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Associations of Angiotensin Converting Enzyme-1 and Angiotensin II Blood Levels and Cognitive Function

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Abstract

Background—Emerging evidence suggests a possible role of the renin angiotensin system in the pathophysiologic process of Alzheimer's disease, of which angiotensin converting enzyme-1 (ACE-1) and angiotensin II (ANGII) are important proteins. Few studies evaluated associations between blood ACE-1 and none between ANGI levels, and cognition.

Objective—Our pilot study was aimed to examine associations between blood ACE-1 and ANGI levels and cognitive function in non-demented participants at baseline and over a 1-year period.

Methods—56 participants were included from the Brain Health Substudy of the Baltimore Experience Corps Study. Linear regression analysis, adjusting for confounders, was used to determine associations between baseline ACE-1 and ANGI, and baseline and 1-year follow-up measures of psychomotor and processing speed, executive function, verbal learning memory and working memory, and whether these associations were mediated by blood pressure.

Results—Participants were predominantly female (75%), African-American (93%), with mean age of 67.8 years and education of 14.3 years. There were no associations between baseline ACE-1 or ANGI levels and cognitive function; however, there were significant association between baseline ACE-1 levels and 1-year follow-up Trail Making Test, Part A ($\beta = 0.003$, $p = 0.04$) and Digit Span ($\beta = -0.001$, $p = 0.02$).

Conclusions—In this cognitively intact sample, elevated ACE-1 levels were associated with worse processing speed and working memory after 1 year. Findings from this pilot study suggest

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SUPPLEMENTARY MATERIAL

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that changes in the RAS are associated with alterations in cognitive function warranting further assessment of the role of RAS in neurodegenerative disorders.

Keywords

Angiotensin II; angiotensin converting enzyme-1; cognition; cohort study

INTRODUCTION

Dementia is a rapidly increasing clinical and public health issue, primarily as a result of the aging of the population [1]. Without effective therapy for dementia, specifically Alzheimer's disease (AD), there will be an estimated three-fold increase in new AD cases, to 13.2 million by the year 2050 [2]. Thus, identifying new and potentially effective approaches to prevention and/or treatment is critical given the lack of effective interventions to date.

Recent advances in research have demonstrated the presence of mixed rather than single brain pathologies in patients with dementia, with combinations of various forms of vascular disease and AD pathology [3, 4]. Additionally, evidence suggests that pathological changes in the brain precede symptoms by years and furthermore, that vascular changes possibly precede AD pathology [5]. The renin angiotensin system (RAS) plays a key role in blood pressure (BP) regulation and there is emerging evidence about its possible involvement in the pathogenesis of AD either by blood pressure or by additional mechanisms [6–8]. For example, it has been shown that levels and/or activity of key component of the RAS are altered in patients with AD, such as increased angiotensin converting enzyme 1 (ACE-1) levels and activity resulting in increased conversion of angiotensin I to II (ANGII) [6–8] and decreased angiotensin converting enzyme 2 (ACE-2) activity resulting in decreased conversion of ANGI to angiotensin 1–7 [9], all resulting in increased levels of ANGI. Increased levels of ANGI result in increased activation of angiotensin type-1 receptor (AT1R), which is associated with accumulation of amyloid- β (A β) and tau [6–8, 10, 11]. Additionally, a recent study in post-mortem brains of people with AD has also found elevated levels not only of ANGI, but also of angiotensin III (ANGIII), and ANGIII levels were strongly associated with elevated levels of A β and tau [12].

Epidemiological studies suggest that antihypertensive medications acting via the RAS, such as ACE inhibitors (ACE-I) and AT1R blockers, protect against cognitive decline [6, 13, 14], and that repurposing these drugs may have therapeutic potential in AD. There are currently few studies available evaluating associations between blood ACE-1 levels and cognitive aging or dementia [15–17], and none between blood ANGI levels and cognitive function. We evaluated the association between blood levels of ANGI and ACE-1 and cognitive function at baseline and over a 1-year follow-up within a non-demented, community-dwelling older adult sample. We further explored whether these associations were mediated by BP.

