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Memory Phenotypes In Early, De Novo Parkinson's Disease Patients with Mild Cognitive Impairment

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ABSTRACT: Background: Memory deficits in mild cognitive impairment related to Parkinson's disease (PD-MCI) are quite heterogeneous, and there is no general agreement on their genesis.
Objectives: To define memory phenotypes in de novo PD-MCI and their associations with motor and non-motor features and patients' quality of life.
Methods: From a sample of 183 early de novo patients with PD, cluster analysis was applied to neuropsychological measures of memory function of 82 patients with PD-MCI (44.8%). The remaining patients free of cognitive impairment were considered as a comparison group (n = 101). Cognitive measures and structural magnetic resonance imaging-based neural correlates of memory function were used to substantiate the results.
Results: A three-cluster model produced the best solution. Cluster A (65.85%) included memory unimpaired patients; Cluster B (23.17%) included patients with mild episodic memory disorder related to a "prefrontal executive-dependent phenotype"; Cluster C (10.97%) included patients with severe episodic memory disorder related to a "hybrid phenotype," where hippocampal-dependent deficits co-occurred with prefrontal executive-dependent memory dysfunctions. Cognitive and brain structural imaging correlates substantiated the findings. The three phenotypes did not differ in terms of motor and non-motor features, but the attention/executive deficits progressively increased from Cluster A, through Cluster B, to Cluster C. This last cluster had worse quality of life compared to others.
Conclusions: Our results demonstrated the memory heterogeneity of de novo PD-MCI, suggesting existence of three distinct memory-related phenotypes. Identification of such phenotypes can be fruitful in understanding the pathophysiological mechanisms underlying PD-MCI and its subtypes and in guiding appropriate treatments.
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Key Words: Parkinson's disease; memory; mild cognitive impairment; cognitive; non-motor symptoms

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Introduction

The International Parkinson and Movement Disorder Society's diagnostic criteria for Parkinson's disease mild cognitive impairment (PD-MCI) include the optional subtype classification of PD-MCI in terms of single-domain versus multiple-domain subtypes.[1] The proposed subtype classification was rooted in the recognized heterogeneity of PD-MCI's clinical profile, study findings of non-amnestic, single domain impairment as a highly common subtype of PD-MCI,[2] and the hope that understanding PD-MCI subtypes by individual domain characteristics (eg, attention/working memory, executive function, language, memory, or visuospatial function) would help elucidate its pathophysiology, inform rates of progression, and guide therapeutics. However, studies applying the PD-MCI diagnostic criteria have highlighted the challenges in identifying purely single-domain subtypes[3] and that the fronto-striatal versus posterior cortical phenotype of cognitive impairment demonstrates use in combining different domains to understand neurobiological correlates and risk of PD dementia.[4,5] Early PD-MCI studies as well as other more recent studies classify PD-MCI as amnestic versus non-amnestic, therefore, reflecting a more Alzheimer's disease (AD)-type approach toward the definition of MCI.[6] Although differing from the original intent of the 2012 PD-MCI diagnostic criteria,[1] the categorization of amnestic and non-amnestic merits further consideration and revisiting as evidence suggests that the risk of progression to PD dementia (PD-D) is higher for patients with PD-MCI showing posterior cortical deficits, related to coexistent AD neuropathological hallmarks, deficits in nondopaminergic neurotransmitters (eg, cholinergic), and apolipoprotein E (APOE) ε4 genotype.[3-5,7-9]

According to the influential "encoding-retrieval deficit hypothesis", in amnestic PD-MCI, memory deficits specifically involve free recall,[10,11] whereas cued recall and recognition are spared or involved only later in the disease course.[12] This hypothesis is based on circuitry research in PD[13] showing that nigrostriatal degeneration causes progressive loss of dopamine neurotransmission in a dorsal to ventral gradient within the basal ganglia, early impacting the "cognitive" neural circuit between the caudate nucleus and the dorsolateral prefrontal cortex.[14] On these bases, memory deficits in PD would be mainly because inefficient use of encoding-retrieval strategies, related to dorsolateral prefrontal-dependent executive deficits, rather than to difficulty in storing memory traces.[15-21] However, the "encoding-retrieval deficit hypothesis" as an exhaustive account of the memory disorders in PD-MCI has been questioned.[22-24] Indeed, growing evidence suggests that patients with prominent episodic memory impairments could be affected by amyloid deposition in mesial temporal lobes and reduced connectivity or integrity within hippocampal regions[25-27] as it is the case for memory disorders in AD.[18,28] Therefore, deficits in hippocampus-dependent storage (associated with cholinergic disturbances and usually assessed by recognition tests) might have been underestimated[29-31] and therefore, suggest other mechanisms for the amnestic deficits. Indeed, few compelling studies have shown that recognition (as a measure of storage stage) and free recall (as a measure of encoding-retrieval stages) performances were below average in PD patients with or without dementia, with neither group performing better on recognition than free recall.[32,33]

In summary, available evidence would demonstrate that patients with PD-MCI can experience deficits in any stages of memory processing (ie, encoding, storage, and retrieval).[24] However, whether these deficits always co-occur in patients with PD or appear in different combination patterns defining specific memory phenotypes remains unresolved. A delineation of specific memory phenotypes in PD-MCI would be very relevant, as certain amnestic phenotypes might predict cognitive decline, map onto different pathophysiological substrates, and help tailor therapeutic interventions.[3,34] This question has been only partially addressed in a few previous studies.[18,35-40] In particular, Weintraub et al[18] maintained that memory processing defects can appear in three memory phenotypes (ie, unimpaired, prefrontal-dependent executive subtype, and hippocampus-dependent amnesia subtype) in PD. This evidence would challenge the long-held assumption that the cognitive changes in PD primarily result from impairments of the "dorsolateral prefrontal-striatal circuitry," but was based on assessment of a cohort of dopaminergic-treated patients at a middle-late disease stage and not defined according to PD-MCI criteria. Instead, determining valid and clinically meaningful memory phenotypes in early, de novo patients with PD-MCI might provide cogent information for prognosis and treatment decisions.

