Published in final edited form as:

J Alzheimers Dis. 2020 ; 75(2): 521–529. doi:10.3233/JAD-200118.

Angiotensin II Blood Levels Are Associated with Smaller Hippocampal and Cortical Volumes in Cognitively Normal Older Adults

Sevil Yasar^{a,*}, Kyle D. Moored^b, Atif Adam^b, Fiona Zabel^c, Yi-Fang Chuang^d, Vijay R. Varma^e, Michelle C. Carlson^b

^aDepartment of Medicine, Johns Hopkins University, School of Medicine, Baltimore, MD, USA

^bDepartment of Mental Health, Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD, USA

^cBaltimore Polytechnic Institute, Baltimore, MD, USA

^dInstitute of Public Health, National Yang-Ming University, Taipei, Taiwan

^eNational Institute on Aging, Intramural Research program, Laboratory of Behavioral Neuroscience, Baltimore, MD, USA

Abstract

Background: There is emerging evidence about possible involvement of the renin-angiotensin system (RAS) in the pathogenesis of Alzheimer's disease (AD) and decline of cognitive function. However, little is known about associations with brain biomarkers.

Objective: Our study aimed to examine associations between blood ACE-1 and ANG II levels and brain MRI based volumes in non-demented participants, and whether these associations were mediated by blood pressure.

Methods: This cross-sectional study was conducted in 34 older participants from the Baltimore Experience Corps Trial (BECT) Brain Health Sub-study (BHS). Blood ANGII and ACE-1 levels were measured by ELISA and brain MRI volumes were generated using FreeSurfer 6.0. Multiple linear regression analysis, adjusting for intracranial volume and confounders, was used to determine associations between log transformed ANGII and ACE-1 levels and MRI volumes (mm³).

Results: Participants were predominantly female (76%), African-American (94%), with mean age of 66.9 and education of 14.4 years. In the fully adjusted model we observed significant inverse associations between log ANGII levels and total grey matter (β =Angiotensin II associated with smaller hippocampus 14,935.50, $\pm$ 7,444.83, $p = 0.05$), total hippocampus (β =-129.97,

*Correspondence to: Sevil Yasar, MD, PhD, Johns Hopkins University, School of Medicine, Department of Medicine, Division of Geriatric Medicine & Gerontology, 5200 Eastern Ave, MFL Center Tower, #727, Baltimore, MD 21224, USA. Tel.: 410 550 2668; Fax: 410 550 2513; syasar1@jhmi.edu.

Authors' disclosures available online (<https://www.j-alz.com/manuscript-disclosures/20-0118r1>).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <https://dx.doi.org/10.3233/JAD-200118>.

± 105.27 , $p = 0.03$), rostral middle frontal ($\beta = -1580.40$, ± 584.74 , $p = 0.02$), and supramarginal parietal ($\beta = -978.90$, ± 365.54 , $p = 0.02$) volumes. There were no associations between ANGII levels and total white matter or entorhinal cortex volumes, or ACE-1 levels and any brain volumes.

Conclusion: We observed that increased blood ANGII levels were associated with lower total grey matter, hippocampal, rostral middle frontal, and supramarginal parietal volumes, which are associated with cognitive domains that decline in preclinical AD.

Keywords

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

INTRODUCTION

There is increasing evidence in recent years for the involvement of the renin angiotensin system (RAS) in Alzheimer's disease (AD) pathogenesis [1–5]. The RAS generates bioactive angiotensin peptides with a wide range of biological activities involved not only in blood pressure regulation, but possibly also in the pathogenesis of AD, either independently or in combination with BP control [1–8]. These peptides likely have effects on vascular function and modulation of amyloid and tau metabolism in AD [5]. Previous autopsy studies have shown that people with AD have increased angiotensin converting enzyme 1 (ACE-1) activity resulting in increased conversion of angiotensin I (ANGI) to II (ANGII) [1, 2, 8], which is a potent vasoconstrictor. Similarly, decreased angiotensin converting enzyme 2 (ACE-2) activity was found to decrease conversion of ANGII to the vasodilator angiotensin 1–7 [9]. All these changes resulted in increased levels of ANGII causing increased activation of angiotensin type-1 receptor (AGT1 R), which is associated with accumulation of amyloid- β (A β) and tau, and also with decreased acetylcholine release, all of which contribute to AD pathogenesis [1–4]. Few studies have been done evaluating role of RAS peptides in AD process in cerebrospinal fluid (CSF) and/or blood. One study measured blood ACE-1 levels and found lower levels and greater reduction in levels in participants with AD when compared to normal controls [10]. While another study evaluated ACE-1 activity and levels in postmortem CSF and found lower levels, but not change in activity, in participants with AD when compared to normal controls [11].

