



Midbrain-striatal Dopaminergic Trajectories As Predictors Of Verbal Learning Outcomes In Parkinson’s Disease



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Background

Cognitive impairment is a common non-motor feature of Parkinson’s disease (PD), and frontostriatal dysfunction related to dopaminergic degeneration is considered one of its major mechanisms. The Hopkins Verbal Learning Test (HVLT) is useful for assessing verbal learning difficulty, particularly encoding-related impairment. However, it remains unclear whether distinct longitudinal dopaminergic trajectories are associated with different verbal learning outcomes, or whether baseline midbrain dopaminergic integrity contributes to later cognitive performance.

Objective

We aimed to identify latent longitudinal trajectory classes of dopaminergic degeneration using serial I-123 FP-CIT SPECT data in PD and to examine whether these classes were associated with differential cognitive outcomes, with a particular focus on verbal learning performance measured by the HVLT over a 4-year follow-up. We also explored whether baseline midbrain dopaminergic integrity was related to long-term verbal learning outcomes within each trajectory subgroup.

Methods

We analyzed 276 patients with PD from the Parkinson’s Progression Markers Initiative (PPMI). Longitudinal dopaminergic imaging markers were derived from I-123 FP-CIT SPECT, including specific binding ratio (SBR) values in the caudate, putamen, and midbrain. Latent class growth analysis (LCGA) was used to model longitudinal striatal dopaminergic trajectories across the 4-year follow-up period and to identify subgroups with distinct progression patterns. Cognitive performance was assessed using the HVLT, Benton Judgment of Line Orientation (JLO), and Semantic Fluency tests. Baseline and longitudinal cognitive profiles were compared between trajectory classes. In addition, correlation analyses were performed to evaluate the relationship between baseline dopaminergic imaging markers and 4-year cognitive outcomes, with particular attention to encoding-recall characteristics reflected by HVLT performance.

Results

1. Latent Dopaminergic Trajectory Classes and Cognitive Profiles

LCGA identified two distinct longitudinal dopaminergic trajectory classes over 4 years. Class 1 included 241 patients (87.3%) and was characterized by lower baseline dopaminergic reserve with gradual decline over time, whereas Class 2 included 35 patients (12.7%) and showed higher baseline reserve but more rapid longitudinal decline.

Results (Continued)

Despite these distinct imaging trajectories, baseline cognitive performance was generally comparable between the two groups. Baseline HVLT Total Recall did not significantly differ between Class 1 and Class 2 (46.2 ± 11.1 vs. 47.3 ± 10.6 , $p = 0.58$), and baseline Benton JLO and Semantic Fluency scores were also similar (Table 1).

2. Year-4 Cognitive Outcomes According to Trajectory Class

At 4 years, the two classes showed different verbal learning outcomes.

Patients in Class 2 demonstrated significantly higher HVLT Total Recall than those in Class 1 (50.5 ± 10.0 vs. 46.5 ± 11.1 , $p < 0.05$), suggesting relatively preserved long-term verbal learning performance in the high-reserve, rapid-decline subgroup. In contrast, Year-4 HVLT Delayed Recall, Retention, Recognition Discrimination Index, Benton JLO, and Semantic Fluency did not show significant between-class differences (Table 1).

3. Clinical Validation Using Year-4 Cognitive Diagnosis

When patients were stratified by Year-4 cognitive diagnosis, MoCA scores did not significantly differentiate cognitively normal patients from those with MCI or PDD. In contrast, HVLT measures, particularly Year-4 HVLT Total Recall and Delayed Recall, showed significant differences between the two groups. This supports the clinical relevance of HVLT measures for detecting cognitive impairment in this PD cohort (Table 2).

4. Baseline Dopaminergic Availability and Long-term Verbal Learning

Correlation analysis showed that, within Class 2, baseline midbrain SBR was strongly negatively associated with Year-4 HVLT Total Recall ($r = -0.87$, $p < 0.05$). This association was not observed in Class 1 and was not evident for baseline caudate or putamen SBRs. These findings suggest that baseline midbrain dopaminergic availability may be linked to long-term verbal learning outcomes specifically in the high-reserve, rapid-decline trajectory subgroup (Table 3).

Conclusion

Distinct longitudinal dopaminergic trajectory subtypes can be identified in PD using serial FP-CIT SPECT data, and these subtypes are associated with differential verbal learning outcomes over time. A subgroup with higher initial reserve but rapid decline showed better 4-year HVLT Total Recall than the group with lower baseline reserve and gradual decline. In addition, the strong association between baseline midbrain integrity and long-term HVLT performance in this subgroup suggests that midbrain dopaminergic status may serve as an important biomarker for cognitive prognosis, particularly for verbal encoding efficiency. These findings support the value of longitudinal imaging-based phenotyping in understanding cognitive heterogeneity in PD.

