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Biological Determinants of Memory Performance In Qur'an Memorizers: Evidence from Cathecol-O-Methyl-Transferase (COMT) Gene Expression and Protein Levels

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Abstract

Memory performance during adolescence is a key aspect of cognitive development and is strongly influenced by dopaminergic regulation in the prefrontal cortex. Catechol-O-Methyltransferase (COMT) plays a critical role in modulating dopamine availability and cognitive function. This study examined the relationships between age, COMT gene expression, COMT protein levels, and memory performance among adolescents engaged in structured memorization activities. A quantitative cross-sectional design was applied involving male adolescent participants. Memory performance was assessed using a standardized psychometric test, while COMT gene expression and protein levels were measured using reverse transcription quantitative polymerase chain reaction and enzyme-linked immunosorbent assay, respectively. Statistical analyses included descriptive statistics and correlation tests. The results demonstrated a significant negative association between age and memory performance within the adolescent range. In contrast, COMT gene expression and protein levels showed strong positive correlations with memory performance, indicating that higher molecular regulation of dopamine was associated with superior cognitive outcomes. Memorization duration and quantity were not significantly related to memory performance. These findings support dopamine-based models of cognitive regulation and highlight the importance of molecular biomarkers in understanding adolescent memory development. The study contributes to developmental cognitive research by emphasizing biologically informed approaches and provides a foundation for future longitudinal investigations.

Keywords: adolescence; Catechol-O-Methyltransferase; dopamine regulation; gene expression; memory performance.

INTRODUCTION

Memory constitutes a fundamental dimension of human cognition and serves as the basis for learning, reasoning, and adaptive behavior across the lifespan. Contemporary neurocognitive research consistently highlights the central role of dopamine (DA) regulation in higher-order cognitive processes, particularly within the prefrontal cortex (PFC), a neural region critically involved in working memory (WM), long-term memory (LTM), and executive control (Weber et al., 2022; Friedman & Robbins, 2021). The functional integrity of the PFC is therefore essential for efficient memory processing, and disruptions or variations in dopaminergic signaling within this region are known to influence cognitive performance. During adolescence, the PFC undergoes accelerated structural and functional maturation, characterized by synaptic pruning, myelination, and refinement of neural networks, rendering this developmental stage especially sensitive to neurochemical modulation and environmental input (Reynolds & Flores, 2021). Consequently, individual differences in dopaminergic regulation during adolescence may exert a disproportionate impact on memory performance and cognitive efficiency.

At the molecular level, Catechol-O-Methyltransferase (COMT) plays a pivotal role in regulating synaptic dopamine availability in the PFC through enzymatic degradation of dopamine. In contrast to subcortical regions where dopamine clearance relies predominantly on dopamine transporters, the PFC depends largely on COMT-mediated metabolism, positioning this enzyme as a key biological determinant of prefrontal cognitive function (Reynolds et al., 2023). Accumulating empirical evidence suggests that variability in COMT function—arising from genetic variation, gene expression, or protein activity—is associated with interindividual differences in memory and executive performance (Yin

et al., 2023). Nevertheless, the majority of existing studies have focused on adult populations or on COMT polymorphisms alone, leaving important developmental and molecular dimensions insufficiently examined.

Within this context, a critical research problem emerges: to what extent do age-related factors and molecular indicators of COMT activity jointly contribute to memory performance during adolescence? Although age is widely recognized as a determinant of cognitive maturation, its interaction with neurobiological markers such as COMT gene expression and protein levels remains poorly characterized. This limitation is particularly evident in studies of adolescents engaged in cognitively demanding activities, where environmental stimulation and biological regulation are likely to converge in shaping memory outcomes. Addressing this problem requires an integrative framework that bridges developmental neuroscience, molecular biology, and cognitive assessment.

