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ORIGINAL ARTICLE

Correlation between Age and Cathecol-O-Methyl-Transferase (COMT) with Memory in Adolescents

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Abstract

Background: The purpose of this research is to examine the association among the gene and the COMT protein, with the memory abilities of al-Qur'an memorizers. **Methods:** This research was conducted by quantitative research using observational methods with cross-sectional vision. The selection of the exhibition was intentional. The memory ability was measured based on Intelligence Structured Tests (IST) and ELISA was performed to determine COMT protein levels. **Results:** A important relationship was found between age, gene, and protein COMT with memory scores in the respondents. Age shows a negative correlation with moderate strength. Younger age and large number of COMTs were linked to improved memory abilities in adolescents. **Conclusion**: The COMT gene and protein as well as age are correlated with memory. The COMT gene and protein showed a very strong positive correlation. In a sense, the higher the expression of the COMT gene and protein, the higher the memory ability to memorize the Qur'an. Age shows a negative correlation with moderate strength. This means, the younger the age of a memorizer of the Qur'an, the better memory power.

Keywords: age, gene, protein, COMT, memory

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Introduction

The ability to remember information is very important and cannot be separated from human life. The brain continuously processes information and stores important information for later use in future events or decisions. Based on its duration, there is a memory that lasts only a short time known as short term memory (STM) and there is also that lasts for a long time for years or even a lifetime known as long term memory (LTM). Rehearsal or repeating the same information over and over again can strengthen the memory of the information and can convert short-term memory into long-term memory [1].

The process of memory is complex and involves various parts of the brain such as the prefrontal cortex (TPFC), hippocampus, and striatum [2]. There is an interaction between these parts of the brain in various stages of memory which includes the process of recording or encoding information, storing, and retrieving (recalling) information. When memory is formed, changes occur in brain synapses in the form of structural changes and changes at the molecular level. One of the neurotransmitters that play a role in this process is dopamine which can modulate the long-term potentiation (LTP) process, which is one of the synaptic plasticity mechanisms in the formation of LTM [3].

Catechol-O-Methyl-transferase (COMT) is an enzyme that catalyzes O-Methylation of catecholamines, a group of central neurotransmitters that regulate cognitive function [4]. COMT is found in almost all body tissues, including various areas of the brain. The part of COMT is particularly prominent in the PFC in the process of eliminating dopamine. Studies on knock-out (KO) mice, genetically engineered mice that do not have the COMT gene, showed that homozygous male mice experienced a threefold increase in dopamine levels in three areas of the frontal cortex but not in other areas [5]. Meanwhile, heterozygous male mice showed behavioral disorders that looked more aggressive than controls (normal mice). On the other hand, transgenic mice created to overexpress the COMT gene (COMT overexpressing mice / COMT-OE mice) show decreased cognitive function [6].

Various human studies have also indicated a link among the COMT gene and cognitive function, including long-term memory [7]. This can be seen in the study of the Val158Met polymorphism of the COMT gene, one of the most common genetic variations in which the amino acid valine is substituted for methionine and results in changes in the activity of the COMT protein. Individuals with the Met allele had relatively low COMT activity while the Val allele was linked with relatively high COMT activity. A preliminary study by Enoch et. al. (2009) on 328 American Indians showed

that the group of participants who had a history of education > 13 years and had the Met allele performed better on the verbal long-term memory test than those who had the Val allele [7].

There are two forms of isoforms of COMT protein namely soluble protein (soluble-COMT/S-COMT) and membrane-bound protein (membrane-bound COMT/MB-COMT) [8]. S-COMT consists of 221 amino acids with a molecular mass of 24.4 kDa while MB-COMT is longer with 271 amino acids and a molecular mass of 30.0 kDa [9]. Both isoforms are found in almost all body tissues where S-COMT dominates in peripheral tissues such as the liver, kidneys, duodenum, and adrenals while MB-COMT isoforms are more dominant in the brain, particularly in the prefrontal cortex [10].

One activity that requires cognitive ability is memorizing the Qur'an. Al-Qur'an is a scarcity (book) that has had such a wide and deep influence on the human soul. For Muslims, the Qur'an is a revelation from God that is the basis of religious belief, worship, and law; guiding social and individual behavior [11]. In addition, in the Qur'an, there is also the story and history of the people of the past, future events, and science [12]. In the Qur'an, there are not only beautiful sentences with various styles of language but there are also aspects of beauty in the pronunciation of the Qur'an so that there is a beautiful harmonization between speech and meaning [13]. All of these things indicate that the person who can memorize the Qur'an is surely a special person with good memory skill.

