Do Dopaminergic Genes Modulate Processing Speed in Cognitive Aging? A Longitudinal Candidate Gene Study

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Abstract

While neuroimaging links dopamine system integrity to cognitive performance in aging, the genetic basis remains unclear. This study tested whether common dopaminergic variants influence processing speed decline, the primary outcome, for its central role in cognitive aging and established dopaminergic links. Analysis was performed on 957 variants across nine key dopamine pathway genes (synthesis: *TH*, *DDC*; receptors: *DRD1-3*; clearance/metabolism: *SLC6A3*, *COMT*, *DBH*; signal integration: *PPPIRIB*) in 434 participants from the University of Manchester Longitudinal Study of Cognition in Normal Healthy Old Age, examining 12-year decline rates and performance at age 70.

Across single-variant, gene-based, and polygenic risk score analyses, no associations survived multiple testing correction (Bonferroni $p < 5.22 \times 10^{-5}$). For processing speed decline rates, the strongest nominal signals were from *DRD2* (gene-based p=0.222) and a *DBH* variant (rs3025383, p=0.008). For performance at age 70, *COMT* had the strongest gene-level signal (p=0.075), while the polygenic score was unassociated with decline (p=0.257). These null findings persisted across secondary cognitive domains (fluid reasoning, episodic memory, vocabulary) and in severely underpowered post-mortem analyses (neuropathology n=116; synaptic density n=50).

Crucially, with 80% power to detect single variants explaining ≥5.3% variance ($\beta \geq 0.24$ SD) and polygenic effects of $|\beta| \geq 0.14$, the absence of detectable effects above these thresholds provides evidence against genetic effects of this magnitude, though smaller effects cannot be excluded.

These findings suggest the disconnect between neurobiology and genetics arises from complex mechanisms not captured by common variant analysis, such as rare variants, epigenetic regulation, or gene-environment interactions. This supports a highly polygenic model of cognitive aging that requires larger samples to detect thousands of variants with minute effects. This study demonstrates how systematic null findings from comprehensive pathway analysis advance understanding of the genetic architecture of cognitive aging.

Introduction

With the global population aged 65+ projected to reach 1.6 billion by 2050 (1), understanding the mechanisms of cognitive aging has become a crucial public health challenge. A fundamental aspect of this process is the decline in processing speed, defined as the time required for basic mental operations. This decline is a robust phenomenon, showing a near-linear trajectory from early adulthood and a strong correlation with age ($r=-0.52$) (2). Its impact is substantial, as processing speed can explain up to 95% of the age-related variance in other cognitive domains like reasoning and working memory (3,4). Furthermore, this cognitive slowing has serious functional consequences, correlating with increased fall risk and compromised driving safety (5,6), and is a key modifiable predictor of dementia (7,8).

Despite this clear population-level trend, longitudinal research has revealed substantial individual variation in the rate and severity of processing speed decline. The landmark Seattle Longitudinal Study, for example, demonstrated that while decline typically begins around age 53, its trajectory accelerates differently across individuals in later decades (9). Similarly, ten-year modeling from the English Longitudinal Study of Ageing identified four distinct profiles of decline, with nearly 20% of participants showing a severe and progressive deterioration from a low baseline (10). The existence of such pronounced heterogeneity underscores a critical gap in our understanding and highlights the importance of identifying the underlying factors that account for these individual differences in cognitive aging.

The dopaminergic system is a compelling neurobiological candidate for explaining individual differences in cognitive aging. A key framework for understanding its role is the "correlative triad," which posits that age-related declines in dopamine system integrity mediate a large proportion of the decline seen in overall cognitive performance (11). This model is built on three components: that dopaminergic markers decline with age, that these markers predict cognitive performance across multiple domains, and crucially, that statistically controlling for dopamine system integrity dramatically reduces the observed effect of age on cognition (11,12).

This framework is supported by extensive neuroimaging evidence and has direct functional significance for processing speed. A large meta-analysis quantified a significant system-wide decline with age, with D1 receptors showing the

steepest effect (r=−0.77), followed by dopamine transporters (r=−0.68) and D2 receptors (r=−0.56) (13). Importantly, this same study found that dopamine synthesis capacity does not decline with age, indicating the primary deficit involves receptor loss and reuptake efficiency. Evidence directly links this decline to speed-related tasks; for instance, PET imaging reveals that lower striatal D2 receptor availability specifically predicts poorer perceptual speed (12), while pharmacological studies show that L-DOPA selectively accelerates stimulus-processing (14).

Beyond its direct role in neurotransmission, an indirect pathway may also link the dopamine system to cognitive aging through the accumulation of brain pathology. Cognitive decline is strongly associated with such pathology, even in clinically normal older adults; for instance, greater tau burden predicts poorer cognition and higher tau and β-amyloid levels are linked to worse memory outcomes (15,16). A plausible biochemical pathway can be hypothesized from convergent evidence: dopamine metabolism generates chronic oxidative stress (17), a process implicated in cognitive aging (18), that also facilitates protein aggregation into pathological lesions via toxic dopamine quinones (19).