METHODS AND MATERIALS

Participants

Participants were recruited from the Brain Health Study (BHS) [18, 19], a substudy within the Baltimore Experience Corps Trial (BECT), following the completion of the trial. The BECT was a sex-stratified, randomized, controlled effectiveness trial to evaluate the health benefits for older adults participating in a high-intensity volunteer service program vs. a control group offered low-intensity volunteer opportunities [20]. BECT [21, 22] and BHS results have been published previously [19]. Enrollment criteria have also been described previously [18, 19]. Briefly, the BHS enrolled 123 participants free of dementia at baseline. Baseline and follow-up evaluations included medical history, neurological, psychiatric and neuropsychological examinations and laboratory studies. In 2010, after completion of the intervention, participants were recruited to our pilot study to explore associations between ACE-1 and ANGII levels and cognition. Based on the 4-year recruitment cohorts of the BECT [20], this included participants attending follow-up visits 2, 3, and 4. Inclusion criteria for the pilot study included consent to a fasting blood draw, free of brain disease (tumor, neurodegenerative diseases, infection, cerebrovascular disease, psychiatric disease, and delirium), inflammatory disease (autoimmune), end stage renal and liver disease, or cancer, and no use of ACE-I or AT1R blockers in previous 3 months. 56 participants agreed to participate in the pilot study; 40 of those were also evaluated one-year later. The study was approved by the institutional IRB of the Johns Hopkins University and participants provided written informed consent.

Demographic information (age, gender, race, years of education) was assessed using questionnaires, medical history was based on self-report history of myocardial infarction, stroke, transient ischemic attack, heart failure, hypertension, and diabetes mellitus. Additionally, anthropometric measures included height and weight, BP readings, cognitive, physical, health data have been collected, along with blood, on an annual basis.

Blood ACE-1 and ANGII assay

Blood collection and storage—All blood drawing and processing followed established protocols using standard venipuncture procedures after an 8-h fast for the proposed study. Peripheral venous blood samples for ACE-1 levels were obtained (5 ml), allowed to clot for 20 min and were centrifuged at 800 rpm for 10 min at 22°C. After centrifugation, serum was aliquoted in 1 ml vials and were taken to the Johns Hopkins University (JHU) Institute for Clinical and Translational Research (ICTR) Core Laboratory, where it was stored at –80°C until assayed. For the ANGII levels blood samples were obtained (5 ml) from the participants and were immediately centrifuged 800 rpm for 10 min at 22°C. After centrifugation, the clear EDTA plasma layer (approximately 1 ml) was collected and taken to the JHU ICTR Core Laboratory, where it was stored at –70°C until assayed. Blood assays were performed using standardized procedures in JHU ICTR Core Laboratory. ACE-1 and ANGII were assayed at the same time with duplicate samples and controls.

Immunoassays—A commercially available sandwich ELISA (R&D systems) was used according to the manufacturer's guidelines to measure ACE-1 levels in serum. ACE-1

concentrations were determined by interpolation from the standard curve determined for each plate from the known. The concentration of ACE-1 is expressed in ng/ml. The interassay coefficient of variance for ACE-1 measurements was 3%. The assay sensitivity was 0.05 ng/ml. The concentrations of ANGII were measured by enzyme immunoassay using plates coated with ANGII monoclonal antibody and a detection antibody labeled with acetylcholinesterase, and ANGII inhibitor cocktail and phenyl cartridges for sample preparation and extraction following the manufacturer's protocol (Cayman Chemical). The concentration of ANGII is expressed in pg/ml. The interassay coefficient of variance for ANGII measurements was 6.2%. The assay sensitivity was 2.0 pg/ml.

Outcome measures

Cognitive function—Standardized neuropsychological tests were administered to evaluate speed of processing, executive function, visual-spatial function and verbal memory. Psychomotor and processing speed, respectively, were measured using the paper-and-pencil versions of the Trail-Making Test Part A (TMT, part A) [23] and the Pattern Comparison task [24]. Executive functioning was measured using the Trail-Making Test Part B (TMT, part B) [32]. Verbal learning was measured using the sum of five trials of the Rey Auditory Verbal Learning Test (RAVLT) [25], short and long verbal memory was measured using Rey Auditory Verbal Learning Test (RAVLT), while working memory was measured using the Digit Span Forward, Backward and Total tasks [24, 26].

Blood pressure—At each study visit, BP was measured by a trained nursing staff according to standard protocols. The participant's BP was measured while the participant was sitting in an upright position with legs uncrossed and feet flat on the floor for approximately 5 min. Three blood pressure readings, with 30-s intervals between each measurement, were obtained on the right arm using a mercury sphygmomanometer with an appropriate-sized occluding cuff and were averaged for data analysis. Measures of systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) were used in analyses.

Statistical analysis

Participants baseline characteristics were summarized using frequencies with percentages or means with standard deviations (SD). Participants undergoing blood analysis were compared to those without blood analysis using analysis of variance test of equal means for continuous measures and Fisher's exact test for categorical measures.