In terms of language, hafidz is someone who can memorize the entire Qur'an. The process of memorization or hafazan comes from the root word hafz or hifz which means "to maintain" or "to maintain" [14]. In Islam, the method of remembering the Qur'an includes the spiritual aspects of the Quran not only being remembered but must also be absorbed in the heart and practiced in daily behavior [15]. By its nature, memorization of the Qur'an in the hafidz can be classified as memory or explicit (declarative) memory because the Qur'an contains facts, events, and various information such as science, law, and rules of behavior daily. This type of memory involves conscious awareness and its work depends on the hippocampus and PFC [16].

Memorizing the Quran is an activity that requires good memory skills. One of these memory capabilities is correlated with COMT. This research aims to see the connection among COMT and memory ability in memorizing the Qur'an

Methods

This research is quantitative research that uses a method of observation with transversal vision. The investigation is part of Tahfizhul Al-Qur. The approval of the Institutional Ethics Committee for Research was achieved (43/UN4.6.5.31/PP36-COMETIK/2019) and informed agreement has been given to all participants in the research study.

Sample size

Based on the sample size calculation using version G*Power 3.1.9.2, 49 participants were needed for this study, with a value of 0.05, a power of 80 and an effect size of .30.

Examination

Examination of Memory Ability

The instrument in this research is the Intelligence Structured Tests (IST) Sub Test 9. This instrument is used to measure the memory ability of the respondents. The IST was developed by Rudolf Amtheuer in Germany in 1970, so it is often referred to as IST 70. The IST used in Indonesia is the adaptation of the IST from the Faculty of Psychology, Padjadjaran University, Bandung. In the Memory subtest, participants were asked to memorize 25 words that represent 5 specific words (1 important word will be represented by 5 specific words) for 3 minutes on a separate sheet with questions. After 3 minutes, participants were asked to fill in their biodata and some important identities for 3-5 minutes. Then participants are asked to work on 20 questions related to words that have been memorized previously. The duration of the question is 6 minutes. If the answer is correct (according to the answer key) then each question is given a score of 1, while the wrong answer is given a score of 0. The Memory subtest assessment is obtained by adding up the scores of each question (number of correct answers). The total score is called the raw score (RS). The RS is then converted into the Standard Score/norm (SS). Match the age of the test taker to the table of age group norms. The standard score/norm is obtained from the results of matching the RS of the test takers to the age group norm table according to the age of the participants. The SS that has been obtained in the norm table is converted back to the standard score conversion table for all ages. Finally, the final value will be obtained for the amount of memory ability, scores below 100 are classified in the Short Term Memory category while scores above 100 are classified in the Long Term Memory category.

Examination of COMT gene mRNA expression.

Real-time PCR method to determine the mRNA expression profile of the COMT gene. The process of examining the primary oligonucleotide-specific gene for Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) as a 'housekeeping gene' (internal control). The way to detect the COMT mRNA gene is by using a forward specific primer: GGCACAGAGTGGAAG CATCTC and a reverse primer: CAGAAACCAGCACTGCATCCT. In the PCR protocol, 66 DNA copies were made with a 94oC cycle for 3 minutes, the cycle was repeated 38 times at a temperature of 94oC (30 seconds). The way to detect the GAPDH gene is detected by using the Forward primer: GCTAAGCAGTT GGTGGTGCA

Examination of COMT protein levels

Enzyme-associated immunosorbent assay (ELISA) to determine COMT protein level. The serum samples were added to the 100 l test diluent and had a protein buffer. Subsequently, the 100 l liquid models were incorporated, with the KIT defined. Subsequently, it entered room temperature for 2 hours and then cleaned with phosphate salts (PBS). Then 200 Liquids, chopper recipe (HRP) streptavidin (HRP) and 2 hours incubated were incorporated, then read with ELISA Reader 270 (Biome Rieux, France), with a wavelength of 450 nm in 30 minutes. It then reads the concentration of COMT proteins in the ng/ml units (COMT ab51984, ABCAM).

Procedure

The research subjects were selected from the Imam Al Ashim Islamic Boarding School Campus 1. The researcher selected the memorizers who matched the research inclusion criteria, namely male, and memorized the Qur'an for at least 1 year. Then the researcher met with the memorizers to explain the purpose and procedure of the research. If the memorizer is willing to participate, the researcher will provide an informed consent form to be signed. On a set schedule, the study subjects' memory abilities were measured. In addition, 2 ml of blood was taken for examination of the COMT gene and protein. Blood collection is carried out by trained personnel.