While this specific cascade requires empirical testing, it adds to the strong theoretical rationale for a genetic investigation. Despite the compelling evidence for dopamine's direct functional role and this plausible indirect pathway, the specific genetic underpinnings of the system remain poorly understood. Therefore, this study examines nine core dopamine pathway genes selected for comprehensive synaptic coverage, spanning synthesis (*TH*, *DDC*), receptor signaling (*DRD1-3*), clearance and metabolism (*SLC6A3*, *COMT*, *DBH*), and signal integration (*PPPIRIB*).

Fig 1. The Dopamine Synapse and the Nine Candidate Genes Analyzed. The schematic illustrates the functional roles of the nine genes retained for analysis, spanning synthesis, receptor signaling, clearance, and metabolism. Star indicates the rate-limiting step in synthesis (*TH*). Adapted from Moura & Vale and Xu & Yang (20,21); created with BioRender.com.

While many of these candidate genes show associations with related domains like working memory and executive control, several have also been directly linked to speed-based cognitive measures. For instance, functional variants in *DRD2* predict perceptual-speed performance (22), variation in *SLC6A3* affects cognitive speed (23), and the *COMT* Val158Met polymorphism is meta-analytically associated with slower reaction times (24). However, direct evidence for their role specifically in the longitudinal decline of processing speed in aging remains sparse. Given that age-related effects on

cognitive domains are highly shared rather than independent, the cumulative genetic architecture of the dopamine pathway plausibly contributes to this decline. Therefore, this study examines whether common variants in nine core dopamine pathway genes influence 12-year processing speed decline trajectories in the University of Manchester Longitudinal Study of Cognition in Normal Healthy Old Age.

Three primary hypotheses were tested: (i) dopaminergic variants associate with individual differences in 12-year processing speed decline rates, given established dopamine-cognition connections; (ii) domain-specificity exists, with strongest effects for processing speed versus fluid reasoning, episodic memory, and vocabulary; (iii) cumulative genetic effects detected through MAGMA gene-based testing and polygenic risk scores exceed single-variant effects. Additionally, exploratory analyses in post-mortem tissue (n=116 neuropathology, n=50 synaptic density) examined potential indirect mechanisms through relationships with Braak stage, Thal phase, cerebral amyloid angiopathy, α-synuclein, TDP-43, and synaptic density measures. Together, these analyses provide a comprehensive test of whether common dopaminergic variation modulates cognitive aging trajectories

Materials and Methods

Participants

Participants were recruited from the University of Manchester Longitudinal Study of Cognition in Normal Healthy Old Age, a prospective cohort study that enrolled 6,542 community-dwelling volunteers between 1983 and 1994. Participants were recruited through newspaper and radio advertising in Greater Manchester and Newcastle, United Kingdom. Entry criteria were age 42–92 years at enrollment and absence of diagnosed dementia or overt cognitive impairment (25). Of 6,356 participants who completed longitudinal cognitive assessments, 1,563 underwent genome-wide genotyping using the Illumina Human 610-Quad BeadChip platform (26). Following quality control procedures and exclusion of participants with missing

covariate data, the final analytic sample comprised 434 individuals with complete genetic, cognitive trajectory, and clinical data. Participant characteristics including demographics, clinical measures, and lifestyle factors were collected at baseline assessment.

Ethics Statement

All participants provided written informed consent. The study protocol was approved by the University of Manchester Research Ethics Committee (Ref: 2021-11274-17829).

Protocol

The study design involved longitudinal cognitive assessment over 12 years with genetic analysis of dopamine pathway variants. Participants completed cognitive testing at four waves with four-year intervals. Baseline clinical assessments included blood pressure measurement (three readings averaged to yield systolic [SBP] and diastolic [DBP] values), body mass index calculation, and depression screening using the Beck Depression Inventory (27). Mean arterial pressure (MAP) was calculated from these readings (MAP = DBP + 1/3 × [SBP − DBP]) and used as the primary blood pressure covariate. Comprehensive lifestyle questionnaires were used to assess smoking status, alcohol consumption, sleep duration and efficiency, and self-rated health.

Weekly minutes of moderate-to-vigorous physical activity (MVPA) were derived from monthly estimates of activity using the formula: MVPA = (hours moderate + hours vigorous) × 60/4.348. A subset of participants had post-mortem brain tissue available through the Manchester Brain Bank, yielding final analytic samples of 116 individuals for neuropathological assessment and 50 for synaptic density measurements.

Genotyping and Quality Control

An initial panel of thirteen genes involved in dopaminergic neurotransmission was prespecified based on a literature review of the pathway. Common single nucleotide polymorphisms (SNPs) located within the genomic boundaries of these genes were identified using the NCBI Variation Viewer on the GRCh38.p14 reference assembly. Variants from dbSNP with a reported minor allele frequency (MAF) of ≥1% were extracted, resulting in an initial list of 1,363 SNPs. Following quality control, the final analysis focused on 957 variants across nine autosomal genes: *TH*, *DDC*, *DRD1*, *DRD2*, *DRD3*, *SLC6A3*, *COMT*, *DBH*, and *PPP1R1B*.