The primary aims of our study were (1) to determine whether early, de novo PD-MCI can be categorized as fitting different memory phenotypes, on the basis of a data-driven approach (cluster analysis) without any a priori assumption; (2) to explore the possible association of the memory measures used for clustering with other cognitive domains, behavioral measures, and magnetic resonance imaging (MRI)-based memory-related brain structural changes; (3) to compare these phenotypes on the main motor and non-motor features and on quality of life measures; (4) to match the phenotypes resulting from cluster analysis with diagnostic classification of amnestic PD-MCI, defined according to AD-type criteria.[41,42]

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Methods

Participants

The study sample was extracted from an ongoing longitudinal project enrolling consecutive patients with early de novo PD according to the Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's disease.[43] As previously described,[44] patients of this project underwent an extensive clinical assessment at the time they were diagnosed with PD by two movement disorders specialists (A.T. and R.D.M.) After the baseline assessments, patients were prospectively followed with a full clinical evaluation every year. From this project, we selected the patients enrolled from September 2015 to January 2021 and fulfilling the following inclusion criteria at their last clinical evaluation: (1) diagnosis of PD[43]; (2) disease duration ≤2 years; (3) modified Hoehn Yahr stage ≤2.5; (4) no ongoing or previous exposure to anti-PD drugs. Exclusion criteria were: (1) presence of PD-D[45]; (2) diagnosis of atypical or secondary parkinsonism, (3) PD onset before the age of 40 years; (3) history of psychosis, cerebrovascular diseases, relevant head injury, or major medical diseases (eg, hepatic insufficiency, neoplasms, or clinically relevant renal disease); (4) exposure to potentially cognitive-interfering drugs, such as anticholinergic and psychotropic drugs. All procedures were approved by the local Ethical Committee, following the Declaration of Helsinki. All participants provided their informed consent.

Estimation of the Morphometric Measures

Patients underwent MRI on a 3 Tesla General Electric scanner (Healthcare, Milwaukee, WI). Structural data was obtained using a three-dimensional T1-weighted sagittal images. All data were processed using FreeSurfer version 7.1.1 on a Hewlett-Packard workstation equipped with two 8-core Intel Xeon Bronze 3106 @1.70 GHz, 128 GB RAM, and Linux CentOS 7. The cortical segmentation available in the FreeSurfer's atlas[46] and the cortical thickness values were estimated bilaterally. In detail, we extracted bilaterally the morphometric data of cortical thickness related to the Papez circuit[47] (ie, caudal anterior, rostral anterior, isthmus, and posterior cingulate area regions; entorhinal cortex; parahippocampal region) and volumes (after intracranial volume correction) associated with three memory-related subregions of the hippocampus (ie, head, body, and tail)[48,49] (for full description, see Supplementary Material S1).

Assessment of Parkinson's Clinical Features and Quality of Life

The severity of motor symptoms was assessed by the Unified Parkinson's Disease Rating Scale part III[50] and the Hoehn and Yahr.[51] Quality of life was operationalized by the 39-item PD.[52] Moreover, the patients were classified according to the age at onset of parkinsonian symptoms as follows: early-onset PD (age at onset<50 years)[53] and late-onset PD (patients in the highest tertile group [age at onset >69 years]).[54,55]

Assessment of Behavioral Variables

Depressive and anxious symptoms and fatigue were rated using the Beck Depression Inventory,[56] the Parkinson Anxiety Scale,[57,58] and the Parkinson Fatigue Scale,[59] respectively. The Apathy Evaluation Scale[60] was used to measure apathy, whereas the PD sleep scale[61] and the Epworth Sleepiness Scale[62] to gauge sleep disorders.

Assessment of Cognitive Measures

The presence of PD-MCI single domain and multiple domains[1] was ascertained by a comprehensive (PD-MCI Level II) neuropsychological battery including two tests for each of the main cognitive domains (ie, attention and working memory, executive functions, visuospatial abilities, language, and memory). For each cognitive test, we generated Z-score by subtracting the raw score from the normative means and dividing it by the normative standard deviations. After that, a composite score for each of the five cognitive domains was computed by averaging the Z-scores of tests assessing the same domain. PD-MCI participants were classified as non-amnestic (naMCI) or amnestic (aMCI), with the subtypes of aMCI single domain and aMCI multiple domains (Supplementary Material S2 for all the details).[41,42]

In line with previous literature,[18,63] we adopted the Prose Recall Test and three indices derived from Rey auditory verbal learning test (RAVLT) (free recall, intrusions, recognition enhancement) as memory measures for the cluster analysis. Age-, education-, and sex-adjusted Z-scores for RAVLT-intrusions and RAVLT-recognition enhancement were derived from a demographic-matched control group of 30 individuals free of cognitive impairment assessed by the Mental Deterioration Battery.[64]

