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Higher Serum Dopamine Is Associated with Greater Hippocampal Volume and Better Cognitive Function Across the Alzheimer's Disease Spectrum

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A B S T R A C T

Purpose: This study aimed to examine diagnostic-stage differences in serum dopamine, bilateral hippocampal volume, and cognitive performance; tested pooled and diagnosis-specific associations of serum dopamine with hippocampal volume and cognition; evaluated serum dopamine-by-diagnosis interactions; and assessed whether bilateral hippocampal volume statistically mediated the association between serum dopamine and cognitive performance.
Methods and Materials: Baseline ADNI data from 428 participants were analyzed. Associations among serum dopamine, MRI-derived bilateral hippocampal volume, and ADAS-Cog13 performance were examined using adjusted pooled and diagnosis-specific regression models. Mediation analysis tested whether bilateral hippocampal volume mediated the association between serum dopamine and cognitive performance. False discovery rate (FDR) correction was applied.
Findings: Serum dopamine and bilateral hippocampal volume declined across diagnostic stages, whereas cognitive impairment increased. In the pooled cohort, higher serum dopamine was associated with larger bilateral hippocampal volume (standardized $\beta = 0.18$, FDR-adjusted $q = .002$) and better cognitive performance ($\beta = -0.17$, $q = .006$). These associations were strongest in participants with mild cognitive impairment (MCI), in whom higher dopamine was associated with both larger hippocampal volume ($\beta = 0.21$, $q = .009$) and better cognitive performance ($\beta = -0.19$, $q = .012$). Larger bilateral hippocampal volume was independently associated with better cognitive performance ($\beta = -0.35$, $q < .001$). Bilateral hippocampal volume significantly mediated the association between serum dopamine and cognitive performance (indirect effect = −0.063), accounting for 37.1% of the total association.
Conclusion: Higher serum dopamine was associated with greater hippocampal volume and better cognitive performance, partly mediated by hippocampal structural integrity.

Keywords: *Dopamine; Cognitive Function; Alzheimer's disease; Hippocampus; Brain Volume; Cognitive Impatient*

1. Introduction

Alzheimer's disease (AD) is defined biologically by amyloid-β and tau pathology, but the clinical expression of the disease also reflects synaptic failure, neurotransmitter disruption, and progressive neurodegeneration (Abubakar et al., 2022; Breijyeh & Karaman, 2020; Stramba-Badiale et al., 2025; Zhang et al., 2025). The hippocampus is particularly relevant because it supports episodic memory and is among the earliest structures to show measurable atrophy across the AD continuum (Mu & Gage, 2011; Rao et al., 2022). Meta-analytic MRI evidence indicates bilateral hippocampal volume loss in mild cognitive impairment (MCI), with substantially greater loss in AD dementia, although the magnitude and laterality of change vary across studies and segmentation methods (Shi et al., 2009). Longitudinal studies similarly show that hippocampal atrophy accelerates from cognitively normal aging through MCI and AD, supporting hippocampal volume as a structural marker of disease severity rather than a change unique to one diagnostic stage (Woodward et al., 2024).

Dopamine is traditionally associated with reward, motivation, and frontostriatal function (Cools, 2008), but it also regulates hippocampal excitability, long-term potentiation, novelty processing, memory encoding, and consolidation (Speranza et al., 2021; Tsetsenis et al., 2023). Experimental work implicates hippocampal D1/D5 and D2-like receptors in the persistence and bidirectional regulation of synaptic plasticity, while the precise source of hippocampal dopamine—ventral tegmental area, locus coeruleus, or both—remains debated (Tsetsenis et al., 2022; Yamasaki & Takeuchi, 2017). Human pharmacological and functional MRI studies support dopaminergic modulation of medial temporal memory networks, but effects are not uniformly beneficial and may depend on baseline dopamine tone, age, receptor availability, and task demands (Clos et al., 2019; Morcom et al., 2010).

Evidence connecting dopamine specifically to hippocampal structure is limited and partly conflicting. In healthy older adults, greater striatal dopamine D2/3 receptor availability has been associated with larger hippocampal volume and better episodic memory, suggesting that dopaminergic integrity and hippocampal preservation may represent coordinated features of brain maintenance (Nyberg et al., 2016). Conversely, not all imaging studies have found consistent relationships between dopamine markers and regional brain volumes, and dopamine–cognition associations may follow nonlinear or receptor-specific patterns. In AD, lower dopamine and dopamine-receptor levels have been reported relative to controls, but the literature is heterogeneous in tissue source, assay, disease stage, and receptor target (Pan et al., 2019).

Additional evidence implicates degeneration of the mesocorticolimbic dopaminergic system in AD-related hippocampal dysfunction. In humans, smaller ventral tegmental area volume and weaker connectivity have been linked to poorer memory and AD-related neurocognitive signatures (De Marco & Venneri, 2018). In experimental AD models, degeneration of ventral tegmental dopamine neurons can produce hippocampal hyperexcitability and memory abnormalities, indicating that reduced dopaminergic input may affect hippocampal physiology before or alongside overt structural loss (Spoleti et al., 2024). Genetic evidence has also linked dopamine-transporter-related variation, together with neurotrophic signaling, to AD pathology and hippocampal atrophy, although such findings do not establish that peripheral dopamine concentrations reflect central dopaminergic activity (Ciampa et al., 2024).

Dopamine may also support cognitive performance through mechanisms that extend beyond structural preservation. In healthy adults, reward anticipation engages dopaminergic midbrain–hippocampal coupling and predicts stronger long-term memory formation, while curiosity enhances hippocampal and midbrain activity and improves both intentional and incidental learning (Wittmann et al., 2005, (Wittmann et al., 2005); Gruber et al., 2014, (Gruber et al., 2014)). Pharmacological enhancement with levodopa has prolonged episodic-memory persistence in older adults, whereas dopamine agonism and antagonism produce age- and baseline-dependent changes in medial temporal and frontostriatal encoding networks (Chowdhury et al., 2012, (Chowdhury et al., 2012); Morcom et al., 2010, (Morcom et al., 2010)). These observations suggest that dopamine can facilitate attention to salient information, strengthen hippocampal encoding, and stabilize newly formed memories; however, the effects are not uniformly beneficial and may follow an inverted-U function in which either insufficient or excessive dopaminergic stimulation impairs performance.

