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Triallelic relationships between the serotonin transporter polymorphism and cognition among healthy older adults

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Abstract

The biallelic serotonin transporter polymorphism (5-hydroxytryptamine transporter linked polymorphic region (5-HTTLPR)) is a common genetic sequence associated with serotonin transporter (5-hydroxytryptamine transporter (5-HTT)) expression, which is further modulated by a triallelic single-nucleotide polymorphism (rs25531). Recent studies using the biallelic 5-HTTLPR have identified a beneficial role of low 5-HTT expression on cognitive performance, although no studies have examined the impact of the triallelic 5-HTTLPR/rs25531 marker on cognitive performance among healthy older adults. In the present study, we addressed this issue in 84 healthy older adults genotyped for biallelic and triallelic variants of 5-HTT. Groups were created based on low, medium and high levels of expression, as indicated by the triallelic marker. Results indicated that individuals with low 5-HTT expression performed significantly better on a test of memory compared with individuals with medium 5-HTT expression. This suggests that possession of low-expressing genetic variants of 5-HTT is modestly associated with enhanced cognitive performance among healthy older adults.

Keywords

5-HTTLPR; memory; executive function; aging

Introduction

5-HTTLPR is a variable repeat sequence in the promoter region of the serotonin transporter (5-HTT) gene [*SLC6A4*; 1]. Analysis of brain tissue has demonstrated that the short allele

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

(S) of the polymorphism [compared with the long allele (L)] is associated with an approximately 50% decrease in the levels of 5-HTT availability [2]. The 5-HTTLPR is further modified by an A/G single-nucleotide polymorphism (SNP; rs25531) that affects gene expression almost exclusively on the L allele (the “G” SNP is rarely present on S alleles), such that the L_G allele shows low expression, nearly equivalent to the S allele [3]. The use of triallelic genotypes provides optimal prediction of 5-HTT expression levels.

Serotonin is involved in the regulation of emotion and the development of psychiatric symptoms. Individuals with less efficient reuptake of serotonin are thought to be at increased risk for emotional disturbance, and the risk appears to increase in a dose-dependent manner with the presence of two S alleles [4]. Many studies have demonstrated that one S allele increases the risk of psychiatric symptoms among individuals with a history of early life stress [5], late life serious adverse events and trauma [6,7], and/or psychiatric symptoms associated with Alzheimer’s disease [8]. Thus, these findings suggest a negative impact on psychiatric health across the adult lifespan.

Although most studies on the 5-HTTLPR polymorphism have focused on psychiatric indices such as depression, psychosis and anxiety, several studies have reported an association between the S allele and brain dysfunction both with and without depression [9,10]. Rhesus monkeys with the SS genotype exhibit significantly poorer performance on tests of object discrimination and extinction compared with monkeys with the LL genotype, indicating impaired cognitive flexibility [10]. In human studies, O’Hara et al. [9] reported a significant interaction between the S allele, high levels of waking cortisol secretion, decreased hippocampal volume and memory impairment among healthy older adults. Furthermore, Marini et al. [11] revealed a heightened risk of mild cognitive impairment among individuals with the S allele. Collectively, these findings suggest that the low-expressing S allele of 5-HTTLPR may be a genetic risk factor for brain dysfunction independent of psychiatric morbidity.

However, not all studies have revealed a negative relationship between the S allele and cognitive impairment. Several studies have reported enhanced cognitive performance among healthy adults with at least one S allele [12–16]. Specifically, S allele carriers have exhibited enhanced performance on tests of executive function [13,14], working memory [12] and attention [16] compared with individuals with the LL genotype. These studies suggest that the S allele is beneficial for optimal cognitive function.