Recent advances in cognitive neuroscience increasingly support biologically informed models that combine behavioral measures of memory with molecular indicators of neural regulation. Such approaches allow for a more precise understanding of cognitive performance as an expression of underlying neurochemical processes rather than as a product of experience or educational exposure alone. In this regard, assessing both COMT gene expression and COMT protein levels provides a more comprehensive representation of dopaminergic regulation than polymorphism analysis alone, which may not fully capture functional enzyme activity (Yin et al., 2023).

Previous research has partially addressed these issues by examining associations between COMT polymorphisms, particularly Val158Met, and cognitive outcomes. Several studies report that COMT-related differences in dopamine metabolism are associated with variability in working memory efficiency and executive control (Islam et al., 2021; Flynn et al., 2024). However, findings remain inconsistent and effect sizes modest, suggesting that genetic variation alone may be insufficient to account for observed cognitive differences. Moreover, direct measurements of COMT mRNA expression and circulating protein levels are rarely incorporated, especially in adolescent populations.

Parallel research has demonstrated that structured and repetitive cognitive activities can enhance memory consolidation and neural efficiency, with sustained memorization linked to strengthened synaptic connectivity and improved cognitive control (Bae et al., 2025). Yet, such cognitively intensive practices are seldom examined alongside biological markers, resulting in a fragmented understanding of how environmental stimulation interacts with molecular regulation to influence memory performance.

Therefore, the present study aims to examine the relationships between age, COMT gene expression, COMT protein levels, and memory performance among adolescent learners. By integrating molecular and behavioral measures, this study moves beyond genetic polymorphism approaches and provides a developmentally grounded examination of dopamine-based cognitive regulation during adolescence. It is hypothesized that higher COMT gene expression and protein levels are associated with superior memory performance, whereas increasing age within adolescence is inversely related to memory capacity

MATERIALS AND METHODS

Study Design

This study employed a quantitative, observational, cross-sectional design to examine the associations between age, Catechol-O-Methyltransferase (COMT) gene expression, COMT protein levels, and memory performance among adolescents. A cross-sectional approach was selected as an appropriate and efficient design to identify relationships between biological markers and cognitive outcomes at a specific point in developmental time. This design is widely used in neurocognitive and biomarker research when the primary objective is to explore correlations rather than establish causal pathways, particularly in adolescent populations.

Study Setting and Participants

The study was conducted at Tahfidzul Qur'an Al Imam Ashim Islamic Boarding School, located at Jalan Tidung Mariolo Lorong 7 No. 1, Makassar, Indonesia, from February to April 2019. The target population consisted of male adolescents who were actively engaged in structured Qur’an memorization activities. Participants were recruited using a purposive sampling technique to ensure homogeneity of cognitive exposure and learning demands. Inclusion criteria comprised adolescents within the predefined age range, active participation in Qur’an memorization, physical and mental health stability, and willingness to provide biological samples. Participants with known neurological disorders, chronic systemic diseases, or conditions that could affect cognitive function were excluded from the study.

Ethical Considerations

Ethical clearance was obtained from the Biomedical Research Ethics Committee for Human Subjects, Faculty of Medicine, Universitas Hasanuddin, prior to the implementation of the study.

Measurement of Memory Performance

Memory performance was assessed using a standardized and validated psychometric instrument derived from the Intelligence Structure Test (IST), focusing specifically on the memory subtest. This instrument was selected due to its established reliability and validity in assessing declarative and working memory capacities in adolescent

populations. The test was administered under controlled conditions by trained personnel following standardized procedures. Raw scores were converted into standardized memory scores based on normative data to facilitate interpretation and comparison.

Assessment of COMT Gene Expression

Blood samples were analyzed at the Biomolecular and Immunology Laboratory, Faculty of Medicine, Universitas Hasanuddin. Gene expression analysis was performed using real-time reverse transcription polymerase chain reaction (RT-qPCR). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as the housekeeping gene and internal control.