A major knowledge gap is that few studies have directly examined whether serum dopamine is associated with MRI-defined hippocampal volume across the AD clinical spectrum. Serum dopamine is biologically distinct from synaptic dopamine and is influenced by peripheral synthesis,

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metabolism, storage, medications, autonomic activity, renal clearance, and preanalytical conditions. Nevertheless, circulating metabolomic measures may capture systemic processes associated with neurodegeneration and can be integrated with standardized neuroimaging and cognitive phenotyping. Determining whether serum dopamine relates independently to hippocampal volume, and whether that structural measure statistically accounts for part of the dopamine–cognition association, could clarify whether the observed signal is linked to a central AD-relevant phenotype rather than cognition alone.

Accordingly, this study examined diagnostic-stage differences in serum dopamine, bilateral hippocampal volume, and cognitive performance; tested pooled and diagnosis-specific associations of serum dopamine with hippocampal volume and cognition; evaluated serum dopamine-by-diagnosis interactions; and assessed whether bilateral hippocampal volume statistically mediated the association between serum dopamine and cognitive performance.

2. Methods and Materials

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (https://adni.loni.usc.edu/). ADNI was launched in 2003 as a multicenter public–private partnership to determine whether serial neuroimaging, biofluid biomarkers, genetics, and clinical and neuropsychological assessments can be combined to measure progression from normal cognition through MCI to AD. The present study used deidentified baseline data downloaded under an approved ADNI data-use agreement.

2.1. Participants

For this cross-sectional study, ADNI participants were eligible when baseline serum dopamine, structural MRI-derived left and right hippocampal volumes, ADAS-Cog13, clinical diagnosis, demographic information, APOE ε4 genotype, and prespecified imaging and analytic covariates were available. The MRI examination closest to the serum collection visit was selected; when measurements were not obtained on the same date, the interval between serum sampling and MRI was calculated and included in adjusted analyses. Participants with missing core variables, failed MRI processing or quality control, or biologically implausible dopamine values after data-quality review were excluded.

Participants were classified at the corresponding baseline visit as cognitively normal (CN), MCI, or AD dementia according to standard ADNI procedures. Diagnostic classification incorporated clinical history, neurological examination, Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), functional assessment, and education-adjusted delayed recall on Logical Memory II. CN participants had no objective cognitive impairment and a CDR score of 0. Participants with MCI had objective memory impairment, generally preserved daily functioning, and a CDR score of 0.5. Participants with AD dementia fulfilled ADNI criteria for probable AD and demonstrated greater cognitive and functional impairment. ADAS-Cog13 was analyzed as an outcome and was not used to define the diagnostic groups. APOE ε4 carrier status was defined by the presence of at least one ε4 allele.

ADNI generally excludes individuals with major neurological disease other than AD, clinically significant cerebrovascular disease, major psychiatric illness, unstable systemic illness, substance misuse, traumatic brain injury, or other conditions likely to interfere with cognition or study procedures. Written informed consent was obtained from all participants or their authorized representatives at participating sites, and each site obtained institutional review-board approval. Additional information on ADNI recruitment, diagnostic procedures, and study protocols is available from the ADNI website (https://adni.loni.usc.edu/).

2.2. Serum Dopamine Measurements

Serum dopamine concentrations were obtained from ADNI metabolomics data generated by the AD Metabolomics Consortium at Duke University using the Biocrates AbsoluteIDQ p180 and/or MxP Quant 500 targeted metabolomics platforms, according to the dataset available for each ADNI phase. Serum samples were collected, processed, and stored under standardized ADNI biospecimen protocols. The targeted platforms quantify predefined metabolite classes, including biogenic amines, amino acids, acylcarnitines, glycerophospholipids, sphingolipids, and related small molecules.

Dopamine was quantified as a serum biogenic amine using ultra-performance liquid chromatography coupled with tandem mass spectrometry. Serum aliquots were prepared in 96-well plates containing isotopically labeled internal standards, followed by drying, derivatization, extraction, chromatographic separation, and metabolite-

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specific multiple-reaction monitoring. Raw data were processed using TargetLynx and Biocrates MetIDQ software. Calibration standards, internal standards, and pooled quality-control samples were used to support analyte identification, quantitative accuracy, and monitoring of analytical variation and batch effects. Only dopamine measurements passing the ADNI/Duke quality-control procedures were retained. Because dopamine concentrations were right-skewed, values were natural-log transformed and standardized before regression and mediation analyses. Detailed information on the ADNI targeted metabolomics resource is available in St John-Williams et al (St John-Williams et al., 2017).

2.3. *Structural MRI and Bilateral Hippocampal Volume*

Structural MRI was acquired at ADNI sites using standardized sagittal T1-weighted protocols. ADNI1 primarily used 1.5-T scanners, with a subset scanned at 3 T, whereas ADNI-GO/2 and later phases primarily or exclusively used 3-T systems. ADNI performs centralized protocol qualification, image quality control, and phase-specific preprocessing. For ADNI1 and early ADNI2, recommended T1-weighted images underwent gradient-nonlinearity correction, intensity nonuniformity correction, and, where applicable, phantom-based scaling for scanner drift.

Hippocampal volumes were obtained from the ADNI-provided University of California, San Francisco cross-sectional FreeSurfer morphometry dataset corresponding to the participant's MRI examination and ADNI phase. In the established ADNI FreeSurfer workflow, each T1-weighted scan is processed independently with the cross-sectional `recon-all` pipeline. Processing includes motion correction and averaging when repeated acquisitions are available, removal of nonbrain tissue, correction of intensity nonuniformity, affine registration to Talairach space, automated labeling of subcortical structures, and generation of regional volumetric statistics. Hippocampal labels are assigned by FreeSurfer's automated probabilistic subcortical segmentation, and left and right hippocampal volumes are extracted from the `aseg.stats` output. FreeSurfer segmentation outputs undergo visual quality control; scans with severe segmentation errors or processing failure are omitted rather than manually edited in the standard ADNI-derived dataset (Fischl, 2012; Schwarz et al., 2016).

Bilateral hippocampal volume was calculated as the sum of the left and right hippocampal volumes. Estimated total intracranial volume (eTIV), generated by FreeSurfer from the atlas-scaling transformation, was included as a covariate rather than using a simple hippocampal-volume/eTIV ratio. MRI field strength, ADNI phase or FreeSurfer processing version, and the interval between MRI and serum sampling were also considered to reduce acquisition- and processing-related confounding.

2.4. *Cognitive Assessment*

Cognitive performance was assessed using the ADAS-Cog13 (Connor & Schafer, 1998; Kueper et al., 2018). The instrument extends the original ADAS-Cog by adding delayed word recall and number-cancellation tasks and assesses memory, language, praxis, orientation, and attention. Total scores were analyzed continuously, with higher scores indicating poorer cognitive performance.