Although previous studies have revealed a significant relationship between reduced 5-HTT expression and enhanced cognitive performance, this relationship has primarily been examined in the context of biallelic classification of 5-HTTLPR. Because the triallelic SNP marker of 5-HTTLPR significantly alters 5-HTT expression, examining individuals only by biallelic genotype does not provide a comprehensive assessment of 5-HTT expression and its association with cognition [17]. Thus, it remains unclear as to what extent low 5-HTT expression represents a biomarker of functional brain integrity among healthy older adults. In the present study, we aimed to clarify this issue among a sample of healthy adults ranging in age from 51–85 using neuropsychological indices.

Methods

Participants

Data were obtained from 84 English-speaking adult men ($n = 30$) and women (n 54) involved in a longitudinal study of healthy aging. Participants were selected through newspaper and periodical advertisements in the local community. Exclusion criteria were evaluated via self-report questionnaires. Individuals with a history of substance abuse or psychiatric diagnosis according to the *Diagnostic and Statistical Manual of Mental Disorders-IV* were excluded from the study (i.e. all Axis I and II disorders with the exception of treated depression). Individuals were also excluded if they reported a history of learning disability, a confounding medical condition capable of significantly impacting cognition including neurological disorders (e.g. multiple sclerosis, thyroid dis ease, stroke, etc.), or history of significant head injury (defined as a loss of consciousness greater than 10 minutes). Individuals were screened for dementia using a cutoff score of 24 on the Mini-Mental Status Examination. All participants who scored below the cutoff were excluded from the study. Individuals were not excluded based on vascular factors such as hypertension given the frequency of hypertension in older populations. Diabetic conditions were only excluded if treated with antidiabetic medication. As indicated in the Data Analysis section below, frequencies of these conditions were examined to account for significant differences between groups.

All subjects provided informed consent prior to enrollment in the study, and all were given financial compensation for their participation. Approval was obtained by the local institutional review board.

Genotyping

Genomic DNA was extracted from saliva samples purified using the Oragene DNA collection kit (DNA Genotek, Ottawa, Canada) and processed using the Autopure LS nucleic acid purification system (Qiagen Pty Ltd., Victoria, Australia).

Genomic DNA was amplified using the QIAGEN Multiplex PCR Kit (Qiagen Pty Ltd., Victoria, Australia) with the following primers: forward, 5′-TCC TCCGGTTTGGCGCCTCTTCC-3′; reverse, 5′-TG GGGGTTGCAGGGGAGATCCTG-3′. Polymerase chain reaction amplification conditions were as follows: 94 °C for 15 minutes; 38 cycles of 94 °C for 30 seconds, 66 °C for 45 seconds and 72 °C for 60 seconds; followed by 72 °C for 10 minutes. Amplicons were digested with *Hpa*II, and fragments were separated by agarose gel electrophoresis. The forward primer introduces an additional *Hpa*II site to enable digestion efficiency to be monitored. Fragment sizes (in bp) for each allele were therefore as follows: L_A, 506 + 6; L_G, 396 + 110 + 6; S_A, 463 + 6; S_G, 396 + 67 6.

To account for the effect of the A/G SNP rs25531 polymorphism, we grouped subjects according to their predicted levels of 5-HTT expression [18]: “Low” (S_AS_A, S_AS_G, S_AL_G, S_GL_G and L_GL_G genotypes), “Medium” (S_AL_A, S_GL_A and L_AL_G genotypes), or “High” (L_AL_A genotypes). Of the 84 participants, 24 were classified as “Low,” 37 as “Medium” and 23 as “High.” To enable a comparison of results with existing literature, we also carried out separate analyses using the S and L alleles, without the added modification of rs25531.

When calculated as two separate biallelic groupings (S/L and A/G), only rs25531 conformed to Hardy Weinberg Equilibrium (HWE; $p > 0.05$). Using a three-allele approach (S/L + rs25531 modification), frequencies were 49.4% for L_A, 42.86% for S_A and 7.74% for L_G and S_G (minor alleles). Chi-square analysis indicated linkage disequilibrium using the entire mixed race sample ($p = 0.045$), which may be a result of population stratification. When examining Caucasians only, frequency distributions were consistent with HWE using both biallelic and triallelic classification (HWE $X^2 > = 3.84$). Because mixed race samples often impact HWE, race distributions were examined between groups to examine the need for covariates in the primary analyses.