For each outcome measure linear regression models were used to evaluate 1) associations between baseline blood levels of log converted ACE-1 and ANGII and cognitive function at baseline and one year later. In exploratory BP mediation analyses, we additionally evaluated whether 2) baseline blood levels of log converted ACE-1 and ANGII were associated with BP measures at baseline and one year later; and whether 3) baseline BP measures were associated with cognitive function at baseline and one year later. The exploratory analyses evaluated whether associations between blood levels of ACE-1 and ANGII and cognition were mediated by BP.

In the first model, linear regression analyses were unadjusted; in the second model analyses were adjusted for potential confounding effects of age, gender, race, education, SBP, DBP, body mass index (BMI), depression and the number of diseases at baseline. The variable of “number of additional diseases” was used to reduce the number of confounders, after we separately assessed individual diseases and found no significant associations between blood levels of ACE and ANGII, and history of hypertension, diabetes mellitus, heart attack, heart failure, stroke, and transient ischemic attack. Additionally, the fully adjusted model was also adjusted for baseline ANGII levels for all analyses evaluating associations between ACE-1 levels and cognition and blood pressure, and vice versa, since levels are dependent from each other.

Analyses were performed using STATA version 12.1 (Stata Corp LP, Inc., College Station, TX). All reported *p* values are two-sided and significance was set at $p < 0.05$.

RESULTS

Participants

There were a total of 56 participants with a mean age of 67.8 (6.3) years, 42 (75%) were females, and 52 (93%) were African Americans with mean years of education of 14.3 (2.6) (Table 1). Mean SBP was 138.58 (18.48), DBP 77.58 (11.33), PP 60.65 (14.87) mm Hg. Participants with blood assay did not differ significantly in their baseline demographic and health related characteristics from participants not assayed with the exception of history of hypertension and diabetes (Table 1). The baseline means for TMT part A and B times were 42.14 (± 20.38) and 106.11 (± 60.77) seconds, for RAVLT-learning, short and long delayed recall were 43.61 (± 8.59), 7.93 (± 3.16), and 7.98 (± 3.08), Digit Span forward, backward and total were 7.98 (± 1.95), 5.42 (± 2.09), and 13.40 (± 3.47), and Pattern Comparison were 727.83 (± 5.83).

Baseline associations

Blood levels of ACE-1 and ANGII—Using Pearson correlation there was a significant correlation between ACE-1 and ANGII levels ($r = 0.37$; $p = 0.01$).

Blood levels of ACE-1 and ANGII, and cognitive function—In the fully adjusted model, there were no significant associations between baseline log converted ANGII or ANGII levels and baseline cognitive measures (Table 2).

Blood levels of ACE-1 and ANGII, and BP measures—In the fully adjusted model, baseline log converted ACE-1 and ANGII levels showed no significant associations with baseline SBP, DBP or PP (Table 2).

BP measures and cognitive function—In the fully adjusted model there was no significant association between baseline SBP, DBP and PP measures and baseline cognition with the exception of a significant negative association between Pattern Comparison score and PP (Supplementary Table 1).

Baseline to one-year follow-up associations

Blood levels of ACE-1 and ANGII, and cognitive function—In the fully adjusted model there was negative association between baseline log converted ACE-1 levels and Digit Span Total ($\beta = -0.030$, 95% CI $[-0.062, -0.003]$; $p = 0.04$), and a positive association between baseline log converted ACE-1 levels and TMT part A ($\beta = 0.003$, 95% CI $[0.001, 0.006]$; $p = 0.04$), at 1-year follow-up, but were not associated with other cognitive measures. There was no significant association between baseline log converted ANGII levels and cognitive function at 1-year follow-up (Table 3).

Blood levels of ACE-1 and ANGII, and BP measures—In the fully adjusted model there was no significant association between baseline log converted ACE-1 and ANGII levels and SBP, DBP, or PP at 1-year follow-up (Table 3).

BP measures and cognitive function—In the fully adjusted model there was a negative association between baseline PP and Pattern Comparison at 1-year follow up, but not with any other cognitive measures. There was no significant association between baseline SBP or DBP and cognitive function at 1-year follow-up (Supplementary Table 2).