2.5. *Statistical Analysis*

Analyses were conducted using SPSS version 27.0 and Python. Continuous variables are presented as mean ± standard deviation and categorical variables as number and percentage. Distributions were evaluated using histograms and Q–Q plots; serum dopamine was natural-log transformed and standardized, and influential observations were examined using standardized residuals, leverage, and Cook's distance. Diagnostic-group differences were tested using one-way analysis of variance or Kruskal–Wallis tests for continuous variables and chi-square tests for categorical variables, followed by multiplicity-adjusted pairwise comparisons. Adjusted general linear models compared serum dopamine, bilateral hippocampal volume, and ADAS-Cog13 across CN, MCI, and AD groups. Multivariable linear regression examined associations of serum dopamine with bilateral hippocampal volume and ADAS-Cog13 and the association of hippocampal volume with ADAS-Cog13. Pooled models adjusted for age, sex, education, APOE ε4 status, and diagnosis; hippocampal-volume models additionally adjusted for eTIV, MRI field strength, ADNI phase or FreeSurfer processing version, metabolomics batch, and the serum–MRI interval. Diagnosis-specific models omitted diagnosis but retained the remaining applicable covariates. Effect modification was evaluated by serum dopamine × diagnosis interaction terms in pooled models. Mediation analysis tested bilateral hippocampal volume as a statistical mediator of the serum dopamine–ADAS-Cog13 association, using 10,000 bias-corrected bootstrap resamples to estimate the indirect effect and 95%

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confidence interval. The pooled mediation model used the same covariate structure as the hippocampal-volume models; diagnosis-specific mediation was considered secondary. Standardized coefficients, 95% confidence intervals, p values, false-discovery-rate-adjusted q values, and partial or adjusted R^2 values were reported as appropriate. The Benjamini–Hochberg procedure controlled the false discovery rate within prespecified families of tests. All tests were two-sided; $q < 0.05$ and a bootstrap confidence interval excluding zero were considered statistically significant.

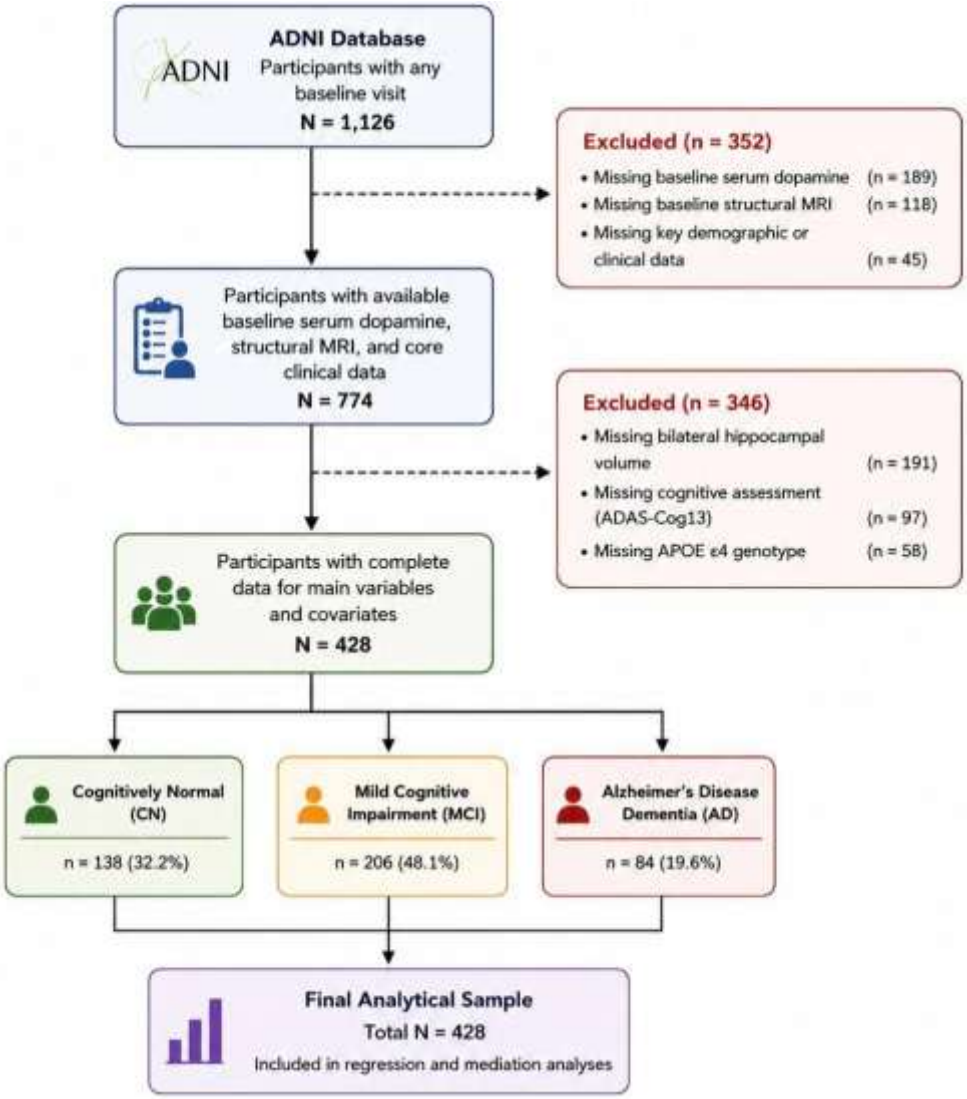
3. Findings and Results

3.1. Participant Selection and Characteristics

The participant-selection process is shown in Figure 1. The final cohort comprised CN individuals, participants with MCI, and patients with AD dementia. Diagnostic groups differed in age, education, APOE ε4 carrier frequency, bilateral hippocampal volume, serum dopamine, and ADAS-Cog13 performance, whereas the sex distribution was comparable. As expected, the AD group showed the highest cognitive impairment and the smallest hippocampal volume, while the CN group showed the most favorable cognitive and structural profile (Table 1).