COMT mRNA expression was detected using the following specific primers: forward primer 5′-GGCACAGAGTGGAAGCATCTC-3′ and reverse primer 5′-CAGAAACCAGCACTGCATCCT-3′. DNA amplification was conducted with an initial denaturation at 94°C for 3 min, followed by 38 cycles consisting of denaturation at 94°C for 30 s.

GAPDH amplification was performed using the forward primer 5′-GCTAAGCAGTTGGTGGTGCA-3′ and reverse primer 5′-TCACCACCATGGAGAAGGC-3′, following the protocol described by Yajima et al. The PCR protocol included an initial denaturation step at 94°C for 10 min, followed by 32 amplification cycles with annealing at 54°C for 30 s.

Real-time RT-PCR was performed using a one-step SYBR® Green QRT-PCR Master Mix Kit optimized for the Mx4000 instrument platform. Protocol modifications were made according to the manufacturer's recommendations, including dye dilution adjustments and thermal cycling parameters. A passive reference dye was added to each reaction tube at a dilution ratio of 1:500 and protected from light throughout the procedure. The 2× SYBR® Green QRT-PCR Master Mix was thawed on ice prior to use. Any unused reagent was stored at −40°C while avoiding repeated freeze–thaw cycles.

SYBR® Green is a fluorescent nucleic acid stain commonly used for DNA detection. Reaction mixtures were prepared to a final volume of 25 μL, including 12.5 μL of 2× SYBR Green QRT-PCR Master Mix, optimized concentrations of forward and reverse primers, nuclease-free PCR-grade water, 0.375 μL passive reference dye solution, and 1.0 μL reverse transcriptase enzyme containing modular polymerase and RNase H activities. The reaction mixtures were gently mixed to avoid bubble formation and aliquoted into PCR tubes. RNA template was added to each reaction tube, followed by gentle mixing and brief centrifugation. Amplification reactions were performed using a CFX Connect™ Real-Time PCR Detection System (Bio-Rad Laboratories, USA; 96-well, 0.1 mL format) according to the manufacturer's instructions

Measurement of COMT Protein Levels

Serum samples and all reagents were equilibrated to room temperature prior to analysis according to the manufacturer's instructions. All serum samples were analyzed in triplicate to ensure assay accuracy and reproducibility. Microplate strips were arranged according to the number of samples to be analyzed. Initially, 100 μL of assay diluent containing stabilizing proteins was added to each well. Subsequently, 100 μL of either recombinant COMT protein standard solution provided in the kit or diluted serum samples were added to the respective wells. The plate was incubated for 2 h at room temperature.

Following incubation, the contents of each well were aspirated, and the wells were washed four times with sterile phosphate-buffered saline (PBS). Thereafter, 200 μL of conjugate solution containing streptavidin–horseradish peroxidase (HRP) was added to each well. The plate was covered with an adhesive seal and incubated for an additional 2 h at room temperature.

The wells were aspirated and washed four times with sterile PBS. Subsequently, 200 μL of substrate solution containing 3,3′,5,5′-tetramethylbenzidine (TMB) was added to each well and incubated for 20 min at room temperature in the dark to prevent light-induced degradation.

The enzymatic reaction was terminated by adding 50 μL of stop solution containing sulfuric acid (H_2SO_4) to each well. Optical density was measured within 30 min using an ELISA Reader 270 (bioMérieux, France) at a wavelength of 450 nm. COMT protein concentrations were calculated and expressed in ng/mL using the standard calibration curve provided with the assay kit (Anti-COMT Antibody ab51984, Abcam)

Data Collection Procedures

Data collection was conducted in a sequential and standardized manner. Cognitive assessments were administered prior to biological sampling to minimize potential stress-related effects on memory performance. Blood samples were collected by qualified laboratory personnel using aseptic techniques. All laboratory analyses were performed in certified facilities to ensure accuracy and reproducibility of results.

