Cardiovascular Pharmacogenomics and Cognitive Function in Patients with Schizophrenia

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Key Words: cardiovascular disease, schizophrenia, cognitive reserve, pharmacogenomics, education, cognitive function, renin-angiotensin system, apolipoprotein E

Abbreviated Title: Cardiovascular Pharmacogenomics and Cognitive Function in Schizophrenia

Abstract

Study Objective: To examine the impact of multiple risk alleles for cognitive dysfunction and cardiovascular disease risk on cognitive function, and to determine if these relationships varied by cognitive reserve (CR) or concomitant medication use in patients with schizophrenia.

Design: Cross-sectional study.

Setting: Ambulatory mental health centers.

Patients: A total of 122 adults with a schizophrenia spectrum diagnosis who were maintained on a stable antipsychotic regimen for at least 6 months prior to study enrollment; patients were divided into three CR groups based on years of formal education: no high school completion or equivalent (low-education group [18 patients]); completion of high school or equivalent (moderate-education group [36 patients]; or any degree of post–high school education (high-education group [68 patients]).

Measurements and Main Results: The following pharmacogenomic variants were genotyped for each patient: *AGT* M268T (rs699), *ACE* insertion/deletion (or *ACE* I/D, rs1799752), and *APOE* ε2, ε3, and ε4 (rs429358 and rs7412). Risk allele carrier status (identified per gene as *AGT* M268 T carriers, *ACE* D carriers, and *APOE* ε4 carriers) was not significantly different among CR groups. The Brief Assessment of Cognition in Schizophrenia (BACS) scale was used to assess cognitive function. The mean ± SD patient age was 43.9 ± 11.6 years. Cardiovascular risk factors such as hypertension and hyperlipidemia diagnoses, and use of antihypertensive and lipid-lowering agents, did not significantly differ among CR groups. Mixed modeling revealed that risk allele carrier status was significantly associated with lower verbal memory scores for *ACE* D and *APOE* ε4 carriers, but *AGT* T carrier status was significantly associated with higher verbal memory scores (p=0.0188, p=0.0055, and p=0.0058, respectively). These results were only significant in the low-education group. Additionally, medication-gene interactions were not significant predictors of BACS scores.

Conclusion: *ACE* D and *APOE* ε4 carrier status, independent of medication use, was associated with lower verbal memory scores in patients with schizophrenia who had relatively lower CR, as identified by formal education. These results suggest that increasing CR may be protective against cognitive impairment that may be worsened by select cardiovascular risk alleles in patients with schizophrenia.

Evidence supporting a connection between cardiovascular disease and cognitive dysfunction has received increasing attention and support in recent research.[1,2] Patients with schizophrenia have the potential to be severely impacted by this association due to high rates of comorbid cardiovascular disease and varying degrees of baseline cognitive dysfunction. In fact, cognitive dysfunction is considered a core feature of schizophrenia that is usually observable prior to the first episode of psychosis, often persists through treatment,[3,4] and contributes significantly to an individual's decreased functional capacity[5] and quality of life.[6] Few investigations have attempted to understand how factors that impact cardiovascular function and cognition, such as medication use, pharmacogenomics, and cognitive reserve (CR), moderate cognitive dysfunction in patients with schizophrenia. Our group was one of the first to report a relationship between cardiovascular health and neurocognition in patients with schizophrenia.[7] Understanding the extent of this complex relationship has potential to improve treatment outcomes in patients with schizophrenia.