DISCUSSION

Our study capitalizes on recent advances in RAS neurobiology and adds new information to fill the gap in understanding of the role of RAS in cognitive aging as a precursor to dementia, and suggests the importance of additional research. In our pilot study, we evaluated associations between blood levels of ACE-1 and ANGII and cognitive functions in a subset of 56 cognitively normal community dwelling participants with high vascular risk factor burden in the Brain Health Study (BHS). We found that higher baseline ACE-1 levels were associated with worse processing speed and working memory at 1-year follow-up. Exploratory analyses suggest that these associations were not mediated through blood pressure control, suggesting alternative mechanisms.

Our study is the first to evaluate associations between ACE-1 or ANGII blood levels and cognitive function in a non-demented older adult population. There are only a few studies evaluating blood levels of ACE-1 in relation to AD pathology or brain imaging, with one cross-sectional study showing lower cerebrospinal fluid (CSF) and serum ACE-1 levels in AD participants when compared to normal controls [17]; another cross-sectional study by the same group showed no association between CSF or serum ACE-1 levels and cortical atrophy [27]. Based on the above mentioned and other studies [6–8], we hypothesized that higher blood levels of ACE-1 and ANGII are associated with worse cognitive function, which was confirmed by our 1-year follow-up evaluation of ACE-1 level and working memory and processing speed. Contrary to our hypothesis, we have found no associations between ANGII and cognitive measures.

Our findings of elevated ACE-1 levels predicting worse processing speed and working memory is in line with literature. Previous studies have shown that processing speed in addition to memory declines with age [28], and that vascular risk factors are associated with

increased white matter burden resulting in worsening processing speed and working memory [29, 30].

The remaining question in our study is the lack of associations between ANGII levels and cognitive function. ANGII levels are the result of cleavage from angiotensin I, which is mediated by ACE-1, thus similar results between ACE-1 levels and cognitive function would have been expected with ANGII. Baseline ACE-1 levels were significantly correlated with ANGII levels, thus dysregulation of this pathway could not explain our findings. One possibility could be, that associations of ACE-1 and cognitive function are not mediated by ANGII, but rather by other angiotensins. For example, ACE-1 is not only involved in the conversion of angiotensin I to II, but also in the conversion of angiotensin 1–9 to angiotensin 1–7, with angiotensin 1–7 being a counter factor to ANGII's vascular effects [8].

Additionally, a recent study using post-mortem brains of people with AD has also shown an increased conversion of ANGII to ANGIII and decreased metabolism of ANGIII, resulting in increased ANGIII levels [12]. Lastly, another enzyme, the angiotensin converting enzyme 2 (ACE-2), has also been shown to play an important role in the metabolism of ANGII, by converting ANGII to angiotensin 1–7 [8, 9, 12]. Thus, measuring levels of additional angiotensins and enzymes, including angiotensin 1–7, ANGIII, and ACE-2 would help to better understand our results and elucidate mechanism by which RAS is involved in cognition.

Recent advances showing the presence of mixed rather than single brain pathologies in patients with dementia, with various forms of vascular disease burden in addition to AD pathology [3, 4], highlight the need to focus on vascular, as well as amyloid, pathologies. The advances in vascular disease detection and the lack of currently available effective medication have resulted in an increased interest in antihypertensive medications (AHM) and their possible role in cognitive function and dementia [31, 32]. Epidemiological studies suggest that AHM acting via the RAS, such as ACE-I and AT1R blockers, protect against cognitive decline [6, 33, 34]. However, results of numerous randomized clinical trials evaluating the effect of ACE-I and/or AT1R blockers on risk of cognitive impairment in hypertensive patients have been mixed [31, 35–39], possibly due to the fact that dementia was a secondary outcome. Our findings regarding ACE-1 levels and worsening cognition could provide one possible mechanistic explanation of the beneficial effects of ACE-I in the prevention of cognitive decline. Our negative findings regarding ANGII levels and cognition however suggests the need for further studies exploring other possible pathways by which ATR1 exert their beneficial effect.

There are a number of advantages of this study. Our study included a well-characterized, sociodemographically at risk cohort of highly functioning, community-dwelling, older participants free of cognitive impairment at baseline with detailed cognitive testing and medical history, who underwent rigorous evaluation. Second, this study is population-based design, which minimizes self-selection on outcomes of interest. Third, the study examined at risk for cognitive impairment participants free of cognitive impairment at baseline. We were able to explore the possible role of blood pressure levels in order to explore one aspect of possible mechanisms.

There are limitations of this study. The sample size of our pilot study is small, which may result in a lack of power. Additionally, a one-year follow-up may have not been sufficient to capture changes in cognitive function in this non-demented cohort. Since this study involved mainly older African American women, its findings may not generalize to other populations. Nonetheless, this under-represented group has numerous medical and demographic risk factors that place them at elevated risk for dementia. Additional weakness is the fact, that only ACE-1 and ANGII levels of the complex RAS were measured, thus the complex mechanisms may not be captured.

