Macular Pigment Optical Density as a Possible Biomarker for Predicting the Effects of Lutein and Zeaxanthin on Cognition among Young Healthy Adults.

by

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Abstract

Past research suggested that lutein (L) and zeaxanthin (Z) play a role in many aspects of cognitive functions including motor speed, working memory, executive function, psychomotor speed and verbal fluency among elderly people. Moreover, L and Z are the only carotenoids found in the eye, and they are correlated with improved contrast sensitivity, improved temporal vision, reduced glare disability, and reduced risk of age related-macular degeneration (AMD). Animal and postmortem research suggests that MPOD may be a biomarker for predicting cognitive decline with age. The purpose of this study is to evaluate the potential relationship between MPOD and cognition in young healthy adults. There were fifty participants in the current study, 25 had low MPOD. The remaining participants exhibited high MPOD, which was measured using a macular pigment densitometer. People with low MPOD did not perform any worse than people with high MPOD. Although low MPOD in young adults may be a biomarker for future cognitive decline, the effects may lay dormant until later in life. Future research should explore this possibility by replicating this study with an older population.

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There are about 600 carotenoids that occur in nature and of these, approximately 40 are found in the human diet (Ma & Ming Lin, 2010; Zimmer & Hammond, 2007). About 20 can be detected in blood serum and only two, lutein (L) and zeaxanthin (Z), cross the blood-retinal barrier and can be found in the eye (Hammond, 2008; Ma & Ming Lin, 2010). Carotenoids are not manufactured within the human body, and must be acquired through a diet high in green leafy vegetables and other yellow, orange or red pigmented vegetables (Zimmer & Hammond, 2007). Dark fruits (e.g., blueberries) are also high in carotenoids. The two subclasses of carotenoids are carotenes and xanthophylls. Both types include one hydrogen atom and one carbon atom, with the key difference being that xanthophylls are oxygenated (Krinsky, Landrum & Bone, 2003). Carotenoids are believed to serve an antioxidant function within the body, and help protect against damage caused by free radicals that result from harmful environmental agents, including smoking, stress, pollution, and UV radiation.

The health benefits of these micronutrients are far reaching. For instance, beta-carotene can be metabolized into vitamin A, which is involved in the repair of body tissue and the maintenance of a strong immune system. Unlike vitamin A, beta-carotene is not toxic when taken in high doses, and can be stored by the body until it is needed, which makes it safer than a diet high in vitamin A. Other research suggest that beta-cryptoxanthin, lycopene, lutein and zeaxanthin may play a role in reducing the risk of lung cancer, and lycopene is correlated with reduced risk of prostate cancer (Stringham, Bovier, Wong & Hammond, 2010).

Of the 16 carotenoids found within the brain, the xanthophylls lutein (L) and zeaxanthin (Z) make up 66% to 77% of the total amount of carotenoids found within the

brain and they are distributed among four regions including the cerebellum, the frontal lobe, the pons and the occipital cortex (Johnson, 2012; Polidori, De Spirt, Stahl & Pientka, 2012; Renzi & Hammond, 2009; Vishwanathan, Neuringer, Snodderly, Schalch & Johnson, 2013; Zimmer & Hammond, 2007). Research has suggested that they play a role in many aspects of cognitive functions including motor speed, working memory, executive function, psychomotor speed and verbal fluency among the elderly. They may also slow the progression of age-related cognitive disorders such as Alzheimer's disease (Johnson, 2012). Moreover, L and Z are the only two carotenoids found in the eye, and they are correlated with improved contrast sensitivity, improved temporal vision, reduced glare disability, and reduced risk of age related-macular degeneration (AMD) (Ciulla & Hammond, 2004; Ma &Ming Le, 2010; Renzi & Hammond, 2010). They may also contribute to slowing the progression of AMD.

It is interesting that L and Z appear to play such a salient role by protecting both the brain and the eye from age-related degenerative disorders. This exploratory study evaluated the potential relationship between L and Z in the eye as they correlate with L and Z in the brain among young healthy participants, to see whether differences exist on cognitive task performance in young, college-age participants with low vs. high macular pigment as there appears to be in older individuals. That is, do the benefits of high macular pigment show themselves in early adulthood? Also, are there any negative/detrimental effects of low macular pigment in this age group?