Neuropsychological testing

A battery of neuropsychological tests was administered to all participants. A trained research assistant administered the neuropsychological tests utilizing standardized procedures and instructions from available manuals. Scoring and data entry were verified by an independent research assistant after completion of the cognitive assessment. The neuropsychological tests were selected based on known sensitivity to cognitive aging. Brief descriptions of the cognitive tests are provided below.

Repeatable battery for the assessment of neuropsychological status (RBANS)

—The RBANS [19] contains subtests of immediate memory, visuospatial, language, attention and delayed memory to assess each of the cognitive domains, and it has been validated as a sensitive tool for detecting cognitive deficits in healthy populations [20]. Immediate memory consists of a verbal list-learning and story memory task. For the list-learning task, participants are read aloud a list of 10 unrelated words and must repeat back as many words as they can remember across four separate trials. For story memory, participants are read a brief story and must repeat back as much information from the story as they can remember across two trials. Visuospatial consists of a figure copy and line orientation task. Figure copy requires participants to complete an exact copy of a complex geometric figure. For line orientation, participants are shown 13-numbered lines stemming from a 180° axis. Below each item are two lines that match two of the lines in the item, which participants must match to their numbered coordinates. Language consists of picture naming and semantic fluency. Picture naming requires participants to correctly identify the names of 10 common objects, whereas semantic fluency requires participants to provide as many examples of a given category (e.g. fruits and vegetables) within 60 seconds. Attention consists of digit span and coding. Digit span is a numerical repetition task with string length increasing from 2 to 9 digits. Coding requires participants to match as many digits to their corresponding shapes in the coding key within 90 seconds. Delayed memory consists of four subtests: list-learning recall, list recognition, story recall and figure recall. For each recall task, participants must freely recall information from the initial memory tasks and figure copy. List recognition requires participants to correctly identify the words presented in the initial list-learning task when they are read aloud with 10 distractor words. Raw subtest scores are scaled for each cognitive domain to create index scores. The outcome measures for each subtest are converted to an index score based on standardized performance scores by age. Total scale scores are provided for ages 20–99 years in 10-year age bands. Index

scores were used as the primary dependent measure to assess cognitive function within each domain.

Trail making test—The Trail Making Test [21] consists of two tasks (Trails A and B) to assess cognitive processing speed and executive function. Trails B is a measure of cognitive flexibility that requires participants to connect numbers to letters in an alternating sequence such that a line is drawn from 1 to A, A to 2, etc. The time to complete the task was the primary outcome measure.

Letter number sequencing—Letter Number Sequencing is a subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III) [22]. Participants are presented with a string of random numbers and letters and are asked to repeat the numbers and letters presented in sequence, numbers first in order then letters in alphabetical order. Initially, the participants are given two characters (three unique trials) and build up to nine characters per trial block or until they are unable to complete a full block. This task focuses on the working memory domain as subjects must remember the letters and numbers presented and be able to correctly order the numbers and letters in sequence. The primary outcome measure was the number of successfully completed trials.

Color-word interference test—The Color-Word Interference Test (CWIT) is a sub-test of the Delis-Kaplan Executive Function System (DKEFS) neuropsychological battery [23]. The CWIT is an adaptation of the Stroop paradigm [24] that measures cognitive flexibility and attention. The CWIT consists of four trials of color naming, word reading, response inhibition, and response inhibition/switching (trials 1–4, respectively). In trials 3 and 4, participants must actively inhibit natural responses to observed stimuli. During trial 3, participants are presented with a color word (i.e. blue) in a contrasting color-word combination (i.e. the word blue printed in red ink) and must name the color of the ink (red) the word is printed in rather than reading the word (blue). Trial 4 requires participants to alternate reading the name of the color word (blue) and naming the color of the ink the word is printed (red). Performance is determined by completion time and the number of corrected and uncorrected errors on each trial. Completion times on trials 3 and 4 were the primary outcome measures.