A number of pharmacogenomic variants exist with potential to moderate cardiovascular health and cognitive function. These include single nucleotide polymorphisms (SNPs) within the renin-angiotensin system (RAS), which is essential to blood pressure maintenance, as well as apolipoprotein E, which has been implicated in the risk for Alzheimer's disease and dyslipidemia. Three variants impacting these systems were chosen for analysis based on study results in the general adult population that support their potential to impact cardiovascular health and cognition.[8–10]

AGT M268T

Increased RAS activity and blood pressure elevation have been linked to cognitive impairment and Alzheimer's disease risk.[11,12] Genetic variability contributes to RAS activity, and one such

variant is contained within the gene coding for the angiotensinogen (AGT) polypeptide. This missense mutation (referred to as *AGT* M268T or *AGT* M235T) leads to an amino acid change in the polypeptide from valine to threonine at amino acid position 268, and the threonine variant has been associated with increased angiotensin II concentrations.[13] A recent study identified a pharmacogenetic relationship between cognitive decline, genotype, and RAS-active medication.[8] Specifically, individuals homozygous for the threonine allele who also used an angiotensin-converting enzyme inhibitor (ACEI) showed significantly less cognitive decline than other genotypes after 8 years of follow-up.[8] Currently, to our knowledge, there are no published studies that have examined the relationship between this variant, medication use, and cognition in patients with schizophrenia.

ACE I/D

The ACE is important in the RAS pathway because it is responsible for the production of angiotensin II, which is the effector molecule ultimately leading to increased blood pressure.[15] A common polymorphism in the gene coding for this enzyme is an insertion/deletion (I/D) variant. Carriers of the D allele produce more ACE[16] and have been shown to be at risk for higher rates of adverse cardiovascular outcomes.[17] A study by in elderly patients (aged 59-71 years) found that scores on the Mini-Mental State Examination declined significantly more after a 4-year follow-up in DD allele carriers compared with ID allele carriers.[18] Further, in elderly individuals (mean ± SD age 64 ± 8.08 years), carriers of the I allele had higher verbal memory scores compared with DD carriers, but the benefit of the I allele was present only in subjects using ACE inhibitors when assessing learning ability.[9] This variant has also been associated with significant changes in white matter that correlated D carrier status with both positive and negative impact on cognition.[19] Like *AGT* M268T, the relationship between this allele, medication use, and cognitive function in patients with schizophrenia has not been well studied, although several investigators have looked at the relationship between this polymorphism, or levels of ACE activity, and schizophrenia incidence.[20,21]

APOE

Apolipoprotein E (APOE) is a plasma lipoprotein involved in synaptic signaling and plasticity, as well as transporting lipids throughout the blood stream.[22] The most studied *APOE* variants (ε2, ε3, and ε4) are based on rs429358 and rs7412 SNP combinations.[23] *APOE* ε4 has been associated with an increased risk for, and earlier onset of, Alzheimer's disease, cognitive dysfunction in nondemented older adults, and dyslipidemias.[24–26] Although the mechanism for

this allele's effect on cognition is not fully understood, some have hypothesized adverse changes in APOE's neuroprotective and neurotoxic profile.[22] Among those with serious mental illness, results regarding the relationship between the ε4 allele and cognitive dysfunction have been somewhat conflicting. In patients with bipolar disorder, worsening cognitive function across several domains has been associated with ε4 carrier status, but this finding has not been replicated consistently in patients with schizophrenia.[27,28] With respect to cardiovascular parameters that have been linked to worsened cognition, *APOE* ε4 carrier status has been related to increased total cholesterol level in patients with schizophrenia taking atypical antipsychotics, and in the general population response to statins has been associated with *APOE* status.[10,29] However, a robust association between statin use, *APOE* ε4 status, and cognition has not been demonstrated.

Although the role of these pharmacogenomic variants in schizophrenia has yet to be thoroughly examined, we also recognize that a patient's CR may play an important role in the complex relationship between pharmacogenetic variability, cardiovascular health, and cognitive function. A core concept of CR is that select environmental experiences are protective against cognitive decline in disease states such as Alzheimer's disease, dementia, schizophrenia, and multiple sclerosis.[30–32] CR was originally postulated following observations in patients with Alzheimer's disease in whom clinical status deteriorated less than would be expected based on changes in brain physiology.[33,34] Additional work has since associated CR characteristics such as degree of formal education, premorbid IQ, and physical activity with a phenotype of higher cognitive function than expected based on underlying diagnosis.[35,36] Studies attempting to identify valid measures of CR in patients with schizophrenia have recognized factors such as educational level, premorbid IQ, and physical activity, as possible proxy measures for CR.[32,37] However, at this time there is no single established proxy measure for classifying degree of CR in any of the aforementioned disease states.