Statistical Analysis

Data were analyzed using statistical software appropriate for biomedical research. Descriptive statistics were calculated to summarize participant characteristics, memory scores, COMT gene expression levels, and COMT protein concentrations. Normality of data distribution was assessed using appropriate statistical tests. Differences between groups were analyzed using independent t-tests where applicable. Pearson correlation analysis was employed to examine the relationships between age, memory performance, COMT gene expression, and COMT protein levels. A significance level of $p < 0.05$ was applied for all inferential analyses.

Methodological Rigor and Validity

Several measures were implemented to enhance methodological rigor and internal validity. The use of standardized cognitive instruments, validated laboratory techniques, and controlled data collection procedures minimized measurement bias. Homogeneity of the study population reduced potential confounding effects related to educational and environmental variability. Nevertheless, the cross-sectional nature of the study limits causal inference, and findings should be interpreted within this methodological context.

RESULTS AND DISCUSSION

Characteristics of Respondents

Respondents in this study were mostly <18 years old, in the sense that most of the respondents were teenagers, had memorized for <3 years, with a total of 1-15 chapters of memorization and the type of memory was Long Term Memory (Table 1). The average age of the respondents is 16.18 years, with a length of 2.4 years to memorize, the number of memorization is 12.64 chapters and the memory score is 101.26. Based on COMT, the average respondent has a COMT gene expression of 9.165 and a COMT protein of 4.22ng/ml (Table 2)

Table 1. General Characteristics of Respondents.

Characteristics	N	%
Age		
< 18 years old	39	78
≥ 18 years	11	22
Long memorization		
< 3 years	33	66
≥ 3 years	17	34
Number of memorization		
1-15 juz	39	78
16-30 juz	11	22
Memory type		
Long Term Memory	30	60
Short Term Memory	20	40

Table 2. Characteristics of respondents based on research variables.

Characteristics	Mean	SD	Min	Max
Age (years)	16.18	±2.07	13	21
Memorizing time (years)	2.4	±0.64	2	5
Number of memorization (Juz)	12.64	±6.16	3	30
Memory (score)	101.26	±15.67	67	131
COMT Gen gene	9.165	±1.59	5.517	12,508
COMT protein (ng/ml)	4.22	±1.62	0.867	7.743

Differences in memory scores, gene expression, and COMT protein based on the characteristics of respondents

There are significant differences in memory scores, COMT gene expression, and the amount of COMT protein based on the age of the respondents, but there is no difference in memory scores, COMT gene expression, and the amount of COMT protein based on the length of memorization and the amount of memorization (Tables 3, 4 and 5)

Table 3. Differences in memory scores based on the characteristics of respondents.

Characteristics	Memory mean	SD	Min	Max	p*
Age					
< 18 years old	104.13	±15.45	71	131	0.013
≥ 18 years	91.00	±12.23	67	109	
Long memorization					
< 3 years	100.97	±16.36	67	131	0.857
≥ 3 years	101.82	±14.72	81	131	
Number of memorization					
1-15 juz	101.79	±16.65	67	131	0.654
16-30 juz	99.36	±12.01	84	124	

p* Independent T-Test

Table 4. Differences in COMT gene expression based on respondent characteristics.

Characteristics	COMT Gen gene				p*
	mean	SD	Min	Max	
Age					
< 18 years old	9.05	±1.56	6	12	0.005
≥ 18 years	7.55	±1.21	5	9	
Long memorization					
< 3 years	8.67	±1.65	5	12	0.747
≥ 3 years	8.82	±1.55	7	12	
Number of memorization					
1-15 juz	8.79	±1.69	5	12	0.540
16-30 juz	8.45	±1.29	7	11	

p* Independent T-Test

Table 5. Differences in COMT protein based on respondent characteristics.