We have previously shown in cognitively normal Brain Health Sub-study (BHS) participants that higher ACE-1 levels predicted worse processing speed and working memory after 1-year follow-up [12]. There are currently no studies available evaluating associations between blood levels of ANGII and or ACE-1 and brain MRI biomarkers. Thus, in our study we have explored associations between blood ANGII and ACE-1 levels and MRI based volumetric measures in the same population from our prior study [12] 1) associated with AD related brain atrophy: total grey and white matter, hippocampus, entorhinal cortex and 2) associated with cognitive domains [13] identified in prior work (i.e., speed and working memory) [12]: rostral middle frontal gyrus, superior frontal gyrus, supramarginal parietal gyrus, and inferior parietal gyrus. We further explored whether these associations were potentially mediated by blood pressure.

METHODS AND MATERIALS

Participants

The Brain Health Study (BHS) [14, 15], a nested study within the Baltimore Experience Corps Trial (BECT). 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 versus a waitlist control group, and details were previously published on the recruitment and design of BECT [16, 17]. The nested BHS simultaneously recruited eligible participants prior to randomization to evaluate the benefits of the program on their brain and biological health. From January 2006 to December 2009, 702 eligible participants were randomized for the 2-year trial to either intervention. During BECT randomization, 123 participants were invited to enroll in the nested BHS who were free of dementia at baseline. Criteria for enrollment in the BHS have been described previously [14, 15]. Baseline and follow-up evaluations BECT included medical history, neurological, psychiatric, and neuropsychological examinations and laboratory studies. Participants also enrolled in the BHS underwent structural and functional brain magnetic resonance imaging (MRI) at baseline and two subsequent annual follow-up visits 12 and 24 months after baseline. Fifty-six participants attending follow-up visits [16] were recruited to our pilot study to collect blood in order to explore associations between ACE-1 and ANGII levels and cognition and volumetric brain imaging. Inclusion criteria for the 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 angiotensin converting enzyme-1 inhibitor (ACE-I) or angiotensin 1 receptor blockers (ATRB) in previous 3 months. Of the 56 participants, 22 participants were missing either MRI (e.g., had no MRI imaging or had poor image quality) or blood assay measures (e.g., undetectable measures), resulting in a final analytic sample of 34 participants where both blood and MRI measures were available from the same visit. 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, and health data were collected concurrently with blood.

Blood ACE-1 and ANGII assay

Blood collection and storage—Blood draw procedures 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 JHUICTR Core Laboratory, where it was stored at -80° 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 to ensure low interassay variance.

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. ACE-1 and ANGII measurements were normalized using log-transformations.

Outcome measures

MRI volumetric measures—T1-weighted imaging was done on 3.0T scanner (Phillips, Best, Netherlands) using the magnetization prepared rapid-acquisition gradient echo (MPRAGE) protocol with TR = 8ms, TE = 3.6ms, matrix size = 256×256, slices 200 and the field of view (FOV) 256×256 mm. Brain volumetric measures are reported in mm³ and include total cortical gray matter, white matter, hippocampal, and entorhinal volumes, which are all affected by AD. Additionally rostral middle frontal gyrus, superior frontal gyrus, supramarginal parietal gyrus, and inferior parietal gyrus were also included since all are associated with processing speed and working memory [13], which we have previously found to be associated with ACE-1 levels [12].

Volumes were generated using FreeSurfer 6.0 [14, 15], adjusted for intracranial volume, and regional volumes were summed to produce bi-hemispheric measures.

Blood pressure—At each study visit, BP was measured by trained staff according to standard protocols. 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 appropriatesized occluding cuff and were averaged for data analysis. Measures of systolic blood pressure (SBP) and diastolic blood pressure (DBP) 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.