Investigations studying the relationship between cognitive function, pharmacogenomic variants in cardiovascular health, and the importance of CR in patients with schizophrenia treated with antipsychotics are lacking. Therefore, the aim of this study was to examine the impact of multiple risk alleles for cognitive dysfunction and cardiovascular disease risk on the Brief Assessment of Cognition in Schizophrenia (BACS) scale performance, and to determine if these relationships varied by CR or concomitant medication use in patients with schizophrenia. To identify variable relationships between BACS scores and CR, patients were divided into three

groups based on their degree of formal education. We hypothesized that the select risk alleles would be significant independent variables in the predication of BACS scores and that these relationships would vary between CR groups and be moderated by ACEI, angiotensin II receptor blocker (ARB), or statin medication use.

Methods

Study Design and Patients

All patients included in this cross-sectional study were part of an ongoing larger study investigating pharmacogenetic predictors of cardiovascular disease risk in patients with schizophrenia, as related to antipsychotic use. To be included in this study, patients had to be diagnosed with schizophrenia, schizoaffective disorder, or psychotic disorder not otherwise specified. All patients were required to be taking an antipsychotic for at least 6 months prior to study enrollment, and only adults were included (18-90 years of age). When possible, medication history was verified by referencing electronic charts and reviewing prescription records. Exclusion criteria included inability to give informed consent, currently pregnant or nursing, or an active substance abuse disorder. Full inclusion and exclusion criteria are available at https://clinicaltrials.gov/ct2/show/NCT00815854. The study protocol was approved by the following organizations: University of Michigan Medical School Institutional Review Board, Washtenaw County Health Organization, Ann Arbor Veterans Affairs Medical Center, and Detroit–Wayne County Community Mental Health Agency.

Diagnostic, Clinical, and Demographic Assessments

The Michigan Clinical Research Unit at the University of Michigan Medical Center housed all study visits. Following informed consent, patients underwent a fasting blood draw that included a blood sample for DNA extraction. Blood pressure, heart rate, medication history, and daily activity level were also obtained. Activity level was translated into a score using the Total Activity Measure 2, which has been validated against RT3 triaxial accelerometer measurements in a population with coronary heart disease.[38] Diagnosis was verified using the *Structured Clinical Interview for DSM-IV-TR Axis I Disorders* (SCID).[39] Education was assessed using SCID scoring that associates a numerical scale with education level on a range of 1 (completion of grade 6 or less) to 8 (completion of graduate/professional school). Patients were divided into three CR groups according to their level of education: low, defined as incomplete high school or equivalent; moderate, defined as completed high school or equivalent; or high, defined as any post–high school education.

Cognitive Assessment

The Brief Assessment of Cognition in Schizophrenia (BACS) scale was used to measure cognitive function. This scale focuses on assessing domains shown to be commonly impaired in schizophrenia: verbal memory, executive function, attention, verbal fluency, working memory, and motor speed.[40]