Characteristics	COMT Proteins				p*
	mean	SD	Min	Max	
Age					
< 18 years old	4.05	1.5	1	7	0.005
≥ 18 years	2.55	1.21	0.8	4	
Long memorization					
< 3 years	3.67	1.65	0.8	7	0.747
≥ 3 years	3.82	1.55	2	6	
Number of memorization					
1-15 juz	3.79	1.69	0.8	7	0.540
16-30 juz	3.45	1.29	2	6	

p* Independent T-Test

Correlation between COMT characteristics, expression and protein with respondents' memory scores

A significant correlation was found between age, gene expression, and the amount of COMT protein with memory scores in the respondents. Age and memory have a negative correlation with moderate correlation strength. However, the expression of the COMT gene and protein had a very strong positive correlation and the strength of the correlation with memory scores in the respondents. Meanwhile, the length of memorization and the amount of memorization did not correlate with the memory score of the respondents (Table 6).

Table 6. Correlation between COMT characteristics, expression and protein with respondents' memory scores.

Variable	Memory		
	R	p**	Interpretation
Age	-0.397	0.04	Medium correlated
Long memorization	0.010	0.946	Uncorrelated
Number of memorization	-0.140	0.332	Uncorrelated
COMT Gen gene	0.988	0.000	Very strong correlation
COMT Proteins	0.988	0.000	Very strong correlation

p** Pearson test

Discussion

The present study provides evidence that memory performance among adolescent Qur'an memorizers is significantly associated with age as well as with COMT gene expression and COMT protein levels. Taken together, the findings support an integrative neurobiological interpretation of memory in adolescence, in which dopaminergic regulation, developmental stage, and intensive cognitive practice interact to shape memory outcomes. The strong positive association between COMT expression and memory performance, alongside the moderate negative association between age and memory, positions this study within contemporary debates on dopamine-dependent cognition and developmental neuroplasticity.

The observed negative relationship between age and memory performance within an adolescent-dominated sample aligns with developmental neuroscience literature emphasizing adolescence as a sensitive period for cognitive efficiency and plasticity. Neuroimaging studies consistently demonstrate that the prefrontal cortex and hippocampus undergo substantial structural and functional refinement during adolescence, including synaptic pruning, cortical thinning, and progressive myelination, all of which are associated with improvements in memory efficiency and executive control (Baum et al., 2022; Corrigan et al., 2024; Zhu et al., 2024). Within this framework, younger adolescents may benefit from heightened synaptic plasticity and more efficient long-term potentiation processes, which are critical for declarative memory formation (Yan & Rein, 2021; Saarikivi et al., 2023). The present findings therefore suggest that even within a relatively narrow age range, incremental age-related neurobiological changes may translate into measurable differences in memory performance.

Beyond developmental effects, the most striking result of this study is the very strong positive correlation between COMT gene expression, COMT protein levels, and memory scores. COMT plays a central role in dopamine degradation, particularly in the prefrontal cortex where dopamine transporter density is relatively low, making COMT-mediated clearance especially influential for cognitive regulation (Korn et al., 2021). Contemporary studies have shown that individual differences in COMT activity modulate working memory, cognitive flexibility, and executive performance through their effects on dopaminergic tone (Gustavsson et al., 2022; Managò et al., 2023). The present findings extend this evidence by demonstrating that not only genetic polymorphisms but also gene expression and protein levels of COMT are closely associated with memory performance in adolescents.

Importantly, the strong association observed in this study may reflect an optimal range of dopaminergic regulation rather than a simplistic linear relationship. While lower COMT activity has often been linked to better working memory through higher dopamine availability, recent evidence suggests that both excessive and insufficient dopamine can impair cognitive performance, consistent with an inverted-U model of dopamine function (Korn et al., 2021; Louis et al., 2021). In adolescents engaged in intensive memorization, elevated COMT expression and protein levels may contribute to more efficient dopamine turnover, preventing excessive synaptic noise and supporting sustained attention and memory consolidation. This interpretation resonates with findings that efficient dopamine clearance mechanisms are as critical as dopamine release itself for behavioral flexibility and memory stability (Korn et al., 2021).