Quality Control Procedures

Genetic data underwent stringent quality control using PLINK v1.9 (28). Four genes were excluded during initial processing: *MAOA* and *MAOB* (X-chromosome location precluded analysis), *DRD4* (absent from genotyping array), and *DRD5* (single variant failed MAF threshold). Individual-level exclusions removed participants with >2% missing genotypes. SNP-level exclusions removed variants with >2% missing data, minor allele frequency <5% in the study sample, or Hardy-Weinberg equilibrium deviation ($p < 1\times10^{-4}$). The final genetic dataset comprised 957 high-quality SNPs across nine autosomal genes (*COMT*: 43 SNPs, *DRD1*: 5 SNPs, *DRD2*: 117 SNPs, *DRD3*: 105 SNPs, *TH*: 2 SNPs, *DDC*: 323 SNPs, *SLC6A3*: 104 SNPs, *DBH*: 49 SNPs, *PPPIRIB*: 8 SNPs). SNP retention by gene after quality control is shown in S1 Table.

Population Structure Assessment

Twenty ancestry principal components (PC1–PC20) were computed from the 957-SNP panel using PLINK to control for population stratification. This specification was selected after comparing genomic inflation factors across models with varying numbers of PCs (PC1–3: λGC = 1.37–1.81; PC1–10: λGC = 1.37–1.81; PC1–20: λGC = 1.03), with PC1–20 demonstrating optimal calibration.

Cognitive Assessment

Cognitive Battery

Cognitive abilities were assessed using a comprehensive battery of 12 pencil-and-paper tests administered at each of four waves. Processing speed (primary outcome) was measured using: (i) visual search task requiring target identification among distractors, (ii) alphabet-coding task requiring symbol-digit substitution (29), and (iii) semantic-reasoning task requiring rapid semantic categorization (30). Fluid reasoning was assessed via the Heim AH4-1 and AH4-2 tests of general intelligence (31) and the Culture Fair Intelligence Test (32). Episodic memory was evaluated through immediate free recall, cumulative learning across trials, and delayed recall of six-letter concrete nouns. Vocabulary was assessed using standardized tests of verbal knowledge. Within each domain, factor analytic methods were used to aggregate performance across the three tasks, creating domain-specific factor scores at each wave (33). Full administration details have been described previously by Rabbitt et al. (34).

Cognitive Trajectory Modeling

Individual cognitive trajectories were estimated using multilevel growth curve models. Models included random intercepts and slopes with age as the time metric, centered at 70 years to represent a meaningful midpoint in the age distribution. Best Linear Unbiased Predictors (BLUPs) were extracted for each participant, yielding two trajectory parameters per cognitive domain: intercepts (cognitive performance at age 70 in standard deviation units) and slopes (annual rate of change in standard deviation units). Decline rates (slopes) served as primary outcomes reflecting aging-related cognitive change, while intercepts served as secondary outcomes reflecting cognitive performance levels (33).

Statistical Analysis

Primary Genetic Association Analyses

Single-SNP associations were tested using linear regression under an additive genetic model in PLINK v1.9 (28). Covariates were selected based on their established roles as potential confounders in cognitive aging. The primary model for processing speed decline rate included the SNP minor allele count (coded 0, 1, or 2) and adjusted for sex; 20 ancestry principal components; hypertension status; body mass index (kg/m2); mean arterial pressure; Beck Depression Inventory score; current smoking status; alcohol consumption frequency; weekly minutes of moderate-to-vigorous physical activity; sleep duration; sleep efficiency; and self-rated health. Identical models were applied to all secondary outcomes, including cognitive intercepts and decline rates in other domains.

Gene-based Analyses

Cumulative genetic effects within individual genes were assessed using MAGMA v1.10 (35), which aggregates single-SNP p-values while accounting for linkage disequilibrium structure. The SNP-wise mean model was applied with linkage disequilibrium patterns estimated from the 1000 Genomes Project Phase 3 European reference panel. Eight genes were tested (*TH* excluded due to insufficient coverage with only 2 SNPs), with Bonferroni correction applied for multiple gene testing ($\alpha = 0.00625$).

Pathway-level Polygenic Risk Score

A dopamine polygenic risk score (dPRS) was constructed to capture cumulative effects across the entire dopamine pathway. The score incorporated all 957 quality-controlled SNPs, which were first pruned for linkage disequilibrium ($r^2 > 0.10$) to retain 25 quasi-independent variants. The unweighted risk allele count was z-standardized and tested for association with cognitive outcomes using linear regression with identical covariate adjustment as single-SNP analyses. As a single hypothesis test of pathway-wide effects, the polygenic score was evaluated at $\alpha = 0.05$.

Multiple Testing Correction

Given the hypothesis-driven candidate gene approach, Bonferroni correction was applied as the primary significance threshold ($\alpha = 5.22 \times 10^{-5}$ for 957 SNPs). Additionally, the Benjamini-Hochberg false discovery rate procedure was implemented with $q < 0.05$. All p-values reported are two-sided.

Power Calculations

Post-hoc power analyses using the pwr package in R (36) indicated 80% power to detect single-variant effects of $\beta \geq 0.24$ standard deviations (5.3% phenotypic variance) at the Bonferroni-corrected threshold with n=434. For the polygenic risk score tested as a single hypothesis, 80% power was achieved for standardized effects $|\beta| \geq 0.14$.

Missing Data Handling

Variables with <5% missingness underwent complete-case analysis. For variables with 5–20% missingness (BDI mood score: 5.7%, alcohol frequency: 17.2%), multiple imputation by chained equations was performed using the mice package in R (37) (20 iterations, predictive mean matching method). Little's MCAR test supported the missing at random assumption ($\chi^2 = 280.0$, df = 296, p = 0.74), and the imputation model included all analysis covariates to preserve multivariate relationships. Imputation diagnostics are shown in S1 Fig.