Statistical Analyses

Cluster analysis (a hierarchical method) was executed by the "*mclust*" package[65,66] in the *R* statistical software. This package performs a model-based hierarchical clustering via Gaussian finite mixture modelling fitted by the expectation–maximization algorithm. The cluster analysis was chosen to define the subgroups of patients with PD-MCI showing different memory phenotypes based on the following age-, education-, and sex-adjusted Z-scores of memory measures: (1) prose

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recall test; (2) RAVLT-free recall; (3) RAVLT-intrusions; (4) RAVLT-recognition enhancement. Bayesian information criteria (BIC) and integrated complete-data likelihood (ICL) were used as information criteria for selecting the best cluster solution among a finite set of alternatives (up to 9 clusters); the cluster solution with lower BIC and ICL was selected as the best one. Moreover, the bootstrap sequential likelihood ratio test statistic (LRTS) (the number of replications = 999) was performed to compare the fit between k and $k + 1$ cluster solutions; the sequential bootstrap procedure terminated when an LRTS was not statistically significant at the P value level of 0.05. To check the reliability and stability of the partition of the patients into three clusters, K-means clustering (a nonhierarchical method executed by the "*NbClust*" package)[67] was also performed. Cohen's κ[68] was used for defining the agreement between the results of the two clustering methods (hierarchical vs. nonhierarchical).

The associations of the above memory measures with the five cognitive domains, behavioral measures, and with memory-related neural structures (brain MRI data available only for 120 of 183 patients) were evaluated by partial Pearson's correlation, using the different MRI as a covariate (ie, 16-channels head-coil = 1 and 32-channels head-coil = 2) (Supplementary Material S1), separately for cortical thickness and volumetric data.

Clusters derived from the PD-MCI subsample and patients classified as with normal cognition (PD-NC)[1] were compared for differences in memory measures using multivariate analysis of variance (MANOVA) followed by post-hoc analyses of variance (ANOVAs). Moreover, ANOVAs and Pearson's χ^2 tests were adopted to explore the differences among PD-MCI clusters and PD-NC in all measures, and in quality of life.

Moreover, we used Pearson's χ^2 test to compare the partition of the PD-MCI subgroups based on the AD-type criteria (ie, amnestic/nonamnestic and single/multiple domains) with that resulting from the cluster analysis.

The statistical analyses were performed using *R* statistical software (version 4.2.1) and Software Package for Social Sciences (version 25; Chicago, Illinois).

TABLE 1 *A summary showing the top-three cluster models with their geometrical characteristics based on BIC and ICL*

Best BIC values	⋆EVE,3	VVI,5	EVI,3
BIC	−1237.40	−1237.70	−1237.81
BIC difference	0.00	−0.29	−0.41
Best ICL values	⋆EVE,3	VVV,2	VEV,2
ICL	−1247.76	−1252.03	−1253.18
ICL difference	0.00	−4.26	−5.41

Note: The best cluster model was signed by (⋆); bootstrap sequential likelihood ratio test statistic (LRTS) confirmed that the EVE, 3-cluster as the best one (1 vs. 2 clusters LRTS = 70.04, $P = 0.001$; 2 vs. 3 clusters LRTS = 42.68, $P = 0.001$; 3 vs. 4 clusters LRTS = 13.02, $P = 0.195$).
Abbreviations: BIC, Bayesian information criteria; ICL, integrated completed likelihood; EVE,3: ellipsoidal distribution, equal volume, variable shape, equal orientation, and 3 clusters; EVI,3: diagonal distribution, equal volume, variable shape, coordinate axes orientation, and 3 clusters; VEV,2: ellipsoidal distribution, variable volume, equal shape, variable orientation, and 2 clusters; VVI,5: diagonal distribution, variable volume, variable shape, coordinate axes orientation, and 5 clusters; VVV,2: ellipsoidal distribution, variable volume, variable shape, variable orientation, and 2 clusters.

Results

One-hundred eighty-three early de novo PD patients were enrolled for the present study (ie, 6.5% with early-onset and 25.7% with late-onset) (Supplementary Material S3 reported all descriptive features), of these 82 (44.8%) were diagnosed as affected by PD-MCI. All patients had impairments in more than one cognitive domain: 35 patients (42.68%) could be classified as showing an amnestic-multiple domain MCI and 47 (57.32%) a non-amnestic-multiple domains MCI, in line with previous findings.[69-71] Comparison between patients with and without MCI were reported in Supplementary Material S4.

Fifty-two of the 82 patients underwent a comprehensive neuropsychological evaluation at their first follow-up visit (mean follow-up period of 1.21 years; cohort retention rate 63.4%). This follow-up visit identified a stable MCI in 41 of them (79%).[6]

Of 183 enrolled patients, MRI was available only for 120 (47 with PD-MCI). We did not find differences between patients with (n = 120) and without (n = 63) available MRI in terms of demographics, clinical, cognitive and behavioral features, and quality of life (Supplementary Material S5).

Cluster Analysis Results

BIC and ICL indicated the three-cluster solution as the best one; therefore, three clusters of patient phenotypes were generated (ie, Cluster A, B, and C) from the subsample of patients with PD-MCI. Bootstrap sequential likelihood ratio test statistic confirmed that the three-cluster solution significantly outperformed the others (Table 1). Furthermore, K-means clustering set on partitioning 82 observations into three clusters resulted in three subgroups of 51, 21, and 10 patients, respectively. The agreement between the two clustering methods (hierarchical vs. nonhierarchical) in profiling the three clusters was almost perfect ($\kappa = 0.90$); only 4 of 82 patients were classified differently between the two methods (Supplementary Material S6). Supplementary Material S7 depicted the flow diagram of referred and enrolled patients.