Genotyping

DNA was extracted from whole blood using a salt precipitation method that has been described previously.[41] All samples were genotyped for the following variants: *ACE* I/D (rs1799752*), AGT* M268T (rs699), and *APOE (*rs429358 and rs7412*).* For the *AGT* M268T variant, Pyrosequencing Technology (Qiagen, Valencia, CA) was used for assay design and creation of polymerase chain reaction (PCR) and sequencing primers. PCR was performed to amplify regions of interest prior to sequencing with a PyroMark MD sequencer, using Qiagen pyrosequencing reagents and following Pyrosequencing recommended protocols. (Primer sequences and PCR conditions are available by request.) The *ACE* I/D variant was assessed entirely by PCR, as previously described.[42,43] Two TaqMan assays (Thermo Fisher Scientific, Waltham, MA) were employed to assign *APOE* epsilon genotype based on results for variant rs429358 and rs7412. TaqMan Master Mix was used for the assay on LightCycler 480 real-time PCR equipment (Roche Molecular Diagnostics, Pleasanton, CA), with temperature and time settings recommended for the *APOE* TaqMan assay. Any uncertain genotype assignments were repeated for confirmation.

Statistical Analysis

JMP Pro 11.0 (2013) (SAS Institute Inc., Cary, NC) was used for all statistical analyses. Demographic data were analyzed by using one-way analysis of variance or χ^2, as appropriate. Mixed modeling was used to predict BACS domain and cumulative scores for each CR group as a function of the following fixed effects: carriers of *ACE* D allele, *AGT* M268T threonine allele, *APOE* ε4 allele, and age. Race was kept as a random effect in the model to correct for significant differences between CR groups. Atypical antipsychotic use, interacting factors of ACEI or ARB use and RAS risk allele, and statin use and *APOE* ε4 carrier status, were not significant predictors in earlier model iterations and were removed to reduce the model parameters to only those significant fixed effects indicated above. Further mixed model analysis of recall ratio was undertaken on an exploratory basis with the final fixed and random effects.

Recall ratio, a derived assessment of verbal memory, was computed by dividing the number of words recalled (score) by the total possible number of words recalled in order to examine relative recall performance in addition to absolute recall performance.

Results

Patient Demographics and Genotypes

A total of 122 patients were included in this study. Demographic characteristics are detailed in Table 1. Race was the only demographic characteristic that was significantly different among the three groups, with the high-education group having a greater percentage of Caucasian patients (p=0.04). Rates of hypertension diagnosis, as well as use of an ACEI and ARB among groups were not significantly different (p=0.19 and p=0.92, respectively). Dyslipidemia diagnosis and statin use were also not significantly different among education groups (p>0.3 for all comparisons). Finally, the distribution of risk allele carrier status was also not significantly different among the three education groups (Table 2), and Hardy-Weinberg distribution did not significantly deviate from expected for the individual genetic variants (p>0.05, data not shown).

Mixed Model Results

Results of the mixed model analysis showed that verbal memory was the only BACS domain significantly influenced by select genotypes, and only in the low-education group; the estimates and probabilities for each fixed effect are shown in Table 3. The exploratory recall ratio performance analysis showed similar significant impact from genotypes, again in the low-education group (Table 4). For both the verbal memory score and recall ratio, a higher score relative to the other patients with schizophrenia within the same education group equated to higher verbal memory capacity. As shown in Tables 3 and 4, all fixed effects parameter estimates influenced the predicted score negatively, with the exception of *AGT* risk allele carrier status. For example, in the verbal memory mixed model described in Table 3, *APOE* ε4 carrier status was associated with an approximate 6.4-point decrease in verbal memory score when all other variables were held constant using this prediction model. Medication use (ACEI or ARB interacted with RAS risk alleles, statin interacted with *APOE* ε4 carrier status, or atypical vs typical antipsychotic use) did not impact these results (data not shown).

Discussion

Our results suggest that in patients with schizophrenia, variants influencing ACE, APOE, and AGT activity may play an important role in determining cognitive function but primarily in those

who have relatively less CR, as indicated by lower formal education. The absence of a significant relationship between risk allele carrier status and BACS scores for patients with schizophrenia in the moderate- and high-education groups also suggests that it is possible for CR to protect against cognitive impairment that may be worsened by select cardiovascular risk alleles in patients with schizophrenia.