Sensitivity Analysis for Sample Selection

To validate the decision to prioritize comprehensive phenotyping over sample size, the primary analysis (n=434 with full clinical covariates) was compared with a sensitivity analysis using all genotyped participants with cognitive data (n=1,179). The larger sample analysis excluded clinical covariates (MAP, BMI, hypertension status, BDI score) due to systematic missingness in Newcastle participants but retained demographic and lifestyle adjustments plus study site as an additional covariate. Genomic inflation factors were compared to assess the impact of covariate specification on population structure control.

Exploratory Post-Mortem Analyses

These analyses were conducted on the subset of UoM participants for whom post-mortem data was available. The detailed pathological and demographic characteristics of this autopsy cohort have been previously described by Robinson et al. (25). To investigate potential indirect pathways linking dopaminergic genetic variation to cognitive decline through brain pathology accumulation, exploratory analyses were conducted in participants with available post-mortem brain tissue. The neuropathology subset (n=116) included assessment of established pathological markers: Braak stage, Thal phase, cerebral amyloid angiopathy, and the presence of α-synuclein and TDP-43 inclusions. The synaptic density subset (n=50) included quantitative measurements from the frontal cortex, hippocampus, parietal, and occipital regions.

The small sample size precluded the use of the full clinical covariate set, as these more complex models failed to converge. Therefore, these analyses were conducted using a basic covariate adjustment which included sex, site, age at death, post-mortem interval, *APOE* ε4 carrier status, and 20 ancestry principal components. To resolve multicollinearity in the synaptic density models, a composite score for sleep quality was created from the sleep duration and efficiency variables. Given the limited statistical power, these analyses were considered hypothesis-generating rather than confirmatory.

Results

Participant Characteristics

The analytic sample comprised 434 participants (69% female) from the University of Manchester Longitudinal Study of Cognition in Normal Healthy Old Age with complete genetic, cognitive trajectory, and covariate data. Participants were predominantly from the Manchester site and represented a subset of the 1,563 individuals with genome-wide genotyping data. Baseline clinical and lifestyle characteristics are detailed in Table 1. The cohort's median body mass index

(BMI) was in the overweight range (25.39 kg/m²), and the prevalence of hypertension was high (86.9%). Other lifestyle indicators were generally positive, with participants reporting high levels of moderate-to-vigorous physical activity, normal sleep patterns, and minimal symptoms of depression.

Table 1. Baseline Characteristics of the Analytic Sample (N = 434).

Characteristic	**Value**
Categorical	n (%)
Sex (Female)	301 (69)
Hypertension status (Hypertensive)	377 (87)
Smoking status (Current smoker)	51 (12)
Continuous	Median [IQR][a]
BMI (kg/m²)[b]	25.39 [23.11, 28.04]
MAP (mm Hg)[c]	103.48 [95.95, 112.05]
BDI mood score[d]	5.00 [2.00, 9.00]
Alcohol freq. (wk^{-1})	0.67 [0.46, 0.77]

Characteristic	Value
MVPA (min wk^{-1})[e]	275.99 [110.40, 496.78]
Sleep hours (h)	7.00 [6.50, 8.00]
Sleep efficiency (%)	86.58 [79.56, 92.31]
Self-rated health	4.00 [4.00, 5.00]

Summary of baseline demographic, clinical, and lifestyle characteristics for the final analytic cohort. Categorical variables are presented as count (percentage); continuous variables are presented as median [IQR].

[a] IQR, interquartile range.

[b] BMI, body mass index.

[c] MAP, mean arterial pressure

[d] BDI, Beck Depression Inventory.

[e] MVPA, moderate-to-vigorous physical activity.

Cognitive Trajectories

Over the 12-year follow-up period, cognitive trajectories differed notably across domains (Table 2). Processing speed and fluid reasoning demonstrated the steepest rates of decline. In contrast, other abilities were more resilient, with episodic memory showing intermediate decline and vocabulary remaining relatively preserved. Given its pronounced rate of decline and substantial inter-individual variability, processing speed was selected as the primary outcome for genetic analysis.

Table 2. Cognitive Trajectory Parameters by Domain Over 12 Years.

Cognitive Trajectory	**Median [IQR][a] (SD[b] units)**
Slopes (Decline Rate)	
Processing Speed	-0.48 [-0.35, 1.35]
Fluid Reasoning	-0.46 [-0.34, 1.15]
Episodic Memory	-0.14 [-0.68, 0.81]
Vocabulary	-0.15 [-0.58, 0.70]
Intercepts (Performance at Age 70)	
Processing Speed	0.55 [-0.09, 1.19]
Fluid Reasoning	0.63 [-0.06, 1.28]

Cognitive Trajectory	Median [IQR][a] (SD[b] units)
Episodic Memory	0.52 [-0.22, 1.20]
Vocabulary	0.43 [-0.23, 1.02]

Summary of cognitive trajectory parameters derived from multilevel growth curve models over a 12-year period. Slopes represent the annual rate of change, while intercepts represent cognitive performance at age 70. All parameters are presented as median [IQR] in standard deviation (SD) units.

[a] IQR, interquartile range.

[b] SD, standard deviation.