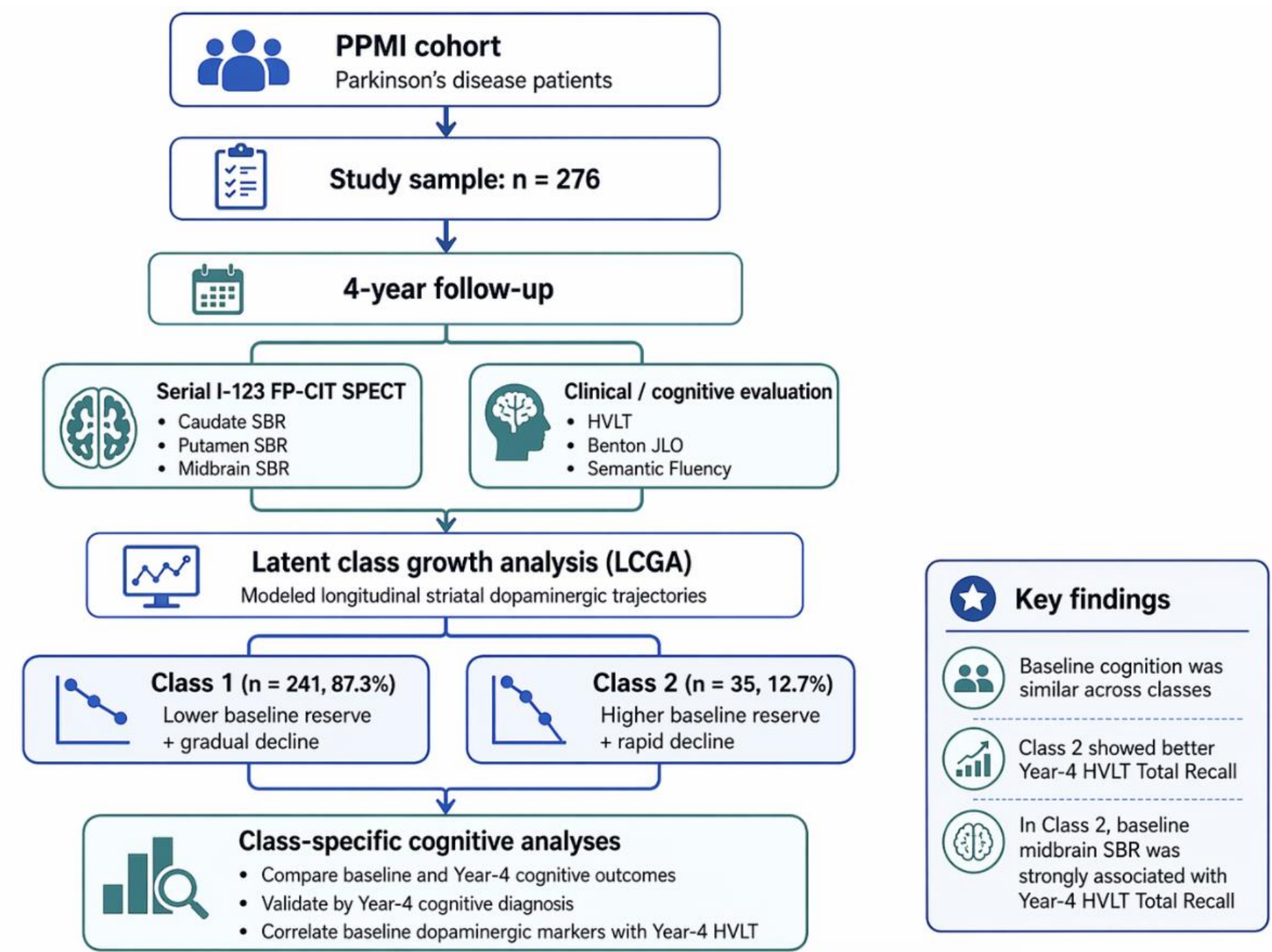


Table 1. Comparison of Baseline and Longitudinal Cognitive Profiles between Distinct Dopaminergic Trajectory Classes.