In this population, medication use (atypical antipsychotic use, ACEI or ARB use interacted with RAS risk alleles, or statins interacted with *APOE* ε4 carrier status) did not moderate the relationship between ACE, APOE, and AGT and cognition. Previous pharmacogenomic research with the RAS risk alleles was primarily performed using ACEIs; however, it was felt important for this study to include ARBs as an interacting factor with RAS risk alleles because they also act directly on this system through angiotensin receptor blockade. Statins, but not other lipid-lowering agents, were included as an interacting term with APOE because literature supporting the pharmacogenomic impact of this risk allele has largely been related to statin use. These results were unexpected based on previously discussed literature suggesting that response to the selected risk alleles is significantly impacted by medication use.[8–10] This is another area of research that deserves more attention due to the small number of patients in our low-education group, where significant impact of these risk alleles was detected. Finally, the lack of relationship between antipsychotic class (atypical vs typical antipsychotic use) and cognition has previously been described by our group and was included in our analysis due to a general lack of consensus on the complex relationship between antipsychotic class and cognition.[7]

The BACS cognitive domain that was significantly associated with risk alleles in this study was verbal memory—specifically, absolute and relative memory performance (i.e., total verbal memory and verbal memory recall ratio, respectively). Verbal memory is a complex cognitive domain that is well known for its moderate to severe impairment in schizophrenia.[44] Our study suggests that verbal memory may be a sensitive measure for assessing the effects of multiple genetic variants on cognition in patients with schizophrenia with low CR, as the polymorphisms selected for this study impact cognition through a wide variety of mechanisms. Age was also a significant fixed parameter in both models, and this is in agreement with other studies that have shown increasing age to negatively influence cognitive function in patients with schizophrenia.[45,46]

The positive relationship between *AGT* M268T threonine allele carrier status and total verbal memory and recall ratio scores warrants further investigation, as this allele would be expected to be associated with worsened, not improved, cognition. In our study this may be due to several factors, including the small sample size, average age, and possible race-specific effects. In a relatively large study by Hajjar et al, the relationship between this allele, ACEI use, and cognition varied by race, and among African-Americans, the relationship was not significant.[8] These results cannot be directly compared to our analysis but do suggest that we may be missing a race-specific effect due to our small sample size. Another factor that may be contributing to these unexpected results is the relatively young average age of our patients. In the limited number of previous trials that have investigated the association between the *AGT* M268T risk carrier status and cognition, studies have focused on older adults with average ages of 63–74 years.[8,47] It is possible that the younger age of our patients is masking the impact of *AGT* M268T on cognition, as suggested by a number of studies showing an increased effect of genetics on cognition that correlates with advancing age.[48]

In our study, *ACE* D and *APOE* ε4 carrier status were associated with worsened verbal memory and recall ratio scores. These results support the rationale that excess angiotensinogen and *APOE* malfunction may worsen cognitive performance. With respect to the observed *APOE* ε4, relationship, these results contradict those described by Thiabut et al, where an association between worse cognitive scores and the presence of this risk allele was not found to be significant in small schizophrenic populations.[28] This investigation compared the prevalence of the *APOE* ε4 risk allele in schizophrenic groups of varying cognitive abilities. As our analysis did not take the same approach, and our sample size is also small, this warrants further investigation. Furthermore, our results show a negative relationship between *ACE* D allele and cognition that has been supported in several studies.[9,18]

Finally, these results also suggest that increased CR, as identified by formal education, may temper the impact of genetic polymorphisms that place patients with schizophrenia at risk for cognitive dysfunction. A number of studies in cognitive remediation therapy also support the impact of educational programs after schizophrenia diagnosis in improving cognitive ability and functional outcome despite low CR.[49] For example, Kontis et al found that patients with schizophrenia with "very low education" benefited significantly from cognitive remediation therapy and that older age was a more significant limiting factor in ability to benefit from therapy.[49] A potentially important future clinical study would be to examine the impact of genetic

polymorphisms known to impact cognition on response to cognitive remediation therapy in a population of patients with schizophrenia with variable CR. It may prove to be the case that certain genetic risk factors for worsened cognitive function in patients with schizophrenia are clinically insignificant when patients receive cognitive remediation therapy.