Model Validation and Sample Selection

Prior to genetic association testing, comprehensive model diagnostics confirmed all regression assumptions were met. Variance inflation factors remained below 2.2 after resolving multicollinearity by using mean arterial pressure as a composite measure. Population structure control was optimized through systematic comparison of principal component specifications. Models using 20 principal components achieved optimal calibration ($\lambda GC = 1.03$), whereas models with fewer components showed substantial genomic inflation (PC1-3: $\lambda GC = 1.37$-1.81; PC1-10: $\lambda GC = 1.37$-1.81), indicating residual population stratification See S2 Fig which shows quantile-quantile plots comparing the distribution of observed versus expected p-values under different PC adjustments.

The decision to prioritize comprehensive phenotyping over sample size was validated by a sensitivity analysis of the single-SNP association results for processing speed decline. This comparison between the primary sample (n=434 with full clinical data) and a larger sample lacking clinical covariates (n=1,179) revealed significant genomic deflation in the larger sample ($\lambda GC = 0.81$). This represents an approximately 19% downward bias in the resulting test statistics (Table 3). This deflation likely stems from omitted variable bias due to heritable confounders, justifying the use of the smaller, more robustly controlled sample for all primary analyses.

Table 3. Comparison of Primary and Sensitivity Analyses for Processing Speed Slopes.

Analysis	**Sample Size**	**Covariate Set**	**Top Signal Location**	**Minimum Raw P-value**	**Bonferroni Significant**	**Lambda GC[a]**
Primary Analysis	n=434	Clinical + Demographics + PC[c]1-20	Chr[b]22 cluster	0.008	0	1.03
Sensitivity Analysis	n=1,179	Demographics + Lifestyle + Site + PC1-20	Chr22 cluster	0.004	0	0.81

Methodological summary comparing the primary analysis, which used a smaller sample with comprehensive covariate adjustment, against a sensitivity analysis using a larger sample with a reduced covariate set. The comparison highlights the trade-off between statistical power and control for confounding variables.

[a] GC, genomic control.

[b] Chr, chromosome.

[c] PC, principal components.

Statistical Power

Post-hoc power calculations established clear thresholds for interpreting null findings. The primary analysis (n=434) achieved 80% power to detect single variants explaining ≥5.3% of phenotypic variance in processing speed decline ($\beta \geq 0.24$ SD per allele) at the Bonferroni-corrected significance threshold ($\alpha = 5.22 \times 10^{-5}$). The dopamine polygenic risk score, tested as a single hypothesis, had enhanced power to detect standardized effects of $|\beta| \geq 0.14$. These power parameters enable interpretation of null findings as evidence against genetic effects above these detection thresholds.

Primary Outcome: Processing Speed Decline

Single-SNP Associations

Analysis of 957 quality-controlled SNPs across nine dopamine pathway genes revealed no statistically significant associations with processing speed decline rate after correction for multiple testing (Bonferroni $p < 5.22 \times 10^{-5}$; minimum FDR q-value = 0.844) (Fig 2). The strongest nominal association was observed for rs3025383 in the dopamine beta-hydroxylase gene (*DBH*), where each copy of the C allele was associated with 0.79 SD less decline per year (95% CI: -1.38 to -0.21, p = 0.008). However, the wide confidence interval reflects substantial statistical uncertainty, and this association did not approach significance after correction.

Fig 2. Manhattan Plot of Single-Variant Associations with Processing Speed Decline Rate. Association results for 957 single-nucleotide polymorphisms (SNPs) with the 12-year rate of processing speed decline. The y-axis shows the

$-\log_{10}$(p-value) for each SNP, plotted by its chromosomal position. The red dashed line is the Bonferroni significance threshold ($p = 5.22 \times 10^{-5}$), and the blue dashed line is the suggestive threshold ($p = 1 \times 10^{-3}$). No SNPs were significantly associated with the outcome.

An examination of the top nominal signals revealed a notable cluster of variants within the catechol-O-methyltransferase gene (*COMT*). As shown in Table 4, four of the five strongest signals were located in this gene, with three variants sharing an identical nominal association (rs2238791, rs2531693, and rs2106140; $\beta = 1.02$, $p = 0.008$). While this pattern is intriguing given *COMT*'s established role in cognitive function, it did not translate into a statistically significant finding.

Table 4. Top SNP Associations with Processing Speed Decline Rate.

SNP ID	Gene	Alleles (Effect / Non-Effect)[a]	EAF[b]	Beta (95% CI)[c]	Raw P-value	FDR q-value	Bonferroni P-value
rs3025383	*DBH*	C / T	0.186	-0.79 (-1.38, -0.21)	0.008	0.844	1
rs2238791	*COMT*	A / C	0.472	1.02 (0.27, 1.77)	0.008	0.844	1
rs2531693	*COMT*	G / C	0.472	1.02 (0.27, 1.77)	0.008	0.844	1

SNP ID	Gene	Alleles (Effect / Non-Effect)[a]	EAF[b]	Beta (95% CI)[c]	Raw P-value	FDR q-value	Bonferroni P-value
rs2106140	*COMT*	A / G	0.472	1.02 (0.27, 1.77)	0.008	0.844	1
rs2238790	*COMT*	G / A	0.321	-0.73 (-1.27, -0.19)	0.009	0.844	1

The table lists the top 5 variants from the single-SNP analysis, ranked by uncorrected p-value. Results are from the primary linear regression model adjusted for all covariates. No associations were statistically significant after multiple testing correction.