Data analysis

Demographic variables including age, gender, race and years of education were examined prior to statistical analyses. Blood pressure (averaged across three time points during the cognitive assessment) and self-report histories of diabetes and psychiatric difficulties were also examined between groups. Using methods similar to Wilhelm et al. [17], individuals with an S_AS_A, S_AL_G or L_GL_G genotype were placed in the low 5-HTT expression group (n = 24, 8 males and 16 females). Individuals with an S_AL_A, S_GL_A or L_AL_G genotype were placed in the medium 5-HTT expression group (n= 37, 15 males and 22 females). Individuals with only the L_AL_A genotype were placed in the high 5-HTT expression group (n = 23, 7 males and 16 females).

Two separate multivariate analyses of variance (MANOVAs) were completed for all of the dependent variables, with 5-HTT expression serving as the independent variable in each MANOVA (high vs. medium vs. low expression groups) and cognitive indices serving as the dependent variables. Scores from the Trail Making Test, Letter Number Sequencing and CWIT served as dependent variables in one MANOVA as measures of executive function. Cognitive variables not assessing executive function were grouped together in the second MANOVA to limit the probability of Type 1 error. Thus, RBANS index scores served as dependent variables in the second MANOVA as measures of cognitive status by domain (e.g. immediate memory, visuospatial, language, attention and delayed memory).

To compare our results to the results of previous studies, analyses were also completed to examine the impact of S and L allele status alone on cognitive performance. As such, individuals were divided into one of three genotypes: SS (n = 21, 5 males and 16 females), SL (n = 31, 16 males and 15 females) and LL (n = 32, 9 males and 23 females). Consistent with the primary analyses, two separate MANOVAs were completed for all the dependent variables, with biallelic status serving as the independent variable in each MANOVA (SS vs. SL vs. LL genotypes).

Results

Demographic variables including gender, race, age and years of education did not differ significantly between groups in either set of analyses (see Table 1). Twenty-three individuals met criteria for hypertension (systolic pressure > = 140; diastolic pressure > =90), although these individuals were not significantly associated with a particular genotype using both classification methods. Only five individuals reported a history of subclinical psychiatric difficulties, and the frequency of these reports did not differ significantly between groups in either set of analyses [X^2 (2, N = 83) = 0.275, X^2 (2, N = 83) = 0.184; psychiatric data were not available for one individual]. Type II diabetes was reported by one individual; however, the condition was managed by diet and did not require medication.

Primary analyses examining the influence of 5-HTT expression on cognitive variables by domain revealed a significant multivariate effect between groups (Wilks' $\wedge$ = 0.775 F(2,81) = 2.098[a], p = 0.028). Specifically, univariate tests indicated significant = differences between groups on tests of immediate memory (F(2,81) 3.26, p = 0.043) and attention (F(2,81) 3.33, p = 0.041), and a trend effect on tests of language = (F =(2,81) 2.88, p = 0.062). Tukey's Honestly Significant Difference (HSD) post hoc analysis was completed to determine the nature of these relationships between groups. Results indicated that individuals in the low 5-HTT expression group exhibited superior performance on tests of immediate memory (p < 0.05) compared with the medium 5-HTT expression group. No significant differences were observed between individuals in the high and low 5-HTT expression groups. Although univariate tests revealed significant differences between groups on tests of attention, these differences only demonstrated a trend effect for superior performance in the low 5-HTT expression group compared with the medium 5-HTT expression group (p = 0.074). No significant differences were observed on tests of executive function between 5-HTT expression groups (see Table 2).

Secondary analyses of 5-HTTLPR biallelic genotypes revealed no significant differences between groups on any measure of cognition (see Table 3).