Multiple linear regression models were used for evaluating associations between log(ACE-1) and log(ANGII) levels, and MRI volumetric measures. In the first model, linear regression analyses were used and adjusted for study randomization (intervention versus control); in the second model, analyses were further adjusted for potential confounding variables (age, sex, education, number of chronic diseases, SBP and DBP, body mass index (BMI), and Geriatric Depression Scale (GDS). The number of chronic diseases variable was a sum of any self-reported medical conditions including hypertension, diabetes mellitus, stroke, coronary artery disease, and chronic heart failure. We did not adjust for race since a majority (94%) of participants were African American. Due to concern of over-adjustment, we have pre-adjusted for intracranial volume (ICV) for volumetric outcomes, thus ICV was not included in the final models. In exploratory analyses, we additionally evaluated potential associations between log(ACE-1) and log(ANGII) and blood pressure measures, and blood pressures and MRI volumetric measures. These exploratory analyses also evaluated whether associations between blood levels of ACE-1 and ANGII and MRI volumetric measures may be mediated by blood pressure.

The *a priori* significance level was set at $p < 0.05$. STATA 15.1 was used for all analyses (Stata Corp, College Station, TX).

RESULTS

Participants

There were 34 participants with a mean age of 66.9 (6.4) years, 26 (76%) were females, and 32 (94%) were African Americans with mean of 14.4 (± 2.6) years of education (Table 1). Mean SBP was 137.8 (± 17.2) and DBP 76.5 (± 10.6) mm Hg while BMI was 31.7 (± 6.0) kg/m², and 21 (64%) participants had history of hypertension. Participants with blood assays were less likely to report hypertension and diabetes than participants not assayed, but they did not differ significantly in other baseline demographic and health related characteristics (Table 1). The ICV-adjusted mean volumes for total grey matter were 504,100 ($\pm 45,428$) mm³, total white matter 393,396 ($\pm 50,780$) mm³, total hippocampus 6,744 (± 704) mm³, 504,100 ($\pm 45,428$) mm³, entorhinal cortex 3,505 (± 727) mm³, rostral middle frontal gyrus 22,341 ($\pm 3,423$) mm³, superior frontal gyrus 33,454 ($\pm 3,487$) mm³, inferior parietal gyrus 19,819 ($\pm 2,377$) mm³, and supramarginal gyrus 16,042 ($\pm 2,294$) mm³.

Cross-sectional associations

Blood levels of ACE-1 and ANGII—Using Pearson correlation there was a significant correlation between ACE-1 and ANGII levels ($r = 0.36$; $p = 0.048$) (Supplementary Figure 1).

Blood levels of ACE-1 and ANGII, and MRI volumetric measures—In the fully adjusted models, there were no significant associations between log(ACE-I) levels and MRI volumetric measures (mm³) (Table 2). However, we observed significant inverse associations between log(ANGII) levels and total grey matter ($\beta = -14,935.50$, $\pm 7,444.83$, p

= 0.05), total hippocampus ($\beta = -129.97, \pm 105.27, p = 0.03$), rostral middle frontal ($\beta = -1580.40, \pm 584.74, p = 0.02$), and supramarginal parietal ($\beta = -978.90, \pm 365.54, p = 0.02$) volumes (Table 2). There were no significant associations between ANGII levels and total white matter or entorhinal cortex volumes.

Blood levels of ACE-1 and ANGII, and BP measures—Mean systolic blood pressure (SBP) was $137.8 (\pm 17.2)$ and diastolic blood pressure (DBP) was $76.5 (\pm 10.6)$ mmHg. In the fully adjusted model, baseline log converted ACE-1 and ANGII levels showed no significant associations with baseline SBP and DBP (Supplementary Table 1).

BP measures and MRI volumetric measures—In the fully adjusted model there was no significant association between baseline SBP and DBP measures and MRI volumetric measures (Table 3).