The present results also converge with age-dependent genetic findings reported in recent literature. Studies examining COMT Val158Met polymorphism indicate that COMT-related cognitive effects are often more pronounced in younger populations than in older adults (Apa et al., 2024; Sivanandy et al., 2021). In older adults, compensatory neural mechanisms and broader neurochemical changes may attenuate the observable impact of COMT-related variation (Pizzonia et al., 2023). The strong COMT–memory association observed here may therefore reflect the heightened sensitivity of adolescent neural systems to dopaminergic modulation, a sensitivity that diminishes with age as neural circuits stabilize and plasticity decreases.

Another notable finding is the absence of a significant association between memory performance and the duration or quantity of Qur'an memorization. While memorization practice has been widely reported to enhance cognitive outcomes, including memory and attention (Khan et al., 2021; Sirin et al., 2021), the present results suggest that biological factors may exert a stronger influence on individual differences in memory capacity than practice-related variables alone. This does not negate the cognitive benefits of memorization but rather indicates that, within a relatively homogeneous group of memorizers, variability in memory performance may be driven more by neurobiological efficiency than by exposure or repetition. This interpretation aligns with studies emphasizing gene–environment interactions, where similar learning environments yield different cognitive outcomes depending on genetic and molecular profiles (Scher, 2021; Radosavljević et al., 2023).

From a broader neurobiological perspective, the findings can be situated within current models of adolescent brain maturation that emphasize the interaction between neurotransmitter systems and structural development. Dopaminergic modulation in the prefrontal cortex interacts with ongoing myelination and synaptic refinement to support working and long-term memory processes (Mendoza et al., 2022; Zhu et al., 2024). Enhanced COMT expression may facilitate more stable dopaminergic signaling during cognitively demanding tasks, such as prolonged memorization, thereby supporting efficient encoding and retrieval. This mechanism is consistent with evidence linking dopamine regulation to long-term potentiation and synaptic plasticity in hippocampal–prefrontal networks (Leisman et al., 2025; Noel et al., 2024).

The findings also carry implications for educational neuroscience. The combination of younger age and favorable dopaminergic regulation appears to confer an advantage in memory performance, reinforcing the notion that adolescence represents an optimal window for intensive learning and memorization. Recent educational and cognitive training studies suggest that interventions aligned with neurodevelopmental timing can yield substantial benefits, particularly when they capitalize on

heightened plasticity and efficient neurotransmitter regulation (Nouchi et al., 2021; Jiang et al., 2022; Ahn et al., 2021). In this context, Qur'an memorization may serve as a naturalistic model of sustained cognitive training, offering insights applicable to broader educational settings.

Nevertheless, the present findings should be interpreted in light of several limitations. The cross-sectional design precludes causal inference, and the relatively modest sample size may limit generalizability. Moreover, the study did not examine COMT polymorphisms, which could clarify how genetic variation interacts with gene expression and protein levels. Future longitudinal studies integrating genetic, molecular, and neuroimaging data are needed to disentangle developmental trajectories and to determine whether COMT-related advantages in memory persist into adulthood or change with ongoing brain maturation.

CONCLUSIONS

The present study demonstrates that memory performance in adolescent Qur'an memorizers is meaningfully associated with developmental stage and, more prominently, with COMT gene expression and protein levels, underscoring the central role of dopaminergic regulation in adolescent cognition. The findings suggest that biological factors related to dopamine metabolism may outweigh practice-related variables in explaining individual differences in memory within relatively homogeneous learning environments. This study contributes to the field by moving beyond genetic polymorphism approaches and integrating molecular expression data with a culturally embedded, real-world cognitive practice, thereby enriching neurocognitive and educational neuroscience perspectives. The results reinforce adolescence as a critical window for intensive learning, with implications for biologically informed educational strategies and timing of cognitive interventions. Future research should adopt longitudinal and multimodal designs, incorporating genetic variation, neuroimaging, and environmental factors, to clarify causal pathways and to determine how COMT-related cognitive advantages evolve across later developmental stages.

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