[a] The effect allele is listed first; the beta coefficient corresponds to one copy of this allele.

[b] EAF, Effect Allele Frequency.

[c] Beta, Standardized effect size and 95% Confidence Interval.

For processing speed performance at age 70 (intercepts), similarly null findings emerged. No variant achieved statistical significance after correction (all FDR q > 0.86). The leading nominal signal was rs165656 in *COMT* (β = -0.30 SD, 95% CI: -0.53 to -0.08, p = 0.009), though this did not survive multiple testing correction. See S2 Table which presents the top nominal associations for processing speed intercepts.

Gene-Based Associations

Gene-based analysis using MAGMA was performed on eight dopamine pathway genes to test for cumulative variant effects. Reinforcing the single-variant results, no gene was significantly associated with processing speed decline after Bonferroni correction ($\alpha = 0.00625$). As detailed in Table 5, the dopamine D2 receptor gene (*DRD2*) showed the strongest nominal signal, though it remained clearly non-significant (117 SNPs; $Z = 0.765$, $p = 0.222$).

Table 5. Gene-Based Association Results for Processing Speed Decline Rate.

Gene	N SNPs[a]	Z-stat[b]	Raw P-value	FDR q-value	Bonferroni P-value
DRD2	117	0.765	0.222	0.786	1
DRD1	5	0.512	0.304	0.786	1
DBH	49	0.512	0.304	0.786	1
SLC6A3	104	0.157	0.438	0.786	1
COMT	43	-0.187	0.574	0.786	1
DRD3	105	-0.227	0.590	0.786	1
DDC	323	-0.620	0.732	0.837	1

Gene	N SNPs[a]	Z-stat[b]	Raw P-value	FDR q-value	Bonferroni P-value
PPP1R1B	8	-1.020	0.846	0.846	1

The table summarizes gene-level association results from MAGMA for eight dopamine pathway genes. Genes are ranked by uncorrected p-value. No gene was significantly associated with processing speed decline after correction for multiple testing. Gene names are italicized.

[a] N SNPs, Number of single-nucleotide polymorphisms included in the gene-based test.

[b] Z-stat, The test statistic from the MAGMA analysis.

Secondary Outcomes: Other Cognitive Domains

To assess the domain-specificity of the primary null finding, identical analyses were performed for fluid reasoning, episodic memory, and vocabulary. Consistent with the primary analysis, no significant associations emerged for any secondary cognitive domain after multiple testing correction.

Single-SNP Associations

At the single-variant level, the strongest nominal signal for decline rates was rs12518222 in *DRD1* for fluid reasoning ($\beta = 0.35$, $p = 0.002$, FDR $q = 0.84$). For performance at age 70 (intercepts), the leading nominal association was rs11575429 in *DDC* with episodic memory ($\beta = -1.53$, $p = 0.006$, FDR $q = 0.84$). The top nominal associations for all secondary outcomes are presented in S3-S6 Tables.

Gene-Based Associations

The gene-based analyses similarly yielded null results across all secondary domains. Nominally significant associations were observed for *DRD1* with fluid intelligence decline ($p = 0.034$) and *PPP1R1B* with vocabulary decline ($p = 0.050$), but neither survived correction. Gene-based results for all secondary domain slopes and intercepts are provided in S7 and S8 Tables, respectively.

Pathway-Wide Analysis: Polygenic Risk Score

A pathway-wide polygenic risk score (dPRS) was constructed from 25 linkage disequilibrium-independent variants ($r^2 < 0.10$) to test for cumulative dopaminergic effects. Despite enhanced statistical power, the dPRS was not significantly associated with the primary outcomes of processing speed decline rate ($\beta = -0.119$, $p = 0.257$) or performance at age 70 ($\beta = -0.049$, $p = 0.470$), as shown in Table 6. Similarly, null findings emerged across all secondary cognitive domains (see S9 Table for full results).

Table 6. Dopamine Polygenic Risk Score Associations with Processing Speed Trajectories.

Outcome	**β (95% CI)[a]**	**SE[b]**	**P-value**
Decline Rate (Slope)	-0.119 (-0.324, 0.086)	0.105	0.257
Performance at Age 70 (Intercept)	-0.049 (-0.182, 0.084)	0.068	0.470

Association results for the standardized dPRS with the primary cognitive outcomes. No associations were statistically significant.

[a] β (beta), Standardized effect size and 95% Confidence Interval.

[b] SE, Standard Error.

Exploratory Neuropathological Analyses

To investigate potential indirect pathways linking dopaminergic variation to cognitive decline through neuropathology, exploratory analyses were conducted in participants with available post-mortem brain tissue. These analyses were severely limited by sample size, achieving <6% power to detect effect sizes of β = 0.10-0.20 and adequate power (>50%) only for effects exceeding β = 0.40.

Genetic Associations with Neuropathology (n=116)

In the neuropathology subset, no associations between dopaminergic variants and pathological markers survived correction. The strongest nominal signal was between rs4819846 in *COMT* and Braak stage (β = -1.60, p = 0.0005, FDR q = 0.083). However, genomic control revealed highly unstable calibration across all outcomes (e.g., Braak stage λGC = 0.929; α-synuclein λGC = 2.712), severely limiting the interpretability of these results. The top associations for each neuropathological marker are provided in S10 Table.