Discussion

The present study investigated the functional impact of the 5-HTTLPR genotype on cognition among healthy older adults. Individuals with low 5-HTT expression performed significantly better than individuals with medium 5-HTT expression on measures of immediate memory, but no differences were noted between the low expression group and the high expression group. The 5-HTT expression status also had no significant impact on measures of executive function. Collectively, our results indicate that low 5-HTT expression, as defined by the S_AS_A, S_AL_G or L_GL_G genotypes, may contribute to enhanced performance on specific measures of cognition among healthy older adults.

This is the first study to demonstrate this association with enhanced cognitive performance among healthy older adults using the triallelic 5-HTTLPR/rs25531 marker. Previous studies have identified a positive relationship between the low 5-HTT-expressing S allele and cognitive performance among healthy adults [12–16]. For example, carriers of at least one S allele (compared with LL carriers) have shown enhanced working memory capacity on a change detection task [12] and enhanced set-shifting abilities on the Wisconsin Card Sorting Task [13,25]. Similarly, individuals with the SS genotype (compared with the LL genotype) have shown higher accuracy in pattern recognition memory [15] and greater performance on 1 and 2-back conditions of a visual *n*-back task [14]. Superior performance on these tasks is indicative of enhanced working memory abilities and executive control. Our results extend these results by using the more refined triallelic genotype by showing that low 5-HTT expression significantly contributes to better performance on tests of memory compared with medium 5-HTT expression.

Importantly, only one of the abovementioned studies examined healthy adults by triallelic genotype [14], although we did not observe genotypic differences in executive function among our cohort of older adults. The key difference between our study and Enge et al. [14] is the selection of cognitive measures. Conditions 1 and 2 of the *n*-back are demanding tests of working memory, and our cognitive battery did not include this measure. By contrast, our study focused on tests of executive function that tapped cognitive flexibility and processing speed. Therefore, it is possible that the *n*-back task is a more sensitive measure to capture variance associated with genetic variation in 5-HTTLPR/rs25531. Cell size may also have limited our ability to detect significant genotypic differences on executive measures, as only 24 individuals carried low-expressing alleles compared with 31 low-expressing allele carriers in Enge et al. [14].

It is also possible that age contributed to the lack of significant relationship between 5-HTT expression and measures of executive function in our study. Previous studies have examined individuals much younger than participants in our study (20–55 years [13], 18–33 years [14], 18–34 years [16]). Interestingly, a study by Barnett et al. [26] examined the impact of the triallelic 5-HTTLPR genotype on executive function in children between 8 and 10 years of age. Consistent with our results, no significant relationship was observed between

genotype and cognitive performance [26]. Taking these results into account, it is possible that low 5-HTT expression only benefits executive function in healthy young adults. This interpretation remains conjecture at this point, and further research is needed to determine the extent of the relationship between age, executive function and 5-HTTLPR.

Although our results are consistent with previous studies demonstrating the functional benefit of the low 5-HTT-expressing S allele, the biological mechanism by which reduced 5-HTT transcription leads to enhanced cognitive performance remains unclear. Early pharmacological studies suggested that reduced 5-HTT function could lead to reductions in 5HT1a receptor density [27,28]. Because these receptors inhibit action potential generation [29], receptor downregulation could theoretically lead to more efficient cognitive processing. Recently, however, Borg et al. [13] reported no significant differences in regional 5HT1a receptor binding between carriers and noncarriers of the S allele. The latter study proposed that the beneficial mechanism of the 5-HTTLPR S allele might be mediated by other genetic polymorphisms [13]. More research is needed to determine the extent of possible gene–gene interactions on cognitive performance.