Figure 1

Participant-selection flowchart



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Table 1

Participant characteristics by clinical diagnosis

Characteristic	CN (n = 138)	MCI (n = 206)	AD (n = 84)	p value
Age, years	73.1 ± 5.9	73.8 ± 7.3	77.0 ± 7.5	<0.001
Women, n (%)	70 (50.7)	88 (42.7)	41 (48.8)	0.287
Education, years	16.5 ± 2.6	15.8 ± 2.8	15.2 ± 3.0	0.002
APOE ε4 carrier, n (%)	35 (25.4)	105 (51.0)	52 (61.9)	<0.001
Serum dopamine, standardized	0.20 ± 0.91	−0.02 ± 0.97	−0.19 ± 1.08	0.001
Left hippocampal volume, mL	3.65 ± 0.43	3.29 ± 0.50	2.76 ± 0.55	<0.001
Right hippocampal volume, mL	3.60 ± 0.42	3.25 ± 0.49	2.72 ± 0.54	<0.001
Bilateral hippocampal volume, mL	7.25 ± 0.80	6.54 ± 0.92	5.48 ± 1.02	<0.001
ADAS-Cog13	6.0 ± 3.2	12.6 ± 6.4	22.4 ± 8.1	<0.001

Values are mean ± SD or n (%). CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease dementia; APOE, apolipoprotein E; ADAS-Cog13, 13-item Alzheimer's Disease Assessment Scale–Cognitive Subscale. Bold values indicate statistical significance.

3.2. Diagnostic-Group Differences in Dopamine, Hippocampal Volume, and Cognition

After covariate adjustment, serum dopamine differed across diagnostic groups and showed a progressive decline across the clinical spectrum. Bilateral hippocampal volume was progressively smaller from CN to MCI and AD, whereas ADAS-Cog13 scores increased across diagnostic stages. Pairwise analyses confirmed marked structural and cognitive differences between groups. Dopamine differences were most apparent between CN and AD, while the contrast between MCI and AD was less pronounced (Table 2 and Figure 2).

Table 2

Adjusted pairwise diagnostic-group comparisons

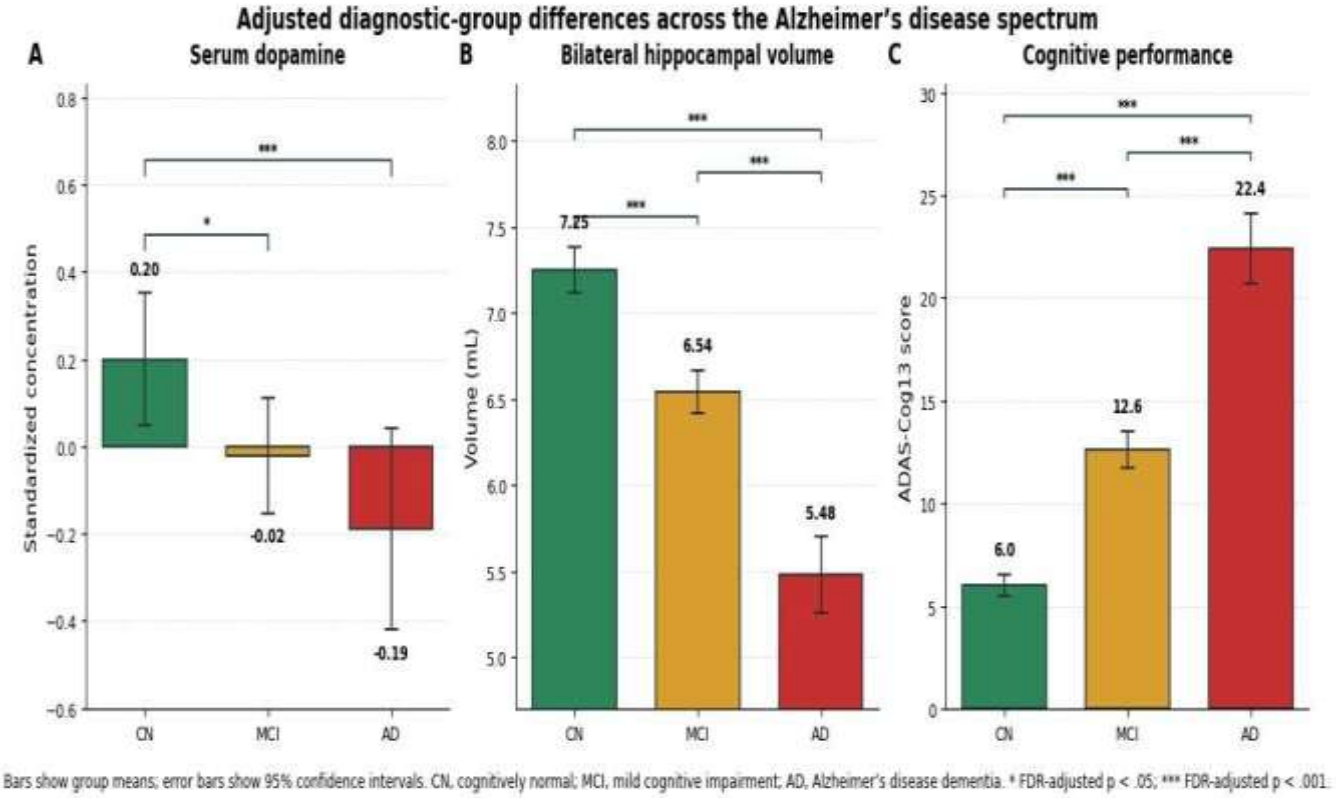
Outcome	Contrast	Adjusted difference	95% CI	Adjusted p	Hedges' g
Serum dopamine	CN vs MCI	0.22	0.04 to 0.40	0.012	0.22
	CN vs AD	0.39	0.15 to 0.63	<0.001	0.39
	MCI vs AD	0.17	−0.05 to 0.39	0.168	0.17
Bilateral hippocampal volume	CN vs MCI	0.71 mL	0.51 to 0.91	<0.001	0.79
	CN vs AD	1.77 mL	1.50 to 2.04	<0.001	1.94
	MCI vs AD	1.06 mL	0.82 to 1.30	<0.001	1.09
ADAS-Cog13	CN vs MCI	−6.60	−7.78 to −5.42	<0.001	−1.17
	CN vs AD	−16.40	−18.05 to −14.75	<0.001	−2.45
	MCI vs AD	−9.80	−11.29 to −8.31	<0.001	−1.33

Differences are first group minus second group. Dopamine is standardized. Pairwise p values were multiplicity-adjusted. Higher ADAS-Cog13 scores indicate worse cognition. Bold values indicate statistical significance.

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Figure 2

Adjusted serum dopamine, bilateral hippocampal volume, and ADAS-Cog13 across diagnostic groups.