To the best of our knowledge, this is the first study to assess the impact of multiple cardiovascular polymorphisms on cognition in patients with schizophrenia with variable levels of CR. However, there are several limitations that must be addressed. One potential limitation is our measure of CR. Formal education has been linked to CR extensively in patients with Alzheimer's disease, but it has been used less frequently in schizophrenia research.[35] It is also possible that a more accurate proxy of CR could be established by incorporating multiple parameters associated with CR into a scoring system (such as education, IQ, and activity level), as suggested recently.[37]   Additionally, investigations in schizophrenia and CR caution that it may not be appropriate to simplify CR with premorbid indicators of cognitive capability in this population. For example, Leeson et al found that IQ following schizophrenia onset is a more reliable predictor of cognitive dysfunction and functional outcome in longitudinal studies when compared to IQ prior to schizophrenia onset.[50] Unfortunately, this information was not available for our current analysis. As IQ correlates with education, and other disease states have established educational attainment as a measure of CR, this suggests that our use of education as a premorbid indicator of CR in patients with schizophrenia should not be entirely discounted.

Finally, there are two more obvious limitations of this study. One is the small number of patients, especially in the low-education group where the significant results with respect to genotype were identified. However, given the a priori prediction that genetic variants would have a differential impact on BACS score depending on education background, we proceeded with the analyses as planned to avoid increasing the possibility of type II error. The second additional limitation is that the potential significance of these results rest on the assumption that the selected fixed effects are linked by their potential to impact cardiovascular health and cognition. However, this is a developing area of study, and as these results are from a small, cross-sectional investigation, they need to be interpreted with caution.

Conclusion

This study suggests that cognitive ability in patients with schizophrenia with relatively less CR may be moderated by risk alleles within the renin-angiotensin system (*AGT* M268T threonine

carriers and *ACE* I/D deletion carriers) and apolipoprotein E (*APOE* ε4 carriers). Interestingly, medications that have previously been shown to temper the impact of these risk alleles on cognition or cardiovascular parameters did not have significant impact in our population. This may be related to our small sample size and relatively young population, and warrants further attention. Future studies that evaluate the importance of cardiovascular pharmacogenomic variants, CR, and cognitive remediation therapy in patients with schizophrenia are needed to determine if these genetic variants and medication use are of clinical importance in improving quality of life in patients with schizophrenia receiving cognitive remediation therapy.

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Characteristic	All Patients (n=122)	Low-Education Group (n=18)	Moderate-Education Group (n=36)	High-Education Group (n=68)	p Value[a]
Age (yrs)	43.9 ± 11.6	43.3 ± 10.2	46.0 ± 10.8	43.0 ± 12.3	0.444
Male	67 (54.9)	12 (66.7)	22 (61.1)	33 (48.5)	0.262
Caucasian	54 (45.0)	4 (22.2)	14 (38.9)	37 (54.4)	0.034
Age at diagnosis (yrs)	25.2 ± 10.5	24.0 ± 12.1	27.0 ± 12.9	24.6 ± 8.5	0.479
Diagnosis					0.170
Schizophrenia	41 (33.6)	6 (33.3)	14 (38.9)	21 (30.9)	
Schizoaffective disorder	63 (51.6)	6 (33.3)	19 (52.8)	38 (55.9)	
Psychotic disorder NOS	18 (14.8)	6 (33.3)	3 (8.3)	9 (13.2)	
Comorbid hyperlipidemia diagnosis	39 (32.0)	9 (50.0)	12 (33.3)	18 (26.5)	0.172
Use of statins	23 (18.9)	6 (33.3)	7 (19.4)	10 (14.7)	0.230
Use of other lipid-lowering agent[1]	11 (9.0)	3 (16.7)	2 (5.6)	6 (8.8)	0.437
Comorbid hypertension diagnosis	47 (38.9)	9 (50.0)	17 (47.2)	21 (30.9)	0.148
Use of ACEI or ARB	25 (20.5)	5 (27.8)	7 (19.4)	13 (19.1)	0.723
Use of other antihypertensive drug	33 (27.0)	2 (11.1)	14 (38.9)	17 (25.0)	0.081