Genetic Associations with Synaptic Density (n=50)

The synaptic density subset similarly yielded null findings. The strongest nominal association was between rs1807066 in *DDC* and hippocampal synaptic density (β = 0.032, p = 0.0002, FDR q = 0.206), though confidence intervals were exceptionally wide, reflecting extreme statistical uncertainty. Synaptic density associations are presented in S11 Table.

Neuropathology and Cognitive Trajectories

Finally, no neuropathological markers showed significant associations with cognitive trajectories after correction (all FDR q > 0.88), providing no evidence for an indirect pathway linking genetic variation to cognitive decline through brain pathology in this cohort.

Discussion

This investigation aimed to determine if common dopaminergic variation modulates processing speed decline. After analyzing 957 variants across nine key genes, the study yielded a striking absence of statistically significant associations across all three analytical tiers. For processing speed decline, the strongest nominal signals (*DBH* rs3025383, p=0.008; *DRD2* gene-based p=0.222) failed to survive multiple testing correction. This null pattern extended to all secondary cognitive domains and post-mortem analyses. These findings align with contemporary evidence that complex traits are highly polygenic, where individual gene effects are too small for detection in candidate-gene studies, consistent with Border et al. (38) who demonstrated that candidate-gene associations often fail to replicate in large-scale studies.

These findings create a significant disconnect from decades of research establishing dopamine's critical role in cognition. The "correlative triad" framework and molecular imaging data provide a powerful biological rationale for expecting an

association. Why does this strong neurobiological relationship not translate into detectable effects from common genetic variants? The answer likely lies in complex biological realities and this study's methodological scope.

Careful consideration of statistical power allows these null results to be interpreted as meaningful scientific evidence. With 80% power to detect single-variant effects of $\beta \geq 0.24$ SD per allele, the analysis could reliably identify variants explaining approximately 5.3% or more of variance in processing speed decline. The absence of such signals supports the absence of this class of genetic effect rather than a failure to detect existing associations. The polygenic risk score analysis, with enhanced power to detect cumulative effects of $|\beta| \geq 0.14$, strengthens this conclusion by demonstrating that even aggregated pathway-wide variation lacks detectable influence.

The study's robust design supports these conclusions. A 12-year longitudinal framework provided dynamic phenotypes of cognitive change, while a multi-tiered analytical strategy ensured the null finding was not a methodological artifact. A sensitivity analysis comparing the primary fully-adjusted model (N=434) with a larger less-adjusted model (N=1,179) yielded genomic deflation (λ=0.813), providing evidence for the importance of deep phenotyping: the precise and comprehensive analysis of phenotypic variables needed to correctly interpret genomic data (39). This deflation likely reflects downward bias from omitting heritable confounders (40,41), specifically clinical covariates like blood pressure and BMI systematically missing in the larger sample. This finding justifies prioritizing the smaller, robustly controlled sample, underscoring that phenotypic data quality may be more critical than sample size for complex aging phenotypes.

The null findings likely reflect extreme polygenicity, where cognitive differences arise from many variants with very small effects. A large-scale meta-analysis found top-associated SNPs for cognitive function individually account for only ~0.1% of variance (42). Within this framework, the failure to detect single-variant associations does not mean dopaminergic genes are uninvolved, but that their effects were too subtle for available statistical power. The null dopamine polygenic risk score (dPRS) result is consistent with this model, as common variants are understood to account for substantial heritability (~21.5%) (42), this influence is distributed across the genome. A dPRS focused on nine genes captures only a fraction of the genetic architecture, reinforcing that any contribution was too subtle for detection.

The study's focus on common SNPs leaves other variation unassessed. Rare variants (MAF < 1%), which can have greater phenotypic influence due to negative selection, may explain missing heritability (43,44). Structural variants like deletions and VNTRs can profoundly impact gene function but are poorly captured by SNP arrays (45). This limitation is particularly relevant given the exclusion of well-studied functional VNTRs in *SLC6A3* and *DRD4*. The *DRD4* gene was not assayed, and while *SLC6A3* was included, its functional VNTR was not analyzed. These specific VNTRs are linked to dopamine signaling. Meta-analyses have confirmed an association between the *DRD4* VNTR and ADHD (46), and more recently, a similar association has been established for the *SLC6A3* VNTR (47).

Beyond static DNA sequence, dynamic gene regulation provides another explanation for null findings. The study relied on single, static genetic measurement to model cognitive change over 12 years. The epigenome dynamically regulates gene expression in response to environment, and its age-related alterations are considered core drivers of cognitive decline (48). The true drivers may be age-related dysregulation rather than inherited variants themselves. DNA methylation patterns in brain tissue change with age, linked to cognitive impairment (49). Two individuals with identical *COMT* genotypes could have different cognitive trajectories due to different methylation of the *COMT* promoter over time. Genetic models that do not account for this dynamic layer average across distinct states, potentially obscuring true relationships.

Gene-Environment interaction (GxE) provides another explanation, where variant effects are conditional on environmental exposures. Such interactions can produce null results when variants with opposing effects in different contexts average to zero in models testing only main effects (50). The *COMT* Val158Met polymorphism exemplifies this; its effect on cognition follows an inverted U-shaped relationship between dopamine and prefrontal function (51). Since this study tested only main effects, the null *COMT* finding could result from GxE, where allelic effects differ based on unmeasured factors like cognitive reserve. This presents an alternative hypothesis requiring future testing in larger cohorts with power to investigate complex interactions.