In summary, this pilot study indicates that ACE-1 levels were associated with decline in processing speed and working memory at 1-year follow up and this effect was not mediated by blood pressure. Our findings are small, but results warrant further research with additional members of the RAS, in a larger sample size including participants with both normal and impaired cognition, and following them for a longer period in order to evaluate possible effects of RAS to improve identification of pharmacologic targets for preventive interventions to slow cognitive decline and delay the progression to dementia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline demographic characteristics of the subset of Brain Health Study (BHS) participants

	ACE-1/ANGII assayed N = 56 N (%) / mean (SD)	ACE-1/ANGII NOT assayed N = 67 N (%) / mean (SD)
Demographic		
Age (y)	67.77 (±6.32)	66.91 (±5.90)
Gender (female)	42 (75)	43 (64)
Race (African American)	52 (93)	61 (92)
Education	14.28 (±2.60)	13.78 (±2.60)
Medical History		
Hypertension	35 (64)	50 (75) *
Heart attack	2 (4)	2 (3)
Heart failure	2 (4)	1 (2)
Stroke	0 (0)	0 (0)
TIA	1 (2)	1 (2)
Diabetes mellitus	11 (20)	24 (36) *
Randomization to intervention	29 (52)	35 (52)
Blood		
ANGII (plasma, pg/ml)	10.92 (±14.91)	—
ACE-1 (serum, ng/ml)	232.83 (±60.01)	—

ACE-1, angiotensin converting enzyme-1; ANGII, angiotensin II; TIA, transient ischemic attack.

* $p < 0.05$.

Table 2

Evaluation of associations between baseline ACE-1, ANG II blood levels and blood pressure measures, and cognitive function using multivariable linear regression model

	ACE-1 N = 56				ANG II N = 56			
	Unadjusted model β (95% CI)	p	Adjusted model [#] β (95% CI)	p	Unadjusted model β (95% CI)	p	Adjusted model [#] β (95% CI)	p
Blood pressure								
Systolic blood pressure	-0.001 (-0.004;0.004)	0.95	-0.002 (-0.010;0.005)	0.55	0.004 (-0.014;0.021)	0.67	0.003 (-0.028;0.034)	0.85
Diastolic blood pressure	0.001 (-0.006;0.007)	0.89	0.006 (-0.004;0.016)	0.23	0.001 (-0.027;0.028)	0.98	-0.012 (-0.053;0.030)	0.58
Pulse pressure	0.001 (-0.005;0.005)	0.95	-0.010 (-0.020;0.041)	0.50	0.007 (-0.016;0.030)	0.56	-0.032 (-0.156;0.092)	0.61
Cognition								
TMT, part A	0.002 (-0.002;0.005)	0.38	0.003 (-0.001;0.007)	0.17	-0.002 (-0.017;0.014)	0.83	-0.007 (-0.025;0.011)	0.42
TMT, part B	0.001 (-0.001;0.001)	0.41	0.001 (-0.001;0.002)	0.26	-0.003 (-0.009;0.002)	0.19	-0.004 (-0.010;0.002)	0.20
RAVLT – learning	0.006 (-0.002;0.014)	0.15	-0.002 (-0.013;0.009)	0.66	0.035 (-0.001;0.070)	0.04 *	0.040 (-0.001;0.082)	0.06
RAVLT – short delayed recall	0.009 (-0.014;0.033)	0.80	0.001 (-0.032;0.033)	0.97	0.034 (-0.068;0.137)	0.50	0.051 (-0.083;0.186)	0.44
RAVLT – long delayed recall	0.001 (-0.001;0.001)	0.28	-0.011 (-0.046;0.023)	0.50	0.002 (0.001;0.005)	0.04 *	0.087 (-0.046;0.221)	0.19
Digit Span Forward	-0.006 (-0.045;0.033)	0.75	-0.025 (-0.077;0.027)	0.33	0.051 (-0.121;0.0224)	0.55	-0.019 (-0.235;0.198)	0.86
Digit Span Backward	0.006 (-0.030;0.042)	0.75	-0.029 (-0.074;0.015)	0.18	0.008 (-0.140;0.155)	0.91	0.051 (-0.137;0.239)	0.58
Digit Span Total	-0.022 (-0.050;0.004)	0.10	-0.017 (-0.044;0.009)	0.19	0.017 (-0.074;0.110)	0.70	0.013 (-0.101;0.128)	0.81
Pattern Comparison Total	-0.001 (-0.002;0.007)	0.88	-0.010 (-0.027;0.007)	0.24	-0.018 (-0.072;0.035)	0.50	-0.007 (-0.083;0.070)	0.86

