L.E., J.S.R., and P.M. – contributed to revising the text for intellectual content.

Competing interests

The authors declare no competing interests.

Additional information

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