Variable	Latent Class 1 (n=241)	Latent Class 2 (n=35)	p value
Baseline Benton JLO (Score)	26.3 ± 4.1	26.5 ± 4.2	0.9
Year 4 Benton JLO (Score)	25.8 ± 4.4	26.5 ± 4.2	0.34
Baseline HVLT Total Recall	46.2 ± 11.1	47.3 ± 10.6	0.58
Baseline HVLT Delayed Recall	46.0 ± 10.5	46.9 ± 10.5	0.6
Baseline HVLT Retention	48.6 ± 10.2	19.5 ± 11.4	0.69
Baseline HVLT Recognition Disc. Index	45.3 ± 11.2	46.4 ± 11.4	0.65
Year 4 HVLT Total Recall	46.5 ± 11.1	50.5 ± 10.0	< 0.05
Year 4 HVLT Delayed Recall	46.1 ± 12.4	48.9 ± 10.9	0.24
Year 4 HVLT Retention	46.5 ± 12.0	46.2 ± 11.1	0.83
Year 4 HVLT Recognition Disc. Index	46.4 ± 11.1	47.0 ± 9.5	0.72
Baseline Semantic Fluency (Animals)	10.9 ± 2.8	10.7 ± 2.6	0.64
Baseline Semantic Fluency (Animals, T-score)	51.5 ± 9.6	48.8 ± 8.9	0.12
Year 4 Semantic Fluency (Animals)	10.7 ± 2.8	11.4 ± 2.8	0.29
Year 4 Semantic Fluency (Animals, T-score)	46.4 ± 11.1	47.0 ± 9.5	0.72

Values are presented as mean ± standard deviation. JLO = Benton Judgment of Line Orientation; HVLT = Hopkins Verbal Learning Test; Disc. = discrimination.

Table 3. Correlation Analysis between Baseline Dopaminergic Availability (Midbrain and Putamen SBRs) and 4-Year Verbal Learning Outcomes across Latent Classes.

	Baseline Midbrain SBR		Baseline Caudate SBR		Baseline Putamen SBR	
	Class 1	Class 2	Class 1	Class 2	Class 1	Class 2
Total Recall	$r = -0.17$ ($p = 0.36$)	$r = -0.87^*$ ($p < 0.05$)	$r = 0.10$ ($p = 0.14$)	$r = -0.04$ ($p = 0.81$)	$r = -0.01$ ($p = 0.86$)	$r = -0.01$ ($p = 0.90$)
Delayed Recall	$r = -0.15$ ($p = 0.43$)	$r = -0.52$ ($p = 0.29$)	$r = 0.06$ ($p = 0.40$)	$r = 0.09$ ($p = 0.59$)	$r = -0.06$ ($p = 0.35$)	$r = 0.20$ ($p = 0.25$)
Retention	$r = -0.16$ ($p = 0.41$)	$r = -0.15$ ($p = 0.78$)	$r = 0.14$ ($p = 0.83$)	$r = 0.19$ ($p = 0.27$)	$r = -0.08$ ($p = 0.20$)	$r = 0.31$ ($p = 0.07$)
Recognition Disc. Index	$r = -0.14$ ($p = 0.45$)	$r = 0.02$ ($p = 0.97$)	$r = 0.05$ ($p = 0.47$)	$r = 0.14$ ($p = 0.42$)	$r = -0.02$ ($p = 0.73$)	$r = 0.08$ ($p = 0.64$)

SBR = specific binding ratio; HVLT = Hopkins Verbal Learning Test; Disc. = discrimination.

Table 2. Cognitive Performance Stratified by Clinical Diagnosis (Normal Cognition vs. Cognitive Impairment) at Year 4 Follow-up.

Variable	Normal Cognition (Year 4)	MCI or PDD (Year 4)	p value
Baseline MoCA	27.4 ± 2.1	27.7 ± 1.7	0.58
Year 4 MoCA	26.3 ± 3.1	25.8 ± 3.2	0.48
Baseline HVLT Total Recall	46.9 ± 10.8	42.9 ± 11.6	< 0.05
Baseline HVLT Delayed Recall	46.4 ± 10.5	44.2 ± 10.0	0.22
Baseline HVLT Retention	48.7 ± 10.4	48.3 ± 9.7	0.61
Baseline HVLT Recognition Disc. Index	45.9 ± 11.0	42.6 ± 11.7	0.09
Year 4 HVLT Total Recall	48.5 ± 9.8	39.5 ± 13.7	< 0.001
Year 4 HVLT Delayed Recall	47.8 ± 11.3	39.4 ± 14.6	< 0.001
Year 4 HVLT Retention	47.4 ± 11.2	41.5 ± 14.2	< 0.05
Year 4 HVLT Recognition Disc. Index	47.5 ± 10.0	40.9 ± 13.6	< 0.05

Values are presented as mean ± standard deviation. MCI = mild cognitive impairment; PDD = Parkinson’s disease dementia; MoCA = Montreal Cognitive Assessment; HVLT = Hopkins Verbal Learning Test; Disc. = discrimination.