| Use of atypical antipsychotic | 113 (92.6) | 17 (94.4) | 33 (91.7) | 63 (92.6) | 0.934 |
| Total activity score | 2669 ± 2977 | 2520 ± 2775 | 3555± 3927 | 2239 ± 2320 | 0.097 |

Table 1. Demographic and Clinical Characteristics of the Study Patients by Education Subgroup

Data are mean ± SD or no. (%) of patients.

Low education = no high school completion or equivalent, moderate education = completion of high school or equivalent, and high education = any degree of post–high school education; NOS = not otherwise specified; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker.

[a]Analysis of variance, χ^2, or the Fisher exact tests were used as appropriate to identify any significant differences in characteristics between the three education groups.

Table 2. Genotype Risk Allele Carrier Status for All Patients by Education Subgroup

Risk Allele Carrier Status	All Patients (n=122)	Low-Education Group (n=18)	Moderate-Education Group (n=36)	High-Education Group (n=68)	p Value[a]
APOE ε4 carrier	35 (28.9)	5 (27.8)	10 (28.6)	20 (29.4)	0.9891
AGT M268T T carrier	89 (73.6)	13 (76.2)	29 (80.6)	47 (69.1)	0.434

ACE I/D D carrier	88 (72.7)	12 (70.6)	30 (83.3)	50 (67.7)	0.227

Data are mean ± SD or no. (%) of patients.

Low education = no high school completion or equivalent, moderate education = completion of high school or equivalent, and high education = any degree of post–high school education

[a]Significance assessments (χ^2) revealed no significant differences in the proportions of patients carrying the listed risk alleles among the three education subgroups.

Table 3. Results of the Linear Mixed-Effects Model Analysis: Verbal Memory Raw Scores in the Low-Education Group (n=18)

Term	Estimate	SE	DF	t-ratio	p value	95% Confidence Interval	
						Lower	Upper
Fixed Effects							
Intercept	41.53	7.58	6.3	5.48	0.001	23.17	59.89
APOE ε4 carrier	-6.43	1.86	10.7	-3.47	0.006	-10.53	-2.34
*AGT*rs699 C carrier	10.70	3.13	11	3.41	0.006	3.80	17.59
ACE D carrier	-4.41	1.58	10.3	-2.79	0.019	-7.92	-0.89
Age	-0.35	0.13	9.2	-2.71	0.024	-0.64	-0.06
Random Effects							
Race	61.27	91.47				-118.02	240.55
Residual	19.87	9.58				9.27	68.65

SE = standard error, DF = degrees of freedom.

Table 4. Results of the Linear Mixed-Effects Model Analysis: Recall Ratio Raw Scores in the Low-Education Group (n=18)

Term	Estimate	SE	DF	t-ratio	p value	95% Confidence Interval	
						Lower	Upper
Fixed Effects							
Intercept	0.554	0.101	6.3	5.48	0.001	0.309	0.798
APOE ε4 Carrier	-0.086	0.025	10.8	-3.46	0.006	-0.140	-0.031
AGT C carrier	0.143	0.042	11	3.41	0.006	0.050	0.235
ACE D carrier	-0.059	0.021	10.3	-2.78	0.019	-0.106	-0.012
Age	-0.005	0.002	9.2	-2.7	0.024	-0.009	-0.001
Random Effects							

Race	0.011	0.016		-0.021	0.043
Residual	0.004	0.002		0.002	0.012

SE = standard error, DF = degrees of freedom.

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