Impact of the *AGTR1* A1166C polymorphism on subcortical hyperintensities and cognition in healthy older adults

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Abstract Vascular aging consists of complex and multifaceted processes that may be influenced by genetic polymorphisms of the renin-angiotensin system. A polymorphism in the angiotensin II type 1 receptor gene (*AGTR1*/rs5186) has been associated with an increased risk for arterial stiffness, hypertension, and ischemic stroke. Despite these identified relationships, the impact of *AGTR1* A1166C on white matter integrity and

cognition is less clear in a healthy aging population. The present study utilized indices of neuroimaging and neuropsychological assessment to examine the impact of the A1166C polymorphism on subcortical hyperintensities (SH) and cognition in 49 healthy adults between ages 51–85. Using a dominant statistical model (CC + CA (risk) vs. AA), results revealed significantly larger SH volume for individuals with the C1166 variant ($p < 0.05$, partial $\eta^2 = 0.117$) compared with those with the AA genotype. Post hoc analyses indicated that increased SH volume in C allele carriers could not be explained by vascular factors such as pulse pressure or body mass index. In addition, cognitive performance did not differ significantly between groups and was not significantly associated with SH in this cohort. Results suggest that presence of the C1166 variant may serve as a biomarker of risk for suboptimal brain integrity in otherwise healthy older adults prior to changes in cognition.

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Introduction

Vascular aging is characterized by a gradual decline in vessel structure and hemodynamic stability (Lakatta 2002; Laurent et al. 2006; Nilsson et al. 2008). Age-related increases in plaque formation, intima-media thickness, and arterial stiffness lead to decreased vascular compliance and variability in perfusion pressure

(Ebrahimi 2009). These mechanical changes render a compromised vascular system vulnerable to the detrimental effects of oxidative stress, inflammation, and cerebral ischemia (Sierra et al. 2011). Although numerous cellular and metabolic factors contribute to compromised vasculature, alterations in the brain renin-angiotensin system (RAS) have been implicated in the pathogenesis of vascular aging (Diz et al. 2011).

Angiotensin II (AngII) is the