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Cognitive, Behavioral, and Brain Structural Correlates of Memory Measures

Cognitive and behavioral measures were available for all patients (n = 183). In this regard, the RAVLT-free recall test or prose recall test scores were strongly associated with the other tests of the neuropsychological battery assessing the memory domain. Moreover, the prose recall test correlated weakly with visuospatial ability domain and moderately with attention and working memory, executive functions, and language domains. RAVLT-free recall test weakly correlated with attention and working memory and with executive functions domains. No correlations were observed for the RAVLT-intrusions and the RAVLT-recognition enhancement. No significant correlations were observed between memory measures and behavioral features (ie, depression, anxiety, apathy, sleep disorders, and fatigue) (Fig. 1).

Brain structural measures were available for 120 patients. In this subsample of patients, we observed statistically significant negative correlations between the RAVLT-intrusions and left caudal anterior cingulate and cortical thickness in right posterior cingulate and positive correlations between RAVLT-recognition enhancement and cortical thickness in left posterior cingulate and right entorhinal cortex. As regards volume data, we observed statistically significant positive correlations between the prose recall test and hippocampus-related left body, left head, left tail, right body, and right tail measures. Similarly, statistically significant positive correlations were observed between the RAVLT-recognition enhancement and volume data of the hippocampus-related left body, left head, right head, and right tail measures. All the statistically significant correlations were weak to moderate. We did not find further significant correlations (Fig. 1).

Intercluster Comparisons

Using Pillai's trace, MANOVA revealed statistically significant differences among all the study groups (Cluster A, B, C, and PD-NC) in memory measures, $V = 0.72$, $F\ (4, 12) = 14.22$, $P < 0.001$, $\eta^2 = 0.24$. Post hoc univariate ANOVAs (Tukey's honest significance test) showed the following (Fig. 2):

- Cluster A (n = 54, 65.85% of MCI group) performed significantly better than Cluster B and C in RAVLT-free recall. Cluster B obtained similar scores

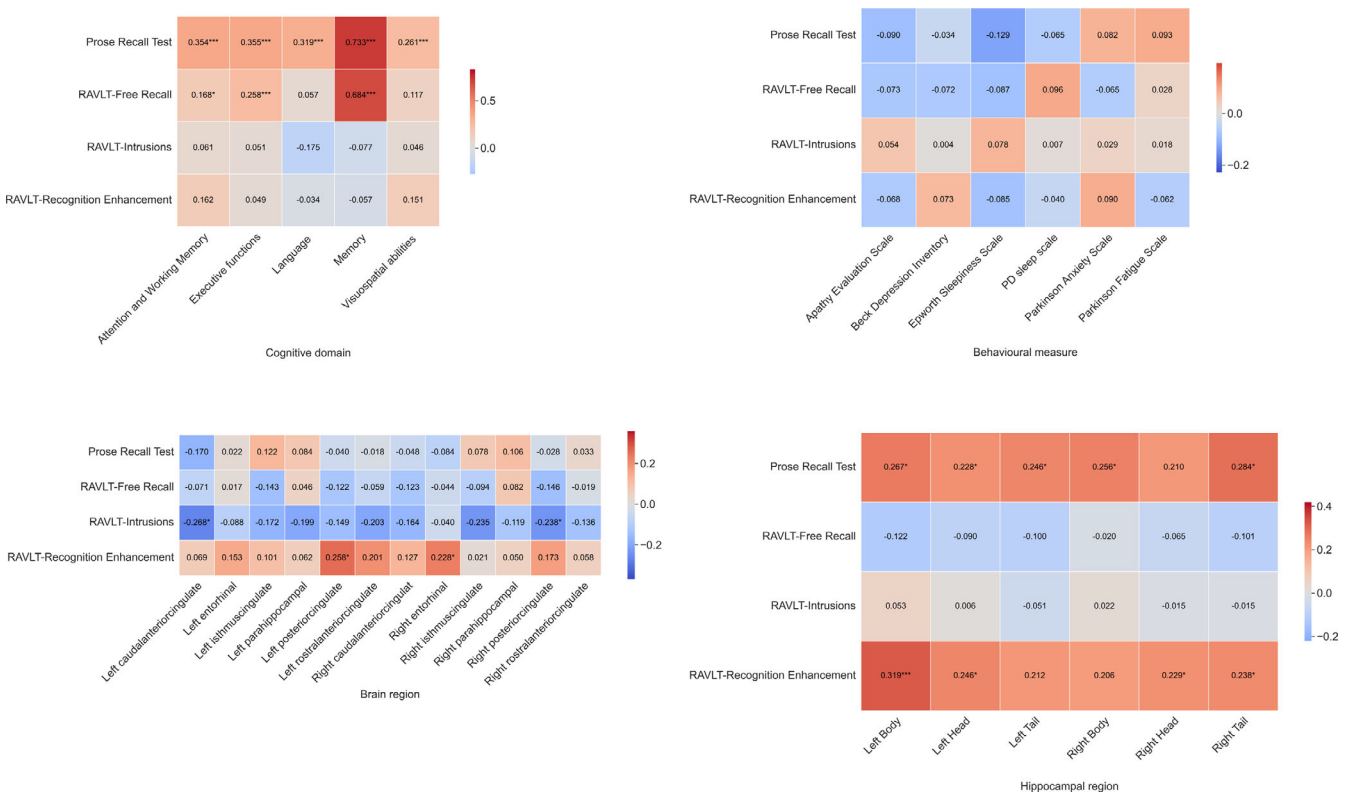

FIG. 1. Heatmaps of the partial Pearson's correlations between the demographic-adjusted Z-scores of the memory measures and the cognitive domains (top left), behavioral measures (top right), cortical thickness data (bottom left), and hippocampal volume data (bottom right); significant correlations ($P < 0.05$ corrected with Benjamini-Hochberg procedure) were indicated with an asterisk (*<0.05, **<0.01, ***<0.001); correlation: $r < 0.10$: negligible; $0.10 \le r < 0.30$: weak; $0.30 \le r < 0.50$: moderate; $r \ge 0.50$: strong; RAVLT, Rey auditory verbal learning test. [Color figure can be viewed at wileyonlinelibrary.com]