Prior to addressing these questions in the current study, a detailed discussion of the role of L and Z in vision and cognitive function is provided as a background for understanding the interaction of carotenoid levels in the retina and cognitive functions.

Ocular Heath and L an Z:

It is well known that L and Z are found in their highest concentrations within the foveal region of the retina and form the macula lutea, also known as the macular pigment. Research shows that macular pigment protects the eye by acting as an antioxidant, and by filtering harmful short wavelength light from reaching the retina and causing damage. Specifically, macular pigment plays an integral role by making the eye less sensitive to the effects of blue light, forming a natural blue light blocking sunglasses effect (Hammond & Fletcher, 2012). The macula can absorb up to 90% of the blue light going through the retina at 460 nm, which is the peak wavelength in the macular pigment optical density spectrum (MPOD). In order to evaluate macular pigment levels, an instrument known as a Macular Pigment Densitometer is used; this utilizes heterochromatic flicker photometry (HFP). HFP is used to compare two similar light sources. The lights are presented in counter phase which produces a flickering sensation. The densitometer presents a critical flicker fusion task at a one degree angle from the center of the fovea. The task involves presenting a blue light 460 nm in counter phase, with a green light 570 nm (Ciulla & Hammond, 2004; Hagen, Krebs, Glittenberg & Binder, 2010; Hammond & Wooten, 2005; Krinsky, Landrum & Bone, 2003; Snodderly, Mares, Wooten, Oxton, Gruber & Ficek, 2004; Wooten & Hammond, 2005; Wooten, Hammond, Land & Snodderly, 1999). The green light is used as a reference because it is outside the range of wavelengths that macular pigment absorbs. The participant slowly adjusts the rate of modulation in the blue light by turning a button on the densitometer until the flicker is no longer visible. This occurs when the luminosities of the opposing light sources are matched at the level of the photoreceptors. At this point the

experimenter instructs the participant to continue to adjust the rate of modulation until the subject sees the flickering light again. Once this is done, the participant is instructed to find the center of the no flicker zone. This data can then be used to get an accurate estimate of macular pigment ocular density (MPOD) because it is assumed that people with higher MPOD will require higher blue light intensity in order to compensate for the attenuation of blue light by macular pigment (Krinsky, Landrum & Bone, 2003). However, the lens also plays a role in the amount of blue light needed to minimize flicker. Therefore, it is necessary to repeat this process at a seven degree angle from the center of the fovea. The parafoveal measurement provides insight into what role the lens plays in blue light absorption.

The protective benefits of macular pigment have been illustrated in multiple research studies evaluating the relationship between macular pigment and real world visual processing. For instance, earlier research regarding visual health began by looking at factors that predicted differences in people's ability to see varying contrast known as contrast sensitivity (CS) and also focused on their ability to adjust to glare conditions or glare disability (GD). In order to take (CS) measurements, an instrument known as a Vector Vision CVS 1000 was used. This apparatus measures contrast at 2, 4, 6 and 8 c/deg. Glare disability (amount of visual interference experienced by a participant under glare conditions) was measured by turning on two lights attached to the 4 c/deg cycle row on the CVS 1000 that mimic an approaching vehicle's head lights at 20 feet. A participant's glare disability score was calculated by subtracting the participant's glare score from his/her score at the 4 c/deg row under a no-glare condition. The Vector Vision test consists of four rows of backlit circular contrast gradients. Each row had a series of 7

light pairs (columns) with one light appearing directly above the other. One of the lights contained a set of vertical lines that matched the lines on a template appearing on the left side of the rows. The other lights did not contain a gradient. Participants were asked to specify verbally whether the gradient lines were on the "top", "bottom" or "neither" column within a specific row for each of 7 light pairs within a row. People with higher MPOD did better than those with lower MPOD on both the contrast and glare disability tasks (Holloway, Nanez, Hammond, Jorgenson & Zimmerman, 2001).

Additional research involving glare disability was conducted in order to find out whether L and Z supplementation improves participants' ability to adjust to glare. This experiment used similar equipment to the previous study. However, in this study participants were instructed to increase the intensity of the glare source until they could no longer see the gradient lines. Participants were supplemented with 10 mg of L and 2 mg of Z for 6 months (Stringman, Bovier, Wong & Hammond, 2010). The participants all exhibited improved MPOD after supplementation and on average were able to withstand 58% greater intensity of glare before no longer being able to see the gradient.