3.3. *Association Between Serum Dopamine and Bilateral Hippocampal Volume*

Higher serum dopamine was independently associated with larger bilateral hippocampal volume in the pooled cohort after adjustment for demographic, genetic, diagnostic, intracranial-volume, and technical covariates. Diagnosis-stratified analyses indicated that the association was most evident in MCI. Associations in CN and AD were directionally positive but did not survive multiple-testing correction. The overall dopamine × diagnosis interaction was not significant, indicating insufficient evidence that the association differed statistically across diagnostic groups (Table 3 and Figure 3).

Table 3

Associations between serum dopamine and bilateral hippocampal volume

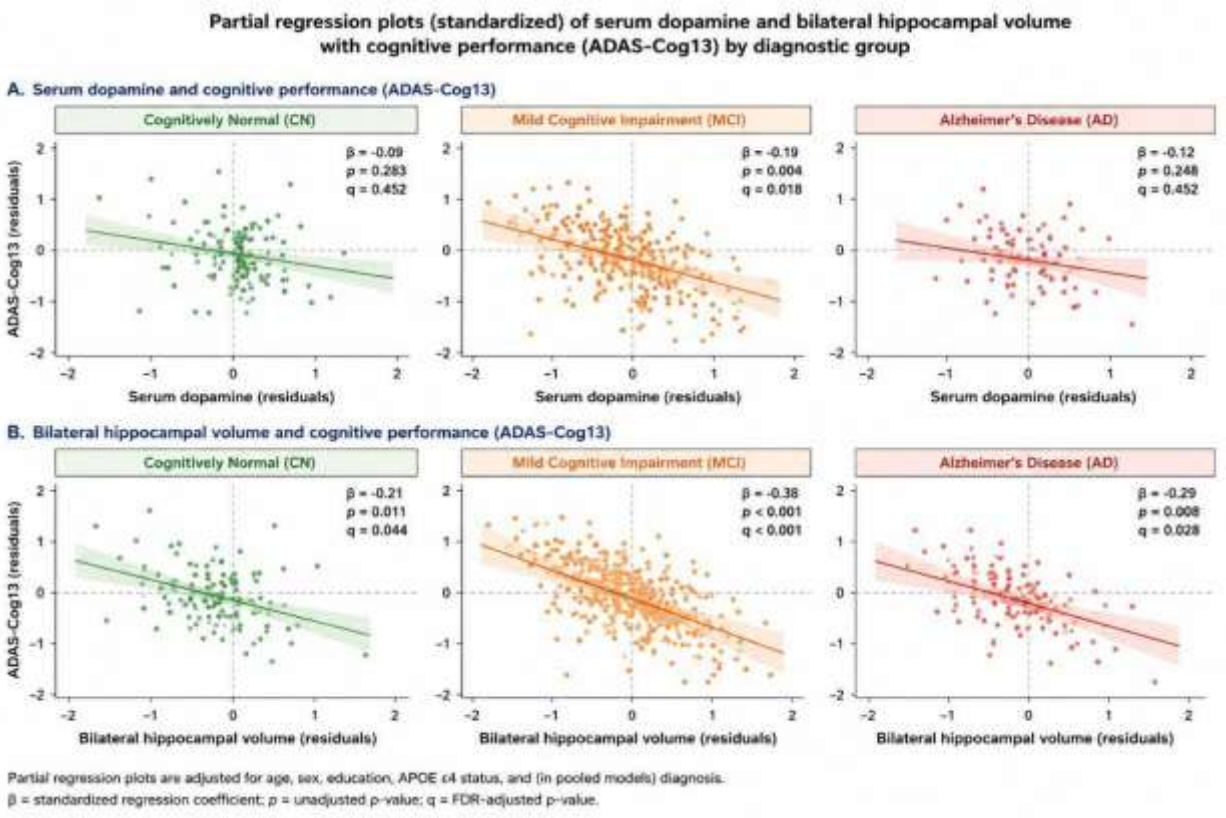
Analysis	Standardized β	95% CI	Raw p	FDR q	Partial R^2
Pooled	0.18	0.08 to 0.28	<0.001	0.002	0.025
CN	0.09	−0.06 to 0.24	0.238	0.238	0.006
MCI	0.21	0.08 to 0.34	0.002	0.009	0.034
AD	0.13	−0.07 to 0.33	0.198	0.238	0.017
Dopamine × diagnosis interaction	—	—	0.184	0.238	0.004

The pooled model adjusted for age, sex, education, APOE ε4, diagnosis, eTIV, ADNI phase/metabolomics batch, MRI field strength or processing version, and serum–MRI interval. Diagnosis-specific models omitted diagnosis. Bold values indicate statistical significance.

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Figure 3

Adjusted associations between serum dopamine and bilateral hippocampal volume in the pooled cohort and diagnostic groups



3.4. Associations of Serum Dopamine and Hippocampal Volume with Cognitive Performance

Higher serum dopamine was associated with better cognitive performance in the pooled cohort. The diagnosis-specific association was most evident in MCI, whereas associations in CN and AD were not significant after FDR correction. Larger bilateral hippocampal volume showed a stronger inverse association with cognitive performance and remained independently associated with cognition after adjustment for serum dopamine. The hippocampal-volume association was significant in the pooled cohort and within MCI and AD. Formal interaction analyses did not demonstrate robust diagnostic differences in either association (Table 4).

Table 4

Associations of serum dopamine and bilateral hippocampal volume with ADAS-Cog13

Predictor	Analysis	Standardized β	95% CI	Raw p	FDR q	Partial R^2
Dopamine → ADAS-Cog13	Pooled	−0.17	−0.28 to −0.06	0.003	0.006	0.020
	CN	−0.08	−0.23 to 0.07	0.292	0.292	0.005
	MCI	−0.19	−0.32 to −0.06	0.004	0.012	0.028
	AD	−0.12	−0.32 to 0.08	0.236	0.283	0.014
Hippocampal volume → ADAS-Cog13	Pooled	−0.35	−0.45 to −0.25	<0.001	<0.001	0.090
	CN	−0.14	−0.29 to 0.01	0.067	0.101	0.018
	MCI	−0.32	−0.44 to −0.20	<0.001	<0.001	0.078
	AD	−0.29	−0.47 to −0.11	0.002	0.008	0.066

Hippocampal-volume models additionally adjusted for serum dopamine. Higher ADAS-Cog13 scores indicate worse cognitive performance. Bold values indicate statistical significance.