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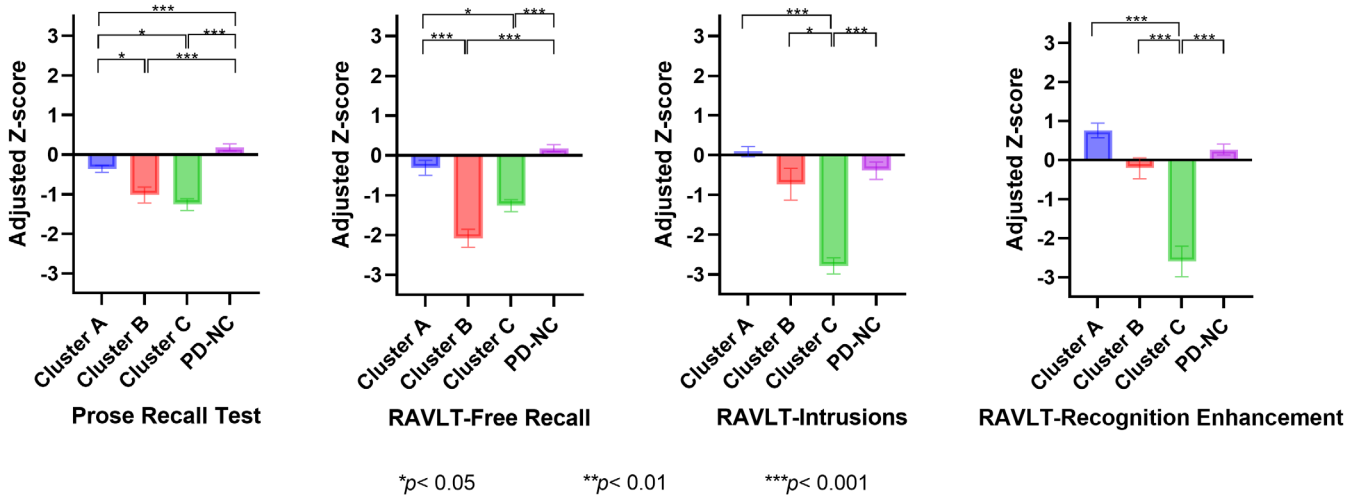

FIG. 2. Comparison among groups in prose recall test and three indices derived from Rey auditory verbal learning test (RAVLT) (free recall, intrusions, recognition enhancement). [Color figure can be viewed at wileyonlinelibrary.com]

to PD-NC in RAVLT-free recall, RAVLT-intrusions, and RAVLT-recognition enhancement;

- Cluster B (n = 19, 23.17% of MCI group) performed like Cluster A and C, but worse than PD-NC in prose recall test. Cluster B did not differ from Cluster C, but had worse performance than Cluster A and PD-NC in RAVLT-free recall. Cluster B was similar to Cluster A and PD-NC, but had better performance than Cluster C in RAVLT-intrusions and RAVLT-recognition enhancement;
- Cluster C (n = 9, 10.97% of MCI group) was similar to Cluster B, but had worse performance than Cluster A and PD-NC in RAVLT-free recall. Cluster C had more RAVLT-intrusions and worse RAVLT-recognition enhancement than Clusters A and B, and PD-NC.

One-way ANOVAs and χ^2 test did not show differences among study groups in clinical, behavioral, and demographic features, except for age at onset and education, as the PD-MCI group had a lower mean educational level and included more patients with late PD onset than the PD-NC group (Table 2). Moreover, the three clusters did not differ from each other in terms of no-memory cognitive measures, but Trail Making Test (TMT). Indeed, the performance on TMT parts A and B worsened from Cluster A, passing for Cluster B, to Cluster C, whereas the PD-NC obtained the best performance (Table 2). In addition, compared to the clusters, PD-NC scored better on the tests exploring all cognitive domains. Finally, among the study groups, Cluster C scored worse on the PDQ-39 (Table 2).

Match between Cluster-Related Memory Phenotypes and AD-like MCI Diagnosis

Table 3 showed the match between the clusters and the presence of naMCI and aMCI, defined according to the AD-type criteria.[41,42] Cluster A had a lower percentage of aMCI and a higher percentage of naMCI relative to Cluster B and C, with no difference between these last two clusters in percentage of aMCI. The motor and non-motor features of aMCI and naMCI were reported in Supplementary Material S8.

Discussion

The main results of the present study demonstrated that it is possible to classify early, de novo patients with PD-MCI as having one of three distinct memory phenotypes: Cluster A (or "memory unimpaired phenotype") without memory impairments, the most prevalent; Cluster B (or "prefrontal executive phenotype") with a mild episodic memory disorder and deficits in tests evaluating encoding and/or retrieval stages,[18,23,24] related to the prefrontal cortex and executive functioning; Cluster C (or "hybrid phenotype") with severe episodic memory disorder because the co-occurrence of deficits in tests evaluating encoding and/or retrieval stages and in those exploring storage stage associated with hippocampal functioning.