DISCUSSION

In our study, we evaluated associations between blood levels of ACE-1 and ANGII and MRI volumetric measures in a subset of 34 cognitively normal community dwelling participants with high vascular risk factor burden in the Brain Health Study (BHS). We found that higher baseline ANGII levels were associated with lower total grey matter, hippocampal, rostral middle frontal, and supramarginal parietal volumes, all associated with memory and executive function and this was independent of blood pressure control. Our findings are in line with a previous study showing that variants of AGTR1 gene, which encodes AGTR1 the main receptor for ANGII, were associated with accelerated hippocampal volume loss over a 4-year period [18]. However, in contrast to another longitudinal study, which showed that presence of ACE I/I genotype associated with lower ACE-1 blood levels, was associated with smaller hippocampus and higher risk for AD over a 6-year period in women [19], we did not find similar associations between ACE-1 levels and hippocampal volume. This could be explained by the cross-sectional nature of our study and the small sample size. Our findings are especially noteworthy since we not only evaluated associations of well-known brain biomarkers involved in AD pathogenesis, but also regional brain volumes, that may better pinpoint the clinical significance and potential mechanisms by which ACE-1 and ANGII may also accelerate age-related cognitive decline.

Our study capitalizes on recent advances in RAS neurobiology and adds new information to fill the gap in understanding the role of RAS in cognitive aging as a potential precursor to dementia. The RAS likely plays an important role in cognitive function [1, 2, 20]. This was supported by our other recent study in the BHS, where we found that higher ACE-1 levels predicted worse cognition one year later [12]. We hypothesized that cognitive changes are preceded by brain volume changes associated in processing speed and/or working memory. There are only a few studies evaluating blood levels of ACE-1 and ANGII in relation to brain volumes in part due to the assay requirement of specifically pre-treated blood. One cross-sectional study showed no association between cerebrospinal fluid and blood ACE-1 levels and cortical atrophy [20]. Our study is the first to evaluate associations between both ACE-1 and ANGII blood levels and detailed MRI volumetric measures in a non-demented

older adult population. Additionally, we took into account the potential mediating role of blood pressure [21] in the effect of ACE and ANGII on brain volumes.

Our findings lend support to findings from epidemiological studies showing that antihypertensive medications acting via the RAS, such as ACE-I and ATRB, are protective against cognitive decline [22–24]. It, however, needs to be noted that results of numerous randomized clinical trials evaluating the effect of ACE-I and/or ATRB blockers on risk of cognitive impairment and function in hypertensive patients have been mixed [25–30], perhaps due to the fact that dementia was a secondary outcome thus studies may have been underpowered.

Our findings however also raise some questions regarding our previous findings of no associations between ANGII and cognitive function [12]. One possible explanation could be that structural changes occur before cognitive changes [31] and longitudinal follow-up longer than one year is needed to suggest associations. Other possible explanation is the fact that only ACE-1 and ANGII levels of the complex RAS were measured, thus lacking evaluation of other peptides potentially involved in the complex mechanisms.

There is very little literature about associations between white matter volume and RAS. In our study we found no association between white matter volume and ANGII or ACE-1 levels. A recent study of healthy older adults showed that the M268T polymorphism of angiotensinogen, the precursor of ANGI which is then converted to ANGII, was associated with increased ANGII and alteration of microstructure of white matter. In this study white matter was measured using T2-weighted fluid-attenuated inversion-recovery (FLAIR) and diffusion tensor imaging (DTI) [32]; therefore, the T1-weighted images used in our study may have not been sensitive enough to detect associations.

There are a number of strengths of this study. First, we explored associations in a well-characterized, sociodemographically at risk cohort of highly functioning, community-dwelling, older participants free of cognitive impairment at baseline with detailed medical history, MRI imaging, and cognitive testing. Second, the study examined participants who were free from cognitive impairment at baseline, however, at risk for future cognitive impairment due to various sociodemographic factors. Third, participants of this study were the same participants from our prior study when we evaluated associations between ACE-1 and ANGII levels and cognitive functions, thus it enables us to draw more mechanistic conclusions. Fourth, we were able to explore the possible role of blood pressure levels in order to explore one aspect of possible mechanisms. Having said that, the small sample size did not allow us to stratify participants by presence of absence of hypertension, which would be important to clearly evaluate the role of blood pressure in these associations.

There are limitations of this study. First, the sample size of our posthoc study was small, which may have limited the power to detect associations while at the same time low power can also increase the possibility of false positive results. The significant associations we observed are particularly meaningful considering the small sample size. Second, since this study involved mainly older African American women, findings have yet to be replicated in other and larger populations. Nonetheless, this under-represented group has numerous

medical and demographic risk factors that place them at elevated risk for dementia. Third, only ACE-1 and ANGII levels of the RAS were measured, thus the entirety of the complex RAS mechanisms may not be captured. Fourth, the MRI volumetric and BP analyses were cross-sectional, and findings should be replicated in future longitudinal studies to better establish the temporal relationship between RAS markers and brain outcomes. Fifth, we did not have measurements of hippocampal subfield available, however future work can examine hippocampal subregions to determine whether RAS biomarkers differentially affect memory subsystems.