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3.5. *Mediation Analysis*

Bilateral hippocampal volume significantly accounted for part of the association between serum dopamine and cognitive performance in the pooled cohort. Serum dopamine was positively associated with hippocampal volume, and larger hippocampal volume was associated with better cognitive performance after adjustment for dopamine. The direct dopamine–ADAS-Cog13 association was attenuated but remained significant after inclusion of hippocampal volume, supporting partial statistical mediation. The indirect association was also evident in MCI but not in CN or AD after correction for multiple testing (Table 5 and Figure 4).

Table 5

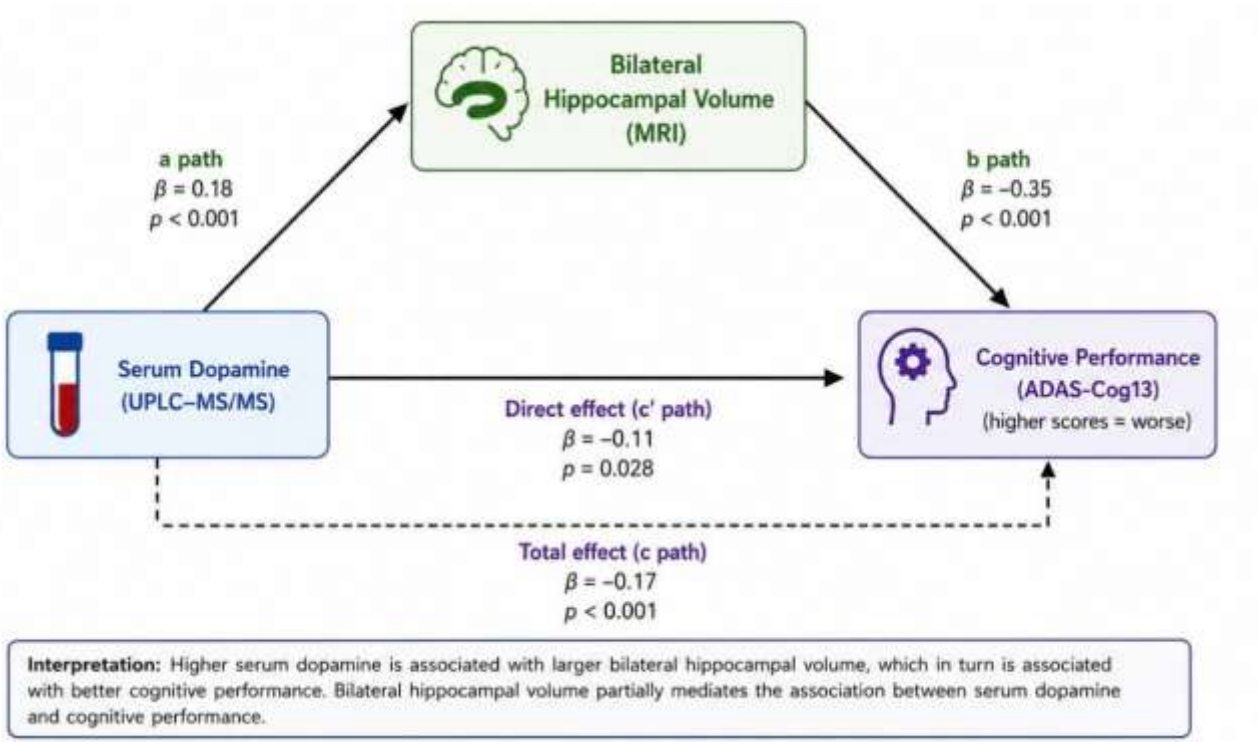
Pooled mediation model

Effect	Standardized estimate	95% CI	p value/inference
Path a: dopamine → hippocampal volume	0.180	0.080 to 0.280	<0.001
Path b: hippocampal volume → ADAS-Cog13	−0.350	−0.450 to −0.250	<0.001
Total effect, c	−0.170	−0.280 to −0.060	0.003
Direct effect, c′	−0.107	−0.204 to −0.010	0.031
Indirect effect, a × b	−0.063	−0.108 to −0.027	Bootstrap CI excludes zero
Proportion statistically accounted for	37.1%	—	—

The indirect effect was estimated using 10,000 bias-corrected bootstrap resamples. The mediation model adjusted for age, sex, education, APOE ε4, diagnosis, eTIV, ADNI phase/metabolomics batch, MRI technical variables, and serum–MRI interval. Cross-sectional mediation does not establish temporal or causal mediation. Bold values indicate statistical significance.

Figure 4

Cross-sectional mediation model relating serum dopamine, bilateral hippocampal volume, and ADAS-Cog13



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4. Discussion and Conclusion

In this cross-sectional study, serum dopamine, bilateral hippocampal volume, and cognitive performance showed graded differences across CN participants, individuals with MCI, and patients with AD dementia. Higher serum dopamine was independently associated with larger bilateral hippocampal volume and better cognitive performance in the pooled cohort, and the diagnosis-specific pattern was most evident in MCI. Bilateral hippocampal volume was itself strongly related to cognitive performance and statistically accounted for part of the dopamine–cognition association. Together, these findings connect a circulating dopaminergic measure with an AD-relevant structural phenotype and suggest that hippocampal integrity may help explain why interindividual differences in serum dopamine track cognitive function.

These findings should be interpreted as cross-sectional associations rather than a temporal or causal sequence. The mediation model does not establish that higher serum dopamine preserves hippocampal tissue, that hippocampal atrophy transmits a biological effect of dopamine to cognition, or that increasing peripheral dopamine would improve clinical outcomes. Reverse and bidirectional explanations remain possible: neurodegeneration may alter central and peripheral catecholamine regulation, disease-related behavioral or autonomic changes may affect serum dopamine, and unmeasured systemic factors may influence dopamine, brain structure, and cognition simultaneously. The indirect effect therefore provides a coherent statistical decomposition of the observed associations, not proof of mechanistic mediation.

The strongest foundation for a dopamine–hippocampus relationship comes from experimental studies of synaptic plasticity. Dopamine acting at hippocampal D1/D5 receptors facilitates late-phase long-term potentiation, synaptic tagging and capture, and the protein-synthesis-dependent stabilization of memories, whereas D2-like receptors modulate excitability and can bidirectionally regulate plasticity according to receptor distribution, timing, and network state (Caragea & Manahan-Vaughan, 2022; Hansen & Manahan-Vaughan, 2014; Jay, 2003). More recent syntheses emphasize that hippocampal dopamine is supplied not only by the ventral tegmental area but also, under some conditions, by catecholaminergic locus-coeruleus projections, creating complementary routes through which novelty and salience can stabilize hippocampus-dependent memories (Duszkiewicz et al., 2019; Takeuchi et al., 2016; Tsetsenis et al., 2022). These cellular and circuit findings make the positive association between serum dopamine and hippocampal volume biologically plausible, although they concern local neural signaling rather than peripheral dopamine concentrations.