The three clusters of de novo PD-MCI patients identified by the present analysis are likely related to the variety of brain structures and neurotransmitters involved in PD pathology (involving not only the dopaminergic system, but also the cholinergic, noradrenergic, and serotonergic systems).[72] About two-thirds of our patients were not affected by memory deficits (Cluster A). This finding is consistent with the Movement Disorder Society (MDS) PD-MCI criteria,[1] which recommended specification of the affected domain(s), because episodic memory function can be impaired in PD, but it is not the prominent cognitive impairment, as in typical AD.[73] The remaining one-third of our

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TABLE 2 *Differences among clusters and patients with Parkison's disease and normal cognition (PD-NC) in demographics, clinical features, no-memory cognitive measures, behavioural measures, and quality of life*

	Mild cognitive impairment							
Variable	**Cluster A (n = 54)**	**Cluster B (n = 19)**	**Cluster C (n = 9)**	**PD-NC (n = 101)**	**F/χ^2**	***P*-value**	**Adj. *P***	**Post-hoc**
Demographics								
Age, years	66.46 ± 8.80	65.00 ± 9.08	70.78 ± 3.15	62.46 ± 8.67	4.44	0.005	0.136	
Education, years	9.39 ± 4.53	10.16 ± 4.29	8.67 ± 3.50	13.76 ± 3.45	18.51	<0.001	**<0.001**	PD-NC > A***, B**, C**
Sex, male	28 (51.9%)	11 (57.9%)	5 (55.6%)	77 (76.2%)	10.54	0.014	0.404	
Clinical features								
Disease duration, years	1.22 ± 0.50	1.78 ± 1.16	1.37 ± 0.74	1.58 ± 0.79	3.51	0.016	0.458	
UPDRS-III	23.79 ± 9.95	25.16 ± 8.39	28.11 ± 6.41	19.37 ± 9.78	4.96	0.002	0.069	
Modified HY stage	1.81 ± 0.51	1.95 ± 0.49	2.11 ± 0.33	1.77 ± 0.55	1.58	0.196	1.000	
Early-onset	1 (1.9%)	1 (5.3%)	0 (0.0%)	10 (9.9%)	4.47	0.214	1.000	
Late-onset	23 (42.6%)	5 (26.3%)	5 (55.6%)	14 (13.9%)	19.69	<0.001	**<0.001**	PD-NC < A***, C**
Cognitive assessment								
Prose recall test	10.50 ± 2.84	8.01 ± 3.49	6.92 ± 1.96	12.71 ± 3.48	19.31	<0.001	**<0.001**	A > B*, C*; PD-NC > A***, B***, C***
RAVLT-free recall	7.01 ± 3.17	3.18 ± 2.22	4.01 ± 2.61	7.67 ± 3.07	14.59	<0.001	**<0.001**	A > B***, C*; PD-NC > B***, C***
RAVLT-intrusions	0.56 ± 1.22	1.54 ± 2.11	4.00 ± 0.72	1.13 ± 2.73	6.22	<0.001	**<0.001**	C > A***, B*, PD-NC***
RAVLT-recognition enh.	5.95 ± 3.31	3.71 ± 2.73	−1.79 ± 2.73	4.83 ± 3.34	15.25	<0.001	**<0.001**	C < A***, B***, PD-NC***
TMT part A	35.00 ± 22.43	51.25 ± 23.65	71.88 ± 30.97	29.86 ± 12.81	19.68	<0.001	**0.002**	B > A**, PD-NC***; C > A***, B*, PD-NC***
Digit span backward	3.78 ± 3.50	3.27 ± 1.35	3.12 ± 0.68	3.86 ± 0.82	0.72	0.537	1.000	
MCST-n. of categories	2.46 ± 1.55	2.68 ± 1.91	1.89 ± 0.92	5.26 ± 1.29	58.45	<0.001	**<0.001**	PD-NC > A***, B***, C***
Letter fluency task	25.24 ± 9.77	23.51 ± 7.81	23.28 ± 10.12	31.03 ± 9.23	7.32	<0.001	**<0.001**	PD-NC > A**, B**
TMT part B	126.34 ± 99.37	202.85 ± 95.65	307.70 ± 112.45	77.23 ± 34.59	42.58	<0.001	**<0.001**	B > A***, PD-NC***; C > A***, B**, PD-NC***; A > PD-NC***
Copying drawings	10.09 ± 2.26	9.97 ± 2.11	10.27 ± 2.24	12.56 ± 1.42	27.81	<0.001	**<0.001**	PD-NC > A***, B***, C**
JOL	19.80 ± 4.05	18.89 ± 5.79	17.67 ± 7.63	25.11 ± 4.42	22.83	<0.001	**<0.001**	PD-NC > A***, B***, C***
Nouns denomination task	9.78 ± 0.49	9.84 ± 0.37	9.87 ± 0.36	9.91 ± 0.42	0.91	0.434	1.000	
Verbs denomination task	8.96 ± 1.22	8.97 ± 1.48	9.41 ± 0.72	9.69 ± 0.73	7.62	<0.001	**<0.001**	PD-NC > A***, B*

(Continues)