In summary, this study indicates that ANGII levels were associated with smaller total grey, hippocampal, rostral middle frontal, and supramarginal parietal volumes, and this effect may be independent of blood pressure. Like with every study in order to confirm our hypothesis we first need to replicate our findings, both cross-sectionally and longitudinally, in a larger cohort, which is more representative of the general population, while using more sensitive MRI imaging to measure small vessel disease. Our results, however, also warrant further research with additional blood and CSF markers of the RAS, in a larger cohort 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.

ACKNOWLEDGMENTS

We thank the Brain Health Substudy (BHS) study participants for their critical contributions to this research along with funding from the Johns Hopkins Neurobehavioral Research Unit, a supplement to the NIH grant #P01AG027735-03 and the Alzheimer's Drug Discovery Foundation.

We acknowledge the support of the Johns Hopkins University Institute for Clinical and Translational Research Clinical Research Core Laboratory for the performance of ACE and ANGII measures. The project described was supported in part by the National Center for Advancing Translational Sciences, NIH #UL1TR001079 and #R37AG19905 grants.

S. Yasar has received research support for this study from the Johns Hopkins University Pepper Center NIA #P30AG021334 and NIA #1R03AG058043 grants. K. Moored is supported by the NIA #T32AG000247 and #1R03AG058043 grants. V. Varma is supported by the Intramural Research Program, National Institute on Aging, NIH. Adam Atif and Fiona Zabel report no funding. M. Carlson report funding from NIA ##1R03AG058043 grant.

The opinions expressed in this article are those of the authors and do not represent the official position of the Corporation for National and Community or the U.S. Government.

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Table 1

Baseline demographic characteristics of BHS study participants

Demographic	ACE-I/ANGII assayed N = 34	ACE-I/ANGII NOT assayed N = 67
	N (%) / mean (SD)	N (%) / mean (SD)
Age (y)	66.9 (±6.4)	66.91 (±5.90)
Sex (female)	26 (76)	43 (64)
Race (African American)	32 (94)	61 (92)
Education	14.4 (±2.6)	13.78 (±2.60)
Medical History		
Hypertension	21 (64)	50 (75)*
Heart attack	1 (3)	2 (3)
Heart failure	2 (6)	1 (2)
Stroke	0 (0)	0 (0)
TIA	0 (0)	1 (2)
Diabetes mellitus	7 (21)	24 (36)*
Randomization to intervention	18 (52)	35 (52)
Blood		
ANGII (plasma, pg/ml)	9.3 (±10.2)	–
ACE-I (serum, ng/ml)	227.1 (±60.0)	–

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

* $p < 0.05$.

Table 2

Evaluation of associations between ACE-I, ANG II blood levels, and MRI volumetric measures using multivariable linear regression model

	ACE-I N = 34				ANG II N = 34			
	Model 1 [§]		Model 2 ^{§§}		Model 1 [§]		Model 2 ^{§§}	
	β (SE)	p	β (SE)	p	β (SE)	p	β (SE)	p
Total grey matter	-19,061.11 ($\pm$ 27,133.99)	0.49	-13,995.05 ($\pm$ 39,228.17)	0.73	-14,935.50 ($\pm$ 7,444.83)	0.06	-14,933.70 ($\pm$ 6,932.44)	0.05*
Total white matter	-9,718.57 ($\pm$ 33,027.05)	0.77	-9,215.05 ($\pm$ 44,227.63)	0.84	-11,769.10 ($\pm$ 8,273.13)	0.17	-9,829.91 ($\pm$ 8,931.99)	0.29
Hippocampus	-347.06 ($\pm$ 432.69)	0.43	-460.49 ($\pm$ 487.29)	0.36	-129.97 ($\pm$ 105.27)	0.23	-190.75 ($\pm$ 79.58)	0.03*
Entorhinal cortex	153.66 ($\pm$ 518.36)	0.77	-50.01 ($\pm$ 666.42)	0.94	-40.54 ($\pm$ 136.61)	0.77	-207.73 ($\pm$ 121.14)	0.11
Rostral middle frontal gyrus	-2,288.04 ($\pm$ 2,165.13)	0.30	-3,635.42 ($\pm$ 3,344.09)	0.29	-1,659.70 ($\pm$ 539.67)	0.01**	-1,580.40 ($\pm$ 584.74)	0.02*
Superior frontal gyrus	-2,145.78 ($\pm$ 2,251.32)	0.35	-2,731.02 ($\pm$ 3,009.94)	0.38	38.63 ($\pm$ 617.42)	0.95	68.71 ($\pm$ 687.51)	0.92
Inferior parietal gyrus	-1,200.24 ($\pm$ 1,485.24)	0.43	-502.96 ($\pm$ 2,089.52)	0.81	-783.93 ($\pm$ 438.70)	0.09	-687.00 ($\pm$ 375.67)	0.09
Supramarginal gyrus	-1,877.93 ($\pm$ 1,433.35)	0.20	-3,236.53 ($\pm$ 1,956.19)	0.12	-910.45 ($\pm$ 391.13)	0.03*	-978.90 ($\pm$ 365.54)	0.02*