There were two aspects of our results that we did not expect. First, it is unclear why significant differences in cognitive performance were not observed between low-and high-expression groups. Although this may be a result of small sample size, the effect sizes and observed power values for the multivariate analyses indicated sufficient statistical power to detect a genuine effect between groups. It is noted, however, that univariate analyses indicated reduced power for immediate memory and attention, which may account for the lack of a dose response effect observed in this study. Therefore, it is critical that future studies with larger sample sizes replicate our work to determine if cognitive differences are limited to low and medium 5-HTT expression groups. Second, it is worth noting that mean cognitive scores fell within normal limits, suggesting that the functional impact of 5-HTTLPR is within the normal range of performance in this sample of healthy older adults. However, a small number of individuals within each group scored below average on indices of immediate memory and attention. Consistent with our statistical findings, there was little difference between high- and low-expression groups in the frequencies of individuals performing below average on immediate memory (high expression, $n = 2$; low expression, $n = 3$) and attention (high expression, $n = 0$; low expression, $n = 1$). By contrast, several individuals performed in the low average-borderline range of functioning for immediate memory ($n = 12$) and attention ($n = 4$). Despite the large difference in below average scores between high- and medium-expression groups, differences were not significantly lower in the medium-expression group due to the high degree of shared variance in these domains. These data suggest that although the average index score for individuals with medium 5-HTT expression was within the normal range, medium 5-HTT expression may represent a risk factor for decreased performance on tests of immediate memory and attention given the number of individuals with below average scores. It is also possible that mean scores did not indicate impairment due to the high level of cognitive reserve (approximately 16 years education) and generally good health of this cohort.

Although our cell sizes may have limited our ability to detect more robust differences in cognitive performance between groups, our numbers are greater than or comparable with

sample sizes of previous studies (with the exception of [14]). Furthermore, our results indicate that significant differences in memory performance were not evident between low and high 5-HTT expression groups, but only between low and medium 5-HTT expression groups. As such, previous studies that have grouped individuals by possession of at least one S allele may have unintentionally masked significant differences in cognitive performance between SS and SL genotypes.

We conducted an analysis using biallelic 5-HTTLPR genotypes to facilitate direct comparison with other results, but this did not show any significant effects. Thus, a strength of our study is the use of both the triallelic and biallelic genotypes to examine cognitive performance. By using both classification methods, we see that 5-HTT expression levels cannot be accurately determined by biallelic genotype alone, as biallelic grouping methods misclassified nine individuals from their designated expression groups. In our study, individuals with the LL genotype could be grouped into the low or medium 5-HTT expression groups if the “G” SNP variant was present on either L allele. Previous studies that have not examined the triallelic marker may have misclassified individuals with a “G” variant into biallelic groups with higher 5-HTT expression. The results of our classification methods were previously demonstrated by Wilhelm et al. [17], suggesting that the variability in results of previous studies may be due to misclassification of participants in biallelic groups. If so, previous examinations of 5-HTTLPR may have observed a false-negative relationship between the biallelic marker and cognition. We agree with the suggestion of Wilhem et al. [17] that these studies should consider reanalyzing their data using the triallelic marker to determine if participant misclassification is responsible for these discrepancies. It is also possible that biallelic discrepancies between studies are due to differences in allelic groupings independent of the triallelic marker. As noted previously, the majority of studies utilizing the biallelic marker have used a dominant model (SS+SL vs. LL) or homozygous dominant/recessive model (SS vs. LL) to compare cognitive performance between groups [12–13,15]. The present study utilized an additive model to examine the independent impact of low-expression genotypes assuming a dose response effect. Although a dose response was not supported by our results, we did observe significant differences between low- and medium-expression groups. As such, we believe the discrepancy between our results and prior findings related to the biallelic marker are grounded in methodological differences of group classification.

It is important to note that we were unable examine the within group impact of the “G” SNP on cognitive performance due to the small cell size of individuals with an S_AL_G and L_GL_G ($n = 4$ and 1, respectively). This is an important consideration and we acknowledge that our hypothesis regarding the “G” SNP should be interpreted with caution as it applies to the current study. Future studies with larger sample sizes should examine the within-group relationship between low-expression triallelic genotypes and cognition to determine if the negative impact of the “G” SNP on cognition is analogous to that of the S_A allele.