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TABLE 2 *Continued*

Variable	Mild cognitive impairment			PD-NC	F/χ^2	*P*-value	Adj. *P*	Post-hoc
	Cluster A (n = 54)	Cluster B (n = 19)	Cluster C (n = 9)	(n = 101)				
Behavioural measures								
Beck depression inventory	7.67 ± 7.83	7.84 ± 5.97	6.89 ± 10.55	7.84 ± 7.20	0.48	0.986	1.000	
Parkinson anxiety scale	9.89 ± 9.36	9.74 ± 7.93	9.22 ± 8.13	10.86 ± 7.70	0.27	0.845	1.000	
Apathy evaluation scale	31.09 ± 8.06	31.37 ± 7.28	32.89 ± 10.97	30.36 ± 7.55	0.37	0.770	1.000	
PD-sleep scale	123.38 ± 18.31	120.59 ± 28.81	113.44 ± 24.24	121.20 ± 25.18	0.45	0.716	1.000	
Epworth sleepiness scale	3.96 ± 3.75	2.63 ± 1.97	6.00 ± 2.29	3.67 ± 2.96	2.48	0.062	1.000	
Parkinson fatigue scale	2.13 ± 1.10	1.73 ± 0.72	2.34 ± 1.10	2.06 ± 0.98	0.92	0.432	1.000	
Quality of life								
PDQ-39	16.96 ± 12.00	13.36 ± 8.15	27.20 ± 18.01	13.15 ± 7.93	5.92	0.001	**0.022**	C > A*, B**, PD-NC***

Note: Data were reported as mean ± standard deviation or count (percentage). Adj-*p* represents *p*-value corrected for multiple comparisons using the Bonferroni procedure, and statistically significant differences are shown in bold.
Abbreviations: HY, Hoehn and Yahr; JOL, Judgement of line orientation test; MCST (Nelson's modification), Modified Card Sorting Test; PDQ-39, 39-item Parkison's disease questionnaire; RAVLT, Rey Auditory Verbal Learning Test; RAVLT-Recognition Enh., RAVLT-Recognition Enhancement; TMT, Trail Making Test; UPDRS, Unified Parkinson's Disease Rating Scale.
*$P < 0.05$;
**$P < 0.01$;
***$P < 0.001$.

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TABLE 3 *Comparison between the partition of the PD-MCI subgroup (n = 82) based on the Alzheimer's disease-type criteria (ie, amnestic/nonamnestic and single/multiple domains) with that resulting from the cluster analysis*

	Mild cognitive impairment					
MCI subtypes	**Cluster A (n = 54)**	**Cluster B (n = 19)**	**Cluster C (n = 9)**	χ^2	***P*-value**	**Post-hoc**
aMCI single domain (n = 0)	0 (0.00%)	0 (0.00%)	0 (0.00%)	–	–	–
naMCI single domain (n = 0)	0 (0.00%)	0 (0.00%)	0 (0.00%)	–	–	–
aMCI multiple domains (n = 35)	13 (24.1%)	15 (78.9%)	7 (77.8%)	13.88	<0.001	A < B*** or C**
naMCI multiple domains (n = 47)	41 (75.9%)	4 (21.1%)	2 (22.2%)	22.38	<0.001	A > B*** or C**

Abbreviations: aMCI, amnestic Mild Cognitive Impairment; naMCI, nonamnestic Mild Cognitive Impairment.
*$P < 0.05$;
**$P < 0.01$;
***$P < 0.001$.

patients with PD-MCI were grouped into two clusters, that is, with encoding-retrieval deficits alone (ie, Cluster B) or in combination with storage impairment (ie, Cluster C). The former, Cluster B (23.17%), showed a mild episodic memory disorder. Indeed, patients of Cluster B achieved low scores in recalling verbal information presented in a list or story format, but their performance improved substantially in recognition tasks, consistent with the idea of inefficient encoding and/or retrieval strategies. These patients also showed few intrusions, as well as patients without memory impairment (Cluster A) and patients with normal cognition (PD-NC). Conversely, the latter, Cluster C (10.97%), was characterized by a more severe "hybrid" episodic memory disorder, in which defective encoding and/or retrieval strategies co-occurred with impaired storage mechanisms, similar to what observed in MCI because AD.[74] These patients had poor performance on memory prose and word list, as the patients included in Cluster B, but did not benefit as much from recognition prompts and made many more intrusion errors than the other clusters.[9] The present findings are consistent with Weintraub et al[18] study, reporting three memory clusters in PD, that is, an "unimpaired" cluster (n = 30) demonstrating intact free recall and few intrusion errors; two clusters with similar impairment on free recall, "impaired retrieval" (n = 22) and "impaired encoding/storage" (n = 11) clusters, with the former being characterized by stronger improvement in recognition tasks and fewer intrusions errors than the "impaired encoding/storage" cluster. In addition, our findings demonstrate that the three memory-related clusters, obtained by an entirely data-driven approach without a priori constraints, are present in early de-novo PD patients with rigorously determined diagnosis of PD-MCI (Level II criteria),[1] in whom the possible biasing effect of pharmacological dopaminergic supply on memory processing was lacking.[75]

Clustering of memory impairments might have a prognostic value in PD-MCI. For example, Chung et al[6] found that reverter PD-MCI patients (ie, patients with MCI at baseline who no longer had a diagnosis of MCI at follow-up) had defective free recall, but could improve with cues on recognition tasks (similar to our Cluster B), whereas non-reverters (ie, patients with persistent MCI both at baseline and follow-up) showed abnormal performance on both free recall and recognition tasks (similar to our Cluster C).[76]