ACE-I, angiotensin converting enzyme I, log converted; ANG II, angiotensin II, log converted.

[§]Model 1: Model was adjusted for randomization.

^{§§}Model 2: Model was adjusted for age, sex, education, BMI, randomization, depression, systolic and diastolic blood pressure, number of chronic diseases.

* $p < 0.05$.

Betas represent the average volumetric change in ICV-adjusted volumes (mm^3) per one point increase in log(ACE) or log(ANGII).

Table 3

Evaluation of associations between systolic and diastolic blood pressure and MRI volumetric measures using multivariable linear regression model

	SBP N = 34				DBP N = 34			
	Model 1 [§]		Model 2 ^{§§}		Model 1 [§]		Model 2 ^{§§}	
	β (SE)	p	β (SE)	p	β (SE)	p	β (SE)	p
Total grey matter	-257.58 ($\pm$ 552.55)	0.65	-202.26 ($\pm$ 644.26)	0.76	-288.49 ($\pm$ 864.82)	0.74	-1572.70 ($\pm$ 948.07)	0.11
Total white matter	-243.95 ($\pm$ 584.12)	0.68	348.03 ($\pm$ 716.82)	0.63	110.28 ($\pm$ 914.25)	0.91	-981.66 ($\pm$ 1054.86)	0.36
Hippocampus	-12.91 ($\pm$ 7.62)	0.10	-12.43 ($\pm$ 8.25)	0.15	16.19 ($\pm$ 11.92)	0.19	14.69 ($\pm$ 12.14)	0.24
Entorhinal cortex	-11.68 ($\pm$ 9.08)	0.21	-12.88 ($\pm$ 10.58)	0.24	1.63 ($\pm$ 14.22)	0.91	6.83 ($\pm$ 15.57)	0.67
Rostral middle frontal gyrus	-1.61 ($\pm$ 43.49)	0.97	-10.06 ($\pm$ 57.26)	0.86	-27.02 ($\pm$ 68.06)	0.69	-141.51 ($\pm$ 84.26)	0.11
Superior frontal gyrus	9.00 ($\pm$ 42.03)	0.83	29.67 ($\pm$ 53.65)	0.59	-56.56 ($\pm$ 65.78)	0.40	-122.27 ($\pm$ 78.95)	0.14
Inferior parietal gyrus	-32.72 ($\pm$ 31.09)	0.30	-18.30 ($\pm$ 33.33)	0.59	4.58 ($\pm$ 48.66)	0.93	-78.12 ($\pm$ 49.05)	0.13
Supramarginal gyrus	-25.69 ($\pm$ 29.61)	0.39	-7.45 ($\pm$ 34.68)	0.83	-7.86 ($\pm$ 46.35)	0.87	-23.42 ($\pm$ 51.04)	0.65

SBP, systolic blood pressure; DBP, diastolic blood pressure.

[§]Model 1: Model was adjusted randomization.

^{§§}Model 2: Model was adjusted for age, sex, education, BMI, randomization, depression, number of chronic diseases.

* p < 0.05.

Betas represent the average volumetric change in ICV-adjusted volumes (mm³) per one-point increase in SBP or DBP.