These findings provide a roadmap for future research requiring enhanced statistical power, broader genetic coverage, and increased demographic diversity.

Future studies must utilize substantially larger samples to detect subtle effects characteristic of highly polygenic traits. This is particularly critical for rare outcomes like post-mortem analyses, highlighting the need for larger, deeply phenotyped brain bank resources. Whole-genome sequencing would capture the full spectrum of variation, including rare variants and structural polymorphisms like the functional VNTRs in *SLC6A3* and *DRD4* unassessed here, while resolving inconsistent SNP coverage across genes.

The cohort's European ancestry limits generalizability, as allele frequencies and linkage patterns differ across populations. Future work must recruit genetically diverse populations to ensure findings are robust across ancestral groups.

Research must move beyond static genetic data through longitudinal methods capturing change over time, including Epigenome-Wide Association Studies to map age-related epigenetic drift and analyses testing gene-environment interactions. The field should expand from single-pathway focus to systems-biology approaches, as dopamine is modulated by complex neurobiological networks. Future work should investigate interactions with BDNF (52,53), the glutamatergic system (54), the circadian system (55), and adjacent regulatory loci like the *ANKK1* Taq1A polymorphism associated with reduced D2/3 receptor binding (56).

The ideal future study would combine WGS, longitudinal deep phenotyping, and in-vivo brain imaging within large, diverse cohorts, enabling causal inference methods like Mendelian randomization to test pathways from genetic variation through brain biology to cognitive decline.

In conclusion, these findings fundamentally challenge the candidate-gene approach for cognitive aging research and demonstrate the value of comprehensive null results in refining biological models. The comprehensive absence of associations suggests against pursuing single-pathway genetic studies for cognitive phenotypes and instead is consistent with the extreme polygenicity model where individual pathway contributions are vanishingly small. Our results highlight a critical gap in the translational pipeline: while dopamine system integrity clearly influences cognitive performance at the neurobiological level, this relationship cannot be captured through inherited common variation alone. This disconnect underscores the need to reconceptualize how genetic, epigenetic, and environmental factors converge to influence dopaminergic function across the lifespan. Moving forward, the field must embrace approaches that match the biological

complexity of cognitive aging, integrating dynamic molecular mechanisms with systems-level neurobiology to bridge the gap between genetic architecture and functional outcomes.

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Supporting information

S1 Fig. Diagnostic Plots for Multiple Imputation. Diagnostic plots comparing the distributions of imputed and observed data for the BDI mood score and alcohol frequency.

S2 Fig. Quantile-Quantile (QQ) Plot for the Primary Association Analysis. QQ plot of observed versus expected p-values for the processing speed decline analysis using the final PC1-20 adjusted model.

S1 Table. SNP Retention by Candidate Gene After Quality Control. The number of single-nucleotide polymorphisms (SNPs) and individuals retained for each of the nine candidate genes after each step of the quality control pipeline.

S2 Table. Top SNP Associations with Processing Speed Performance at Age 70. Variants are ranked by uncorrected p-value for their association with the cognitive intercept. No associations were significant after multiple testing correction.

S3 Table. Top SNP Associations with Fluid Reasoning Decline Rate. Variants are ranked by uncorrected p-value for their association with the 12-year decline rate (slope). No associations were significant after multiple testing correction.

S4 Table. Top 5 SNP Associations with Episodic Memory Decline Rate. Variants are ranked by uncorrected p-value for their association with the 12-year decline rate (slope). No associations were significant after multiple testing correction.

S5 Table. Top SNP Associations with Vocabulary Decline Rate. Variants are ranked by uncorrected p-value for their association with the 12-year decline rate (slope). No associations were significant after multiple testing correction.

S6 Table. Top SNP Associations with Secondary Cognitive Domain Performance at Age 70. Variants are ranked by uncorrected p-value for their association with performance at age 70 (intercept) for each secondary domain. No associations were significant after multiple testing correction.

S7 Table. Gene-Based Association Results for Secondary Cognitive Domain Decline Rates. Results from MAGMA gene-set analysis for the 12-year decline rates (slopes) in each secondary domain. No gene-level associations were significant after correction for multiple testing.

S8 Table. Gene-Based Association Results for Secondary Cognitive Domain Performance at Age 70. Results from MAGMA gene-set analysis for performance at age 70 (intercepts) in each secondary domain. No gene-level associations were significant after correction for multiple testing.

S9 Table. Dopamine Polygenic Risk Score Associations with Secondary Cognitive Trajectories. Association between the standardized dPRS and trajectories (slopes and intercepts) for all secondary cognitive domains. No associations were statistically significant.

S10 Table. Top SNP Associations with Neuropathological Markers. Variants are ranked by uncorrected p-value for each of the five post-mortem neuropathological markers. Analyses were conducted in the neuropathology subset (n=116). No associations were significant after multiple testing correction.

S11 Table. Top SNP Associations with Synaptic Density. Variants are ranked by uncorrected p-value for synaptic density in four cortical regions. Analyses were conducted in the synaptic density subset (n=50). No associations were significant after multiple testing correction.