This research led to additional studies evaluating the relationship between contrast sensitivity and glare disability among participants diagnosed with macular degeneration. Over time, oxidative damage to the macula leads to age-related macular degeneration (AMD). The risk of AMD is increased for people with low MPOD (Ciulla & Hammond, 2004). Early stages of AMD tend to be asymptomatic, but as the disease progresses, it eventually leads to central vision blindness. AMD is the leading cause of blindness in western culture, and AMD prevalence rates increase with age. For instance, about 2% of

American's between the age of 40 and 49 have intermediate AMD and .1% have advanced AMD (Renzi & Johnson, 2007). Moreover, the numbers increase dramatically and prevalence rates among people between 70 and 79 are 12% and 2.4%, respectively, while prevalence increases to 23.6% and 11.8% for people over 80. Currently, there is no cure for AMD and research has been focused on strategies that show promise for slowing down the progression of the disease.

The Lutien Antioxidant Supplementation Trial was a double blind placebo controlled study that contributed the most to the current paradigm for slowing the progression of AMD (Richer, Stiles, Statkute, Pulido, Frankowski, Rudy, Pei, Tsipursky & Nyland, 2004; Renzi & Johnson, 2007). In this 12 month longitudinal study, 90 participants were randomly assigned to one of three groups. Two experimental groups were compared to a control group that received only a maltodextrin placebo (i.e, suger pill). The first experimental group received 10 mg of lutein while the other experimental group received 10 mg of lutein with additional carotenoids and multivitamins. The goal of this study was to evaluate the relationship between supplementation and MPOD, contrast sensitivity, and glare disability among participants diagnosed with AMD. After a year of supplementation, the research found that participants supplemented with lutein only had a mean MPOD improvement of 36% and participants supplemented with lutein and antioxidants had a mean MPOD improvement of 43%. MPOD declined slightly in the placebo group. Both of the experimental groups also exhibited improved acuity, increased contrast sensitivity and reduced glare disability with the lutein and antioxidant group performing slightly better than the lutein only group. The results suggest that the progression of AMD can be slowed with an aggressive lutein and multivitamin regimen.

Cognition and L and Z:

Interestingly, research has shown that L and Z are also correlated with cognitive function among elderly populations, and animal research has been conducted to determine whether MPOD might be a reliable biomarker for xanthophyll concentrations within the brain (Johnson, 2012; Vishwanathan et al, 2013). Specifically, a group of monkeys were put on a lifetime diet of monkey chow supplemented with L and Z. After the monkeys were sacrificed, researchers used high-performance liquid chromatography to separate L and Z from retinal tissue and brain tissue. Results showed that L and Z levels in the cerebellum were related to L and Z in the retina. There was a trending correlation between L and Z levels in the occipital cortex when compared to L and Z in the retina. Z concentrations in the retina were significantly related to Z levels found in the pons and in the frontal cortex.

Human research suggests that L and Z serum levels are depleted for people with Alzheimer's disease and Mild Cognitive Impairment (MCI). Specifically, it has been reported that participants in the lowest quintile regarding cognitive measures had an increased likelihood of having low levels of total plasma carotenoids. Low Z levels were correlated with decreased performance on cognitive tests evaluating scanning, processing speed, mental flexibility and executive function (Akbaraly, Faure, Gourlet, Favier & Berr, 2007).

Moreover, a 4-month double masked supplementation study with L and DHA illustrated improved performance on a battery of cognitive tests (Johnson, 2012; Johnson, McDonald, Caldarella, Chung, Troen & Snodderly, 2008). This research consisted of 49

women who were randomly assigned into one of three groups, a control (placebo only) group consisting of 10 women, and three experimental groups. Fourteen women received only 800 mg of DHA while 11 women received only 12 MG of lutien. The remaining women received a combination of DHA and lutien. Supplementation improved verbal fluency scores for all experimental groups while the combination group displayed improved scores for memory as well. This suggests that supplementation may help slow cognitive decline among elderly people at risk of developing MCI or Alzheimer's disease. These findings are encouraging; however, the study needs to be replicated with a much larger participant population, in order to verify whether the findings are supported.