Human functional and pharmacological studies provide complementary evidence that dopamine can enhance hippocampus-dependent cognition, but they also reveal important boundary conditions. Reward anticipation increases coordinated activation of dopaminergic midbrain and hippocampal regions and predicts improved long-term declarative memory (Wittmann et al., 2005). Curiosity similarly recruits the hippocampus and midbrain and improves memory for both target and incidental information (Gruber et al., 2014). In older adults, levodopa enhanced the persistence of weakly encoded episodic memories, consistent with dopamine-dependent consolidation rather than a nonspecific immediate performance effect (Chowdhury et al., 2012). By contrast, bromocriptine and sulpiride altered encoding-related activity in an age- and region-dependent manner, and subsequent work showed that dopaminergic effects on memory specificity vary with baseline performance and age (Abdulrahman et al., 2017; Morcom et al., 2010). Thus, the present association with better cognitive performance is consistent with facilitation of hippocampal encoding and consolidation, but it should not be interpreted as evidence that more dopamine is invariably beneficial.

Dopamine may improve cognitive function through several partially separable processes. During encoding, dopaminergic signaling increases the priority assigned to novel, motivationally relevant, or rewarding information and strengthens communication among the hippocampus, midbrain, striatum, and prefrontal cortex (Mehta & Riedel, 2006; Seamans & Robbins, 2009). After encoding, D1/D5-dependent signaling supports persistence of hippocampal synaptic changes, allowing initially labile representations to survive over longer intervals (Hansen & Manahan-Vaughan, 2014; Rossato et al., 2009). Dopamine also contributes to attention, cognitive flexibility, working-memory updating, and goal-directed behavior through frontostriatal and mesocortical circuits; these functions can indirectly improve performance on multidomain cognitive measures by supporting task engagement, error monitoring, and strategic retrieval (Westbrook & Braver, 2016). The association observed here may therefore reflect a combination of hippocampal memory processes and broader executive–

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motivational influences rather than a single cognitive mechanism.

At the same time, dopaminergic modulation follows a nonlinear, context-sensitive pattern. Human and experimental evidence supports an inverted-U relationship in which cognitive performance is optimized within an intermediate range of receptor stimulation, while low dopamine produces insufficient signal amplification and excessive stimulation increases neural noise or destabilizes working-memory representations (Cools & D'Esposito, 2011; Vijayraghavan et al., 2007). Receptor subtype, regional receptor density, age, baseline performance, disease stage, and concurrent noradrenergic signaling can all shift this optimum. This framework may explain why the pooled association was clearer than associations in every diagnostic group and why MCI, rather than CN or established AD dementia, showed the most evident diagnosis-specific pattern. It also cautions against translating an observational serum association into a simple pharmacological prediction.

Direct structural evidence linking dopamine to hippocampal volume remains limited. In healthy older adults, multimodal PET–MRI studies have related preserved dopamine D2/3 receptor availability to hippocampal–striatal network integrity and episodic memory, supporting coordinated maintenance of dopaminergic and medial temporal systems (Nyberg et al., 2016). Other PET–MRI work has shown associations between striatal D2/3 receptor availability and selected subcortical volumes, although effects differ by radioligand, receptor state, age, and anatomical region and are not uniformly observed for the hippocampus (Caravaggio et al., 2017).These studies measured receptor availability rather than circulating dopamine and often involved cognitively healthy samples, making them methodologically distinct from the present study. Nevertheless, their convergence with our findings supports the broader proposition that dopaminergic integrity and structural brain maintenance are related, while the inconsistencies underscore that the relationship is unlikely to be anatomically or biologically uniform.

Evidence from aging and neurodegenerative disorders also suggests that dopamine-related cognitive impairment frequently coexists with hippocampal abnormalities. Structural MRI studies in Parkinsonian disorders have reported hippocampal atrophy in patients with cognitive impairment and associations between hippocampal loss and memory deficits, although these studies cannot determine whether dopaminergic denervation causes hippocampal degeneration or whether both reflect parallel disease processes (Ibarretxe-Bilbao et al., 2009). In normal aging, reductions in dopamine receptors and transporters accompany declines in memory-system specificity, and pharmacological manipulation can partly alter age-related hippocampal dedifferentiation (Abdulrahman et al., 2017). Such findings are compatible with the present results but differ in disease context, dopamine measure, and imaging endpoint; consequently, they provide convergent rather than directly confirmatory evidence.

Within AD, prior work has generally focused on dopaminergic nuclei, receptor expression, postmortem neurochemistry, or cerebrospinal-fluid metabolites rather than serum dopamine combined with hippocampal morphometry. A systematic review and network meta-analysis reported lower dopamine and reduced D1 and D2 receptor measures in AD compared with controls, but substantial heterogeneity arose from differences in tissue source, analytical method, receptor target, medication exposure, and clinical stage (Pan et al., 2019). Human MRI studies have linked smaller ventral tegmental area volume and disrupted mesocorticolimbic connectivity to poorer memory and AD-related neurocognitive signatures (De Marco & Venneri, 2018). Experimental AD studies further indicate that ventral tegmental dopamine-neuron degeneration can precede or promote hippocampal hyperexcitability and memory dysfunction (Spoleti et al., 2024). Our findings extend this literature by relating a peripheral dopamine measure to MRI-defined hippocampal volume, but they do not show that serum dopamine indexes ventral tegmental degeneration or synaptic hippocampal dopamine.

One probable mechanism linking lower dopaminergic integrity to smaller hippocampal volume involves impaired activity-dependent trophic support. D1/D5 receptor activation engages cyclic-AMP/protein-kinase-A signaling, CREB-dependent transcription, synaptic tagging, and synthesis of plasticity-related proteins (Chua et al., 2026); these pathways interact with brain-derived neurotrophic factor signaling and are important for maintenance of dendritic spines, synaptic efficacy, and memory consolidation (Jay, 2003; Yagishita et al., 2014). Chronic attenuation of these signals could reduce the capacity of hippocampal circuits to stabilize synapses and adapt to metabolic or pathological stress. In AD, where amyloid-β, tau, excitotoxicity, and network hyperactivity already compromise hippocampal neurons, reduced dopaminergic modulation could lower neural resilience and amplify structural vulnerability. The observed association with larger

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hippocampal volume is consistent with this model, although total MRI volume cannot distinguish neuronal loss, dendritic simplification, synaptic depletion, glial changes, or other microstructural processes.