Conclusions

Low-expressing genotypes of 5-HTTLPR are modestly associated with significant increases in memory performance among our sample of healthy older adults, yet the biological

mechanism by which low 5-HTT expression enhances cognitive performance remains unknown. The absence of a dose-dependent relationship emphasizes the importance of future studies directed at investigating the relationships between age, cognitive performance, and 5-HTTLPR genotypes using the triallelic marker among healthy individuals.

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Table 1.

Demographic variables.

Triallelic/biallelic groups	Age mean (SD)	Education[a] mean (SD)	Gender male, female (*n*)	Race[b] distribution (*n*)			
				C	AA	H	A
Low	64.04 (8.02)	15.21 (2.55)	8, 16	22	0	2	0
Medium	61.57 (7.21)	15.86 (2.58)	15, 22	24	9	3	1
High	64.39 (7.99)	15.91 (1.98)	7, 16	19	2	2	0
SS	62.86 (7.81)	15.10 (2.72)	5, 16	19	0	2	0
SL	63.68 (7.58)	15.97 (2.54)	16, 15	26	4	1	0
LL	62.56 (7.90)	15.81 (2.07)	9, 23	20	7	4	1

[a]Education = Mean number of years.

[b]C = Caucasian, AA = African American, H = Hispanic, A = Asian.

Table 2.

Cognitive performance between predicted 5-HTT expression groups.

Test	Low 5-HTT expression mean (SD)	Medium 5-HTT expression mean (SD)	High 5-HTT expression mean (SD)	*F*	*p* Value	Partialeta^2	Observed power
Cognitive status by domain (RBANS)							
Immediate memory	105.21 (10.46)	98.03 (11.67)	102.74 (10.95)	3.263	0.043 *	0.075	0.606
Visuospatial	101.33 (13.50)	94.41 (16.86)	92.17 (15.49)	2.280	0.109	0.053	0.451
Language	102.71 (9.27)	99.14 (8.99)	105.00 (10.44)	2.880	0.062	0.066	0.549
Attention	111.25 (12.47)	104.43 (11.71)	110.91 (10.95)	3.333	0.041 *	0.076	0.615
Delayed memory	99.88 (12.07)	97.35 (13.70)	99.17 (12.06)	0.310	0.734	0.008	0.098
Executive function							
Trails B	77.19 19.974)	87.69 (60.98)	76.62 (26.33)	0.616	0.543	0.015	0.150
Letter number sequencing	11.08 (2.23)	10.32 (1.68)	10.61 (2.81)	0.873	0.422	0.021	0.195
CWIT trial 3	56.33 (12.15)	57.17 (17.54)	60.12 (15.29)	0.394	0.676	0.010	0.112
CWIT trial 4	59.54 (10.51)	67.15 (20.30)	66.18 (16.05)	1.604	0.208	0.038	0.330

* Statistically significant $p < 0.05$.

Table 3.

Mean performance scores between biallelic genotypes.

Cognitive test	SS mean (SD)	SL mean (SD)	LL mean (SD)
RBANS immediate memory	105.81 (11.02)	99.81 (10.37)	99.97 (12.27)
RBANS visuospatial	101.76 (13.86)	94.71 (14.66)	92.87 (17.47)
RBANS language	103.43 (9.67)	101.00 (8.16)	101.41 (11.15)
RBANS attention	112.71 (12.23)	105.68 (11.93)	107.56 (11.60)
RBANS delayed memory	101.76 (11.27)	97.65 (13.33)	97.38 (13.38)
Trails B	74.22 (15.82)	84.22 (50.25)	84.07 (50.29)
Letter Number Sequencing	11.19 (2.36)	10.58 (1.59)	10.28 (2.54)
CWIT trial 3	55.18 (12.38)	57.33 (17.48)	59.81 (15.35)
CWIT trial 4	58.76 (10.40)	67.96 (21.72)	65.48 (14.54)