In any case, some previous research points toward a positive relationship between L and Z and both visual abilities and cognitive processes. Moreover, supplementation may reduce adverse effects on vision for people of all ages. Supplementation may also slow the progression of cognitive impairment among the elderly. Since HFP may serve as a noninvasive measurement of L and Z in brain tissue, the proposed exploratory study would be the first to use it among young healthy participants. The goal here is to evaluate the relationship between MPOD and cognition among young adults. As stated above, if there are differences in cognitive function among young adults with high vs. low MPOD it would indicate that such a relationship is present relatively early in development. If no significant differences are observed among this age group, but a trend is present, it would suggest low MPOD may be an early warning sign regarding development of future cognitive impairment with age.

Methods

Participants

Seventy-five participants from a large southwestern university were screened with a macular pigment densitometer in order to identify participants with high and low MPOD. Participants with average MPOD were excluded from the study. The experimenter explained to them that the study involved participants at the higher and lower ends of the MPOD spectrum. Participants not included in the study due to their average MPOD levels were thanked for their time and dismissed. Participants' MPOD levels were determined in accordance with Renzi and Hammond's (2010) work that suggests low MPOD ranges between .00-.20 while high MPOD ranges between .41-1. After excluding 25 participants with average MPOD, the subject pool included 25 people with low MPOD and 25 people with high MPOD (Males =14, Females =36, aged 18-40 years) (Table 1). All participants self-reported good ocular health, and had at least a best corrected visual acuity of 20/40 Snellen.

Materials and Procedure

HFP was used to assess MPOD. This measurement has been validated on normal subjects, and prior research has tested the reliability of this method (Ciulla & Hammond, 2004; Wooten, Hammond, Land & Snodderly, 1999). It has been determined that with proper instruction, participants recruited from the general population can undergo testing and researchers will obtain reliable results. Test stimuli were presented in the center of a 6-degree, 10.5 cd/m^2 470-nm circular background. The test stimuli were presented in counter phase that included a 460 nm testing field and a 570 nm reference field. The

radiance of the LEDs was between 11-12 Hz in the foveal condition and 6-7 Hz in the parafoveal condition. Participants were instructed to focus on the center of the blue flickering circle and were allowed a practice trial to find the center of the no flicker zone. Participants then repeated this process six times and each participant's average was calculated to get the foveal value. After the first six trials, a red led light was turned on that participants saw on the left side of their visual field. Participants were instructed to focus their central vision on the red LED while watching the blue light with their peripheral vision. Participants were then instructed to find the no flicker zone six more times in order to obtain their parafoveal measurement. The two averages were then used to calculate MPOD. Following MPOD testing, all participants that met the visual acuity selection criteria were administered a battery of cognitive assessments provided by CNS Vital Signs (Table 2). This consisted of an on-line set of tests that took about one hour to complete. These tests measured 12 cognitive domains including reasoning, memory, psychomotor speed, reaction time, complex attention, cognitive flexibility, processing speed, executive function, verbal memory, visual memory, working memory and sustained attention. Participants were advised to ask for clarification if they did not understand any of the test instructions and were also allowed to take breaks between assessments. When a participant completed the tests, the experimenter evaluated the results of the test battery, which provided insight into the validity of the outcome for each domain. If a subject received invalid results for any of the tests, he/she was re-administered the instructions and retested in the areas that were deemed invalid.

Results

In order to determine whether a relationship between macular pigment level and cognition exists in young healthy individuals the analyses focused on the difference in cognitive scores for people with low MPOD as compared to people with high MPOD. A 2 (MPOD) x12 (Cognitive Domian) multivariate analysis of variance (MANOVA) was preformed with MPOD (high vs low) as a between subject factor predicting the twelve measures of cognitive ability. The reason the MANOVA was used is because we were interested in examining the relationship between MPOD and the cognitive measures, namely, reasoning, memory, psychomotor speed, reaction time, complex attention, processing speed, executive function, verbal memory, visual memory, working memory and sustained attention. Moreover, a correlation matrix was preformed to show that most of the dependent variables were strongly related to each other which justifies using a MANOVA. Analyses of the various cognitive scores revealed no significant relationship between MPOD levels and cognition, $F(12,36) = .253, p = .456$ (Tables 3,4).