The blood sample is then further processed by researchers to get the serum. The blood serum was then taken to the Biomolecular Laboratory, Faculty of Medicine, Hasanuddin University for examination of the COMT gene and protein. Data collection was carried out from February to April 2019.

Statistical Analysis

Data processing is done with SPSS version 23.00. The analysis was used in different test and correlation tests. Different tests on research variables were carried out using an independent t-test. While the correlation test on the research variables was carried out using the Pearson testing. The implication of this study was decided by the p-value <0.05.

Results

Respondents in this study were mostly less than 18 years old, in the sense that most of the respondents were teenagers, had memorized for less than 3 years, with a total of 1-15 chapters of memorization and the type of memory was Long Term Memory (Table 1).

Table 1: General Features of Respondents

Features	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)

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).

There are important 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).

A strong association was found among age, gene expression and the number of COMT proteins, with respondents' memory scores. Age and memory have a negative correlation with moderate correlative strength. However, gene expression and COMT protein had a very positive correlation and a strong correlation with respondents' memory scores. Meanwhile, the duration of memorization and the amount of memorization do not correspond to the respondents' memory score. (Table 6).

Discussion

Most of the respondents in this study were teenagers. The average respondent has memorized for 2.4 years with an average number of memorization of 12.64 juz. Most of these memorizing teenagers have long-term memory with an average score of 101.26.

The formation of memory in adolescence has a relationship with conditions in childhood. One study found that low physical activity in preschool and elementary school was associated with low memory skills in adolescence [17]. Exposure to polybrominated diphenyl ether (PBDE) in childhood is associated with working memory in adolescent girls. Prenatal and postnatal exposure can reduce memory skills in the early adolescent phase [18].

Depression can reduce cognitive abilities in adolescents [19]. In addition, the use of alcohol and illegal drugs such as marijuana can also damage memory in adolescents [20]. However, marijuana use damages adolescent brain development more severely than alcohol use [21]. In adolescents who consume alcohol, visual memory is more susceptible to damage than working memory [22]. Sleep quality is also a factor that affects adolescent memory, especially working memory. Adolescents who do not get enough sleep show lower working memory abilities [23]. Increasing or decreasing working memory capacity is associated with emotion, executive attention ability, and motivation [24].

Memorizing the Quran requires some working memory, such as long-term memory, short-term memory, and sensory memory [25]. Memorizing the Qur'an requires special abilities related to the ability to identify, motivate and intend [26]. Long-term memory is sensitive to intrinsic and extrinsic motivation. Curiosity as well as certain rewards can improve working memory [27]. Working memory capacity is related to response time to stimuli. The faster a person responds to stimuli, the better his memory capacity [28].

Memorizing the Qur'an is proven to have benefits for intelligence. A study found that memorizing the Qur'an can increase intelligence in children [29]. In addition, memorizing the Qur'an has a better mental health score [30]. Another study found that memorizing the Qur'an can help learn English vocabulary [31]. In particular, memorizing the Qur'an is related to memory. Memorizing the Qur'an affects individual short-term memory abilities [32]. Memorizing the Qur'an also has an optimistic effect on verbal memory, visual memory, and attention processes [33]. Although there are also studies that do not find a relationship between learning the Qur'an and short-term memory [34].

Table 2: Characteristics of respondents based on research variables

Characteristics	mean	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

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

Characteristics	Memory			
Age	Mean ± SD	Min	Max	p*
< 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			
Age	**mean±SD**	**Min**	**Max**	**p***
< 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*
Age	**mean±SD**	**Min**	**Max**	
< 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

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

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

p* Independent T-Test

The tasks in memorizing the Qur'an are limited time, low motivation, low memory ability, and noise [35]. Other factors that affect the ability to memorize are awareness, motivation, and the role of the supervising teacher [36]. The ability to memorize the Qur'an can be done by looking at the Qur'an directly when memorizing, repeating memorization, organizing memorization, doing physical activity, eating balanced, getting enough sleep, and using study aids [37]. Age is a vital aspect under the variations that occur in the brain, microvascular and executive work is more susceptible than memory function [38]. Younger age and COMT genotype Met are associated with better performance in most cognitive domains [39].