ACE-1, angiotensin converting enzyme 1, log converted; ANG II, angiotensin II, log converted; TMT, part A, Trail Making Test, part A; TMT, part B, Trail Making Test, part B; RAVLT – learning, Rey Auditory Verbal Learning Test – learning; RAVLT – short delayed recall, Rey Auditory Verbal Learning Test – short delayed recall; RAVLT – long delayed recall, Rey Auditory Verbal Learning Test – long delayed recall.

[#] Adjusted model: Model was adjusted for age, gender, race, education, BMI, randomization, chronic disease, depression, systolic and diastolic blood pressure, and baseline ACE-1 or ANGII levels.

* $p < 0.05$.

Table 3

Evaluation of associations between baseline ACE-1, ANG II blood levels and 1-year follow-up blood pressure measures and cognitive function using multivariable linear regression model

	ACE-1 N = 40			ANG II N = 40		
	Unadjusted model β (95% CI)	p	Adjusted model [#] β (95% CI)	Unadjusted model β (95% CI)	p	Adjusted model [#] β (95% CI)
Blood pressure						
Systolic blood pressure	0.002 (−0.002;0.007)	0.30	−0.002 (−0.018;0.014)	0.007 (−0.012;0.025)	0.47	0.018 (−0.044;0.080)
Diastolic blood pressure	0.002 (−0.007;0.010)	0.69	−0.010 (−0.033;0.013)	−0.005 (−0.041;0.031)	0.79	−0.018 (−0.120;0.084)
Pulse pressure	0.004 (−0.003;0.010)	0.24	0.004 (−0.019;0.026)	0.014 (−0.011;0.040)	0.26	0.040 (−0.038;0.118)
Cognition						
TMT, part A	0.001 (−0.002;0.003)	0.78	0.003 (0.001;0.006)	−0.005 (−0.015;0.004)	0.26	−0.001 (−0.022;0.003)
TMT, part B	−0.001 (−0.003;0.003)	0.92	0.001 (−0.004;0.005)	−0.001 (−0.009;0.009)	0.94	−0.006 (−0.023;0.010)
RAVLT – learning	0.007 (−0.002;0.016)	0.11	−0.003 (−0.019;0.013)	0.009 (−0.045;0.027)	0.62	0.042 (−0.011;0.096)
RAVLT – short delayed recall	0.024 (−0.003;0.052)	0.08	0.027 (−0.023;0.078)	−0.001 (−0.121;0.118)	0.98	0.025 (−0.185;0.234)
RAVLT – long delayed recall	0.007 (−0.020;0.034)	0.59	0.014 (−0.023;0.051)	0.051 (−0.054;0.157)	0.33	0.053 (−0.092;0.199)
Digit Span Forward	−0.001 (−0.001;0.001)	0.11	−0.037 (−0.002;−0.001)	−0.001 (−0.003;0.001)	0.45	0.101 (−0.184;0.386)
Digit Span Backward	−0.001 (−0.001;0.001)	0.12	−0.062 (−0.118;−0.051)	−0.001 (−0.003;0.001)	0.45	0.137 (−0.164;0.438)
Digit Span Total	−0.001 (−0.001;0.001)	0.11	−0.030 (−0.062;−0.003)	−0.001 (−0.003;0.001)	0.46	0.071 (−0.089;0.232)
Pattern Comparison Total	−0.009 (−0.029;0.010)	0.34	−0.009 (−0.036;0.018)	0.040 (−0.031;0.111)	0.26	0.036 (−0.067;0.139)

ACE-1, angiotensin converting enzyme 1, log converted; ANG II, angiotensin II, log converted; TMT, part A, Trail Making Test, part A; TMT, part B, Trail Making Test, part B; RAVLT – learning, Rey Auditory Verbal Learning Test – learning; RAVLT – short delayed recall, Rey Auditory Verbal Learning Test – short delayed recall; RAVLT – long delayed recall, Rey Auditory Verbal Learning Test – long delayed recall.

[#] Adjusted model: Model was adjusted for age, gender, race, education, BMI, randomization, chronic disease, depression, systolic and diastolic blood pressure and baseline ACE-1 or ANGII levels.

* $p < 0.05$.