Discussion

This study was highly exploratory in nature, and there may be many reasons for the lack of significant results. Previous research has suggested that L and Z play a role in the maintenance of visual health for people of all ages and may also protect against cognitive decline for the elderly. However, the research suggesting that MPOD can be used as a biomarker in order to determine the amount of L and Z that people have in their brain tissue is in its infancy, limited to research with elderly participants to date. Although animal research and postmortem research on humans have suggested that MPOD is a reliable indicator of xanthophyll levels in brain tissue, only one other study

has attempted to compare MPOD to cognitive function (Johnson, 2012; Johnson et al, 2006). This study measured MPOD and serum levels of L in a group of women that underwent four weeks of supplementation and took a battery of cognitive tests both pre- and post-supplementation. Participants supplemented with L and DHA had the most improved cognitive scores and had the largest increase of lutein in the macula. This suggests that amount of lutein in an individual's diet may not be as important as how it is transported across the blood brain barrier.

Specifically, research of Johnson et al (2006) suggests that while lutein is important with regards to cognitive improvement among the elderly, a balanced long-term diet that helps facilitate the absorption and transport of nutrients across the blood brain barrier may be essential in order to receive the best results from supplementation. Although this study found that MPOD did not correlate with cognition the increased level of L in the retina may also suggest increased concentrations in other brain areas. It is noteworthy that this was a healthy group of women and MPOD tends to remain constant for people that maintain a healthy lifestyle. It is possible that including all MPOD levels made it impossible to see any potential effects on cognition. Therefore, it may be beneficial to replicate this study while excluding people with average MPOD because this may illustrate that individuals with low MPOD preform significantly worse on cognitive tests when compared to people with high MPOD.

The above findings could help develop insight into the weaknesses of the current study and suggest future directions for this type of research. It is clear that some of the participants in this study have low MPOD, yet their performance on the cognitive tests did not differ from that of participants with high MPOD. This could be related to the

degenerative nature of mild cognitive impairment. Although these people may be at risk of future cognitive impairment, the effects may be dormant until later in life. Therefore, it may be advantageous for future research to replicate the current study within an older population. Also all the participants in the current study were university students. It is possible that being in an environment that encourages constant intellectual exercise may protect them from experiencing or exhibiting any early indications of cognitive decline. Therefore, replicating the study in the general population may produce different results with young people.

An alternative way to find out whether MPOD can be used as a biomarker for cognition would be to conduct a longitudinal study. This research could recruit participants without any signs of cognitive impairment and follow them across time. Participants with average MPOD should not be included in the study. All qualifying participants should undergo MPOD testing and cognitive evaluation every five years. This would enable researchers to see at what age MPOD is indicative of impaired cognitive function if a relationship is found to exist, as previous research with older subjects suggests. Moreover, this would also provide the opportunity to conduct further studies to continue exploring the role of L and Z supplementation on participants experiencing the earliest sign of cognitive impairment, as well as on participants with different levels of MPOD. Future studies may also explore the relationship between MPOD and cognitive function and other factors, such as behavior (e.g. smoking, alcohol consumption, UV sunglass wear), long-term dietary differences, gender, and ethnicity, for example.

In sum, as stated above, the fact that the current study did not find differences in cognitive abilities between university students with low vs. high MPOD, may be due to the fact that the they are young and, although they differ in MPOD levels, harmful effects of low MPOD may not appear until later in the developmental cycle. Alternatively, the results could be due to the fact that the participants were all students enrolled in the daily rigors of university academics that requires consistent cognitive challenges (i.e. they are highly cognitively active). The results could also be due to an interactive effect between age and cognitive activity levels among university students. Follow-up studies could help to clarify the results picture by testing young, non-university students in the general population.

In conclusion, much work remains to be done in order to disentangle the relationship between MPOD in the visual system and in the brain and their on ocular health and cognitive functioning in the in humans as we age.