Research conducted on adults found that memory skills decline with age [40]. Age-related memory decline is caused by the difficulty of older adults in distinguishing between old and new information. The memory decline is related to the discrimination of cognitive processes (recognition of old/new information) in the visual cortex [41]. Older adults show a decreased capacity for short-term memory and long-term memory compared to younger adults [42]. Aging is associated with neuron differentiation (reduced selectivity of nerve cells in cortical brain regions). Neural differentiation is associated with 2 independent factors, namely age and cognitive performance [43]. The age difference at the time of memory formation affects the quality of memory. This situation when coupled with a decrease in the quality of neurons leads to worsening of memory abilities in older adults [44]. Research conducted on experimental animals has shown that older age is associated with decreased processes of inducing and maintaining LTP and LTD processes [45]. However, different results were found in studies conducted on adults aged 18 to 83 years. The study shows that memory is more related to education level than age [46]. Research conducted on experimental animals has shown that older age is associated with decreased processes of inducing and maintaining LTP and LTD processes [45]. However, different results were found in studies conducted on adults aged 18 to 83 years. The study shows that memory is more related to education level than age [46]. Research conducted on experimental animals has shown that older age is associated with decreased processes of inducing and maintaining LTP and LTD processes [45]. However, different results were found in studies conducted on adults aged 18 to 83 years. The study shows that memory is more related to education level than age [46].

This research found that there was an important connection among the COMT gene and protein and memory scores. According to Mannisto and Kaaakkola, 1999, the main work of COMT is to remove lively (or noxious) catecholamines and several other hydroxyl metabolites. However, catecholamine elimination generally occurs through a reuptake process, which is the process of transporting the active substance back into the cell. This means that COMT will play a role in the place where the reuptake process is experiencing obstacles. For example, the process of inactivation of dopamine in most tissues is mediated by dopamine transporters (DAT) pre-synapse which transport dopamine back into cells for further degradation by the enzyme monoamine oxidase (MAO) [47]. Therefore, the role of COMT will stand out in networks where DAT exists in a limited number.

In the brain, COMT can affect the amount of dopamine's and nominal actives, so it can participate in cognitive function, mood and other mental processes [9]. In studies on the general polymorphism of the COMT gene, Val158Met shows that people with high COMT activity (Val alleles) give physiological responses to PFC, less effective on cognitive tests, compared to people with low COMT activity (meta alleles) [7].

The outcomes of this research are similar to a study conducted on people with psychiatric disorders. According to the research, it was compared with COMT IQ. The higher the COMT statement, the higher the IQ score [48]. According to other studies, COMT is related to cognitive abilities [49,50]. Several studies have found that the COMT gene is related to cognitive skills, such as memory capacity and cognitive control [51].

Genetic differences have a great importance in the cognitive differences of each individual. Several studies have found that COMT and BDNF polymorphisms define their cognitive abilities. However, not all research supports this. In an 8-year long-term study, a population-based sample found that there is a important interaction between COMT and BDNF genotypes, with the reaction time and internal variability of the individual. The COMT Met Allele team had a much faster reaction time. The research also found that the relations among common COMT and BDNF variants explained reaction times between individuals [52].

COMT has several variations of polymorphism, such as Val and Met. This variation has something to do with memory. One study showed that COMT with Val homozygotes slowed visual memory responses whereas COMT, containing MET, accelerated working visual memory [53]. Another study found that there was no effect of COMT status on behavior. However, the prefrontal hippocampal area showed a relationship among COMT Val (158) Met and brain areas with declarative memory processing [54]. Studies in young adults found no difference in the link among memory and the 3 types of COMT genotypes, although the correlation was highest in the Val homozygotes. Based on the study it was concluded that episodic memory and working memory did not change based on COMT in the age group. In older adult subjects, it was found that Val homozygotes exhibit lower memory abilities than heterozygous COMT and Met homozygotes [55]. In brain tumor patients, multivariate analysis showed that there was a important connection among the COMT SNP rs 4680 (Val15Met) and memory. COMT

was importantly associated with attention, executive function, and memory scores [56]. COMT Val carriers are better to train because they have been shown to play a role in increasing brain plasticity thereby improving working memory [57]. The study was conducted on healthy men and found that there was a strong and important relationship among COMT Val 158-Met and cognitive and affective skills. The met allele has higher scores on reasoning, but in general knowledge it has lower scores [58].

Conclusion

The COMT gene and protein as well as age are correlated with memory. The COMT gene and protein showed a very strong positive correlation. In a sense, the higher the expression of the COMT gene and protein, the higher the memory ability to memorize the Qur'an. Age shows a negative correlation with moderate strength. This means, the younger the age of a memorizer of the Qur'an, the better memory power.

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