A second plausible mechanism involves interactions among dopamine, network activity, inflammation, oxidative stress, and vascular–metabolic regulation (Channer et al., 2023; Lisco et al., 2023). Physiological dopamine can restrain or reshape inflammatory signaling through receptor-dependent effects on microglia and immune cells, regulate hippocampal excitability, and influence cerebral energy use (Channer et al., 2023; Gurram et al., 2023). Conversely, dopamine metabolism can generate reactive intermediates, and excessive cytosolic dopamine may become neurotoxic; therefore, the biological consequence depends on compartment, concentration, receptor balance, and antioxidant capacity (Bucher et al., 2024; Meiser et al., 2013). Peripheral dopamine may additionally reflect sympathetic, renal, gastrointestinal, or metabolic states that themselves relate to brain aging. These competing pathways offer a reason to view serum dopamine as a systems-level correlate rather than a direct measure of beneficial central neurotransmission. Future studies integrating serum measures with dopamine-sensitive PET, cerebrospinal-fluid catecholamine metabolites, inflammatory markers, and longitudinal MRI would be needed to determine which mechanism best accounts for the association.

The diagnostic pattern may be clinically informative. MCI represents a stage in which hippocampal atrophy and cognitive impairment are established but remain heterogeneous, leaving sufficient structural and cognitive variability for dopamine-related differences to be detected (Ritsner, 2009; Rivas-Vazquez et al., 2004). In CN participants, restricted ranges and ceiling effects may weaken observable associations, whereas in AD dementia, advanced hippocampal damage, widespread cortical pathology, medication exposure, and floor effects in residual neural reserve may reduce the relative contribution of dopamine. Importantly, significance in MCI but not in the other groups does not by itself demonstrate a true difference in slopes; the formal interaction models are therefore more informative than comparing subgroup p values. The pattern nevertheless supports further longitudinal evaluation of dopamine–hippocampal coupling during the prodromal phase.

The mediation finding offers a coherent structural interpretation of the dopamine–cognition relationship. Hippocampal atrophy is consistently associated with progression from normal aging to MCI and AD and with memory-related impairment (Schuff et al., 2009; Shi et al., 2009). In the present model, higher serum dopamine was related to larger hippocampal volume, which in turn was related to better cognitive performance. The persistence of a direct dopamine association after inclusion of hippocampal volume suggests that hippocampal structure explains only part of the relationship. Remaining pathways may include frontostriatal function, attention, motivation, cortical network efficiency, neurovascular factors, or unmeasured disease biology. Thus, the mediation result is more consistent with partial convergence of structural and neurotransmitter-related processes than with a single linear mechanism.

From a biomarker perspective, serum dopamine is unlikely to function as a stand-alone indicator of central dopaminergic activity. Peripheral dopamine has multiple sources, crosses the blood–brain barrier poorly, and is sensitive to medications, autonomic state, renal handling, diet, sampling conditions, and metabolomic batch (Kawatra et al., 2024). Its value may instead lie in multimodal models in which circulating metabolites are interpreted alongside MRI, amyloid and tau biomarkers, genetics, and clinical measures. Replication would be particularly convincing if serum dopamine predicted subsequent hippocampal atrophy or cognitive decline and if the association were concordant with central dopaminergic markers. Until then, serum dopamine should be viewed as an accessible exploratory correlate of an AD-relevant structural–cognitive phenotype rather than a validated surrogate of brain dopamine.

Several limitations should be considered. The cross-sectional design precludes inference about temporal ordering, progression, or causality, and the mediation analysis represents a statistical indirect association only. Serum dopamine is a peripheral measure that may not reflect central dopamine synthesis, release, receptor availability, or hippocampal exposure. Residual confounding may remain from medications, renal function, autonomic activity, cardiovascular factors, diet, fasting status, sample handling, and unmeasured comorbidity. MRI data were acquired across ADNI phases, scanner platforms, field strengths, and FreeSurfer processing versions; although standardized ADNI procedures, quality control, and covariate adjustment reduce this concern, measurement heterogeneity cannot be eliminated. Automated hippocampal segmentation may be less accurate in advanced atrophy, and bilateral volume may obscure lateralized or subfield-specific relationships. Complete-case selection may introduce bias, diagnosis-

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specific mediation models may have limited power, and the highly selected ADNI cohort may not represent community populations or diverse clinical settings. Future studies should use longitudinal designs to test whether serum dopamine predicts subsequent hippocampal atrophy and cognitive decline; replicate findings in independent and more diverse cohorts; harmonize MRI processing; evaluate hippocampal subfields and other dopamine-sensitive regions; incorporate amyloid, tau, neurodegeneration, vascular, and inflammatory biomarkers; and compare serum dopamine with direct or proximal measures of central dopaminergic integrity.

Higher serum dopamine was associated with larger bilateral hippocampal volume and better cognitive performance across the AD clinical spectrum, with the clearest diagnosis-specific pattern in MCI. Bilateral hippocampal volume independently related to cognitive function and statistically accounted for part of the dopamine–cognition association. These findings support a link among peripheral dopamine, hippocampal structural integrity, and cognition, while longitudinal and multimodal studies are required to determine temporal direction, central specificity, and clinical utility.

Abbreviations

AD, Alzheimer's disease; ADAS-Cog13, 13-item Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE, apolipoprotein E; CI, confidence interval; CN, cognitively normal; eTIV, estimated total intracranial volume; FDR, false discovery rate; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; UPLC-MS/MS, ultra-performance liquid chromatography–tandem mass spectrometry.

Authors' Contributions

Maryam Zare: Literature search and manuscript preparation. Dr. Behnsm Safarpour Lima: Supervision and revision of the manuscript. All authors read and approved the final manuscript.

Declaration

In order to correct and improve the academic writing of our paper, we have used the language model ChatGPT.

Transparency Statement

The data used in this research were obtained from the Alzheimer's Disease Neuroimaging Initiative and are available to qualified researchers following approval of a data-use application and compliance with the ADNI Data Use Agreement.

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Declaration of Interest

The authors report no conflict of interest.

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Ethical Considerations

This study was conducted using deidentified ADNI data. ADNI was approved by the institutional review board at each participating center and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants or their legally authorized representatives before study procedures.

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