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Tables

Table 1

Demographic Data

	Low MPOD			High MPOD		
	N	M	SD	N	M	SD
Age	25	21.60	5.11	25	21.96	4.85
Sex	25	1.76	.436	25	1.64	0.49
Education	25	14.32	1.55	25	14.40	1.61

Sex: 1= Male, 2 = Female

Education: Number of years in school

Table 2

Cognitive Assessments

Test	Assessment	Task
Verbal Memory	Verbal Learning Memory for Words Word Recognition Immediate and Delayed Recall	Fifteen Words are presented one by one. For immediate recognition subjects have to recognize those words nested among 15 new words. Than after 8 more tests there is a delayed recognition trial.
Visual Memory	Visual Learning Memory for Geometric Shapes Geometric Shape Recognition Immediate and Delayed Recall	Fifteen shapes are presented one by one. For immediate recognition subjects have to recognize those words nested among 15 new words. Then after 7 more tests there is a delayed recognition trial.
Finger Tapping	Motor Control Fine Motor Control	Participants are required to press the space bar with their right index finger as many times as they can in 10 seconds. This process is repeated with their left index finger.
Symbol Digit Coding	Information Processing Speed Complex Attention Visual Perceptual Speed	This test consists of serial presentations on the screen, each consisting of 8 symbols above and empty boxes below. Participants are presented with a key indicating what symbols correspond with each number. The participant enters the number that corresponds with the highlighted symbol.
Stroop Test	Simple Reaction Time Complex Reaction Time Stroop Reaction Time Inhibition/Disinhibition Frontal or Executive Skills Processing Speed	Words are presented in black and the participant presses space bar as soon as they see the word. In the second part participants press space bar when the color and the word match. In the third part participants press space bar when the color does not match the words meaning.

Shifting Attention Test	Executive Function Shifting Sets and Rules Rapid Decision Making Reaction Time	This test measures the ability to shift from one set of instructions to another quickly. Three figures appear on the screen, one on top and two on the bottom. Participants are asked to match one of bottom shapes to the top either by shape or color as the rules change rapidly.
Continuous Performance	Sustained Attention Reaction Time Impulsivity	A series of letters is flashed on the screen. Participants are asked to press the space bar when the letter B is flashed.
Non-Verbal Reasoning	Reasoning Reasoning Recognition Speed	This test is comprised of 15 visual analogies that get progressively harder. Participants must decide what shape goes in the empty box.
Four Part Performance	Sustained Attention Working Memory	This is a four part test. Part one is simple reaction time. Part two measures choice reaction time. Part three is a one back test. Participants are only supposed to respond if the figure on the screen is the same as the previous figure. Part four is a two back continuous performance task.

Table 3

Low vs. High MPOD on Cognitive Ability

Measures	Low MPOD		High MPOD			
	M	SD	M	SD	*F*	*p*
Memory	71.44	24.54	61.12	28.67	1.19	.18
Psychomotor Speed	48.48	26.17	52.88	31.50	0.29	.59
Reaction Time	65.08	22.81	54.24	34.00	1.75	.19
Complex Attention	46.76	30.13	44.32	31.69	.08	.78
Cognitive Flexibility	53.60	32.88	48.04	33.45	.35	.56
Processing Speed	46.40	32.79	53.08	33.31	.51	.48
Executive Function	56.60	29.89	50.48	32.92	.47	.50
Verbal Memory	71.52	28.88	60.40	31.32	1.70	.20
Visual Memory	64.04	24.05	61.00	31.99	.14	.71
Reasoning	46.80	31.19	53.32	28.12	.60	.44
Working Memory	55.52	30.54	49.96	28.65	.44	.51
Sustained Attention	52.20	23.99	52.64	26.74	0.00	.95

Table 4.

Correlation Matrix of Dependent Variables

Measures	1	2	3	4	5	6	7	8	9	10	11	12
1. Memory	-											
2. Psychomotor Speed	.30*	-										
3. Reaction Time	.46**	.65**	-									
4. Complex Attention	.26	.30*	.22	-								
5. Cognitive Flexibility	.32*	.46**	.51**	.86**	-							
6. Processing Speed	.19	.70**	.47**	.70**	.61**	-						
7. Executive Function	.32*	.44**	.52**	.81**	.98**	.60**	-					
8.Verbal Memory	.76**	.29*	.31*	.31*	.25	.07	.23	-				
9.Visual Memory	.78**	.14	.35*	.08	.20	.18	.21	.23	-			
10. Reasoning	.10	.27	.06	.29*	.28*	.28*	.22	.24	.00	-		
11.Working Memory	.44**	.56**	.38**	.52**	.62**	.62**	.60**	.39**	.27	.25	-	
12.Sustained Attention	.35*	.52**	.40**	.43**	.54**	.63**	.53**	.38**	.14	.24	.81**	-