The MRI structural data indirectly support the inter-cluster distinction in terms of prefrontal executive-dependent encoding and/or retrieval deficits alone (Cluster B) or in combination with hippocampus-dependent storage impairment (Cluster C). Indeed, we found that the RAVLT-recognition enhancement (as a measure of storage stage) was significantly associated with hippocampal volumes and cortical thickness in the entorhinal cortex, and Cluster C obtained worse performance than the other clusters and PD-NC in most memory measures, including RAVLT-recognition enhancement. Instead, RAVLT-intrusions (as a measure of encoding-retrieval stages) were related to reduced cortical thickness in the cingulate regions, that modulate hippocampal retrieval processes to prevent unwanted memories from coming to mind,[77] and Cluster C was the most prone to producing intrusions. Moreover, we found that the memory tests requiring verbal recall of information presented in the story (prose recall test) or word list (RAVLT-free recall) formats (as a measure of the encoding-retrieval stages) related to the domain of executive functions which in turn is mediated by prefrontal brain regions. Cluster B and Cluster C achieved significantly worse scores on these memory tests than Cluster A or PD-NC. However, no significant correlations were observed between memory measures and behavioral features (ie, depressive symptoms, anxiety, apathy, sleep disorders, and fatigue).

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Comparing the three clusters on cognitive measures, we observed that the severity of memory deficits worsened with a progressive impairment of attention/executive cognitive functioning in PD-MCI. Deficits in attention/executive functions (assessed by TMT parts A and B) increased from patients with PD-MCI and unimpaired memory (Cluster A), to patients included in Cluster B, and to patients of Cluster C. This scenario is consistent with the main view that cognitive disorders in PD without dementia are primarily mediated by attention/executive dysfunctions,[10,12,78,79] because of dopamine deafferentation of prefrontal-striatal circuitries.[4,5,80] Therefore, it can be argued that the deficits in dopamine-related attention/executive functions contribute to the episodic memory disorder of patients included in both Clusters B and C. Probably, in the former these deficits are the main factor affecting memory recall, whereas in the latter cluster the more severe recall impairment could be co-determined by prefrontal attention/executive deficits and by hippocampal-dependent storage dysfunctions, usually depending on alterations in basal forebrain cholinergic system.[9,11,29,30] The "hybrid phenotype" of patients in Cluster C might hamper compensation for memory impairments and have a detrimental impact on the adaptive ability to life demands (quality of life), whereas the three phenotypes did not differ for visuospatial abilities, language domain, or demographic, clinical, and behavioral features (eg, apathy, depression) as in Weintraub et al's study.[18] It is worth mentioning that the three clusters showed poorer performances in all cognitive domains and lower educational attainment than patients with normal cognition, in line with previous literature.[69]

Although several recent studies classify PD-MCI as amnestic versus non-amnestic, therefore, reflecting an AD-type approach, our results also highlight that this classification might be too simplistic, as the memory deficits in amnestic PD-MCI may have different pathophysiological mechanisms. Indeed, we found that the prevalence of non-amnestic multi-domain MCI was significantly higher in unimpaired memory Cluster A (75.9%) than in Clusters B and C (≈20%), but these two latter clusters, characterized by two distinct memory phenotypes, did not differ in prevalence of amnestic multi-domain MCI (78.9% for Cluster B vs. 77.8% for Cluster C). Therefore, in line with the MDS diagnostic criteria for PD-MCI,[1] our results strongly support the use of a variety of memory measures, including both recall and recognition formats, to delineate the nature of memory impairment in PD and its basis in encoding, storage, and retrieval stages.

Our study has limitations that offer opportunities for further research. First, the age at diagnosis of our cohort (ie, 64 years) was lower than that commonly reported for the international PD consortiums (eg, 71 years for the Parkinson's Incidence Cohorts Collaboration)[81]; this may limit the generalization of our findings and prompt future studies to replicate our results in a more representative study sample. Second, the relatively small sample size did not allow to test the stability of the clustering results by dataset split and to evaluate the contribution of other explanatory variables (eg, mood disorders or sleep disorders) possibly influencing memory functioning. Third, the lack of a comparison group of healthy participants assessed on a comparable neuropsychological test battery did not allow us to comprehend possible differences in cognitive measures between patients with PD and age-, education- and sex-matched healthy adults. Fourth, neuroimaging data were available only for a subset of patients (120 of 183) and our analysis focused on the morphometry and the volumetry of the regions related to memory as available from the standard FreeSurfer pipeline (eg, Papez circuit structures), therefore, limiting exploration of the inter-cluster differences regarding structural neural measures in other brain regions (eg, basal forebrain regions) for which a more robust and tested application of a different analysis pipelines will be needed.[82] Finally, we did not longitudinally evaluate all cohort patients and could not assess the prognostic value of our results and their relationship with biomarkers and genetics.

In summary, the present study adds new evidence to the critical issue of memory deficits in MCI associated with PD and to the definition of tests needed to identify these deficits. A better understanding of specific memory phenotypes at disease onset is relevant to identifying the pathophysiological mechanisms underlying PD-MCI and for guiding appropriate pharmacological and nonpharmacological treatments. Moreover, our data support the independence of memory phenotypes from clinical and behavioral features (eg, apathy, depression) and their differential negative impact on patients' quality of life. Therefore, it is crucial to use a comprehensive neuropsychological battery (ie, Level II),[1] including recall and recognition formats of memory tests, to profile the heterogeneity of memory phenotypes in PD-MCI, which might represent markers for different outcomes of the disease. ■

Data Availability Statement

Research data are not shared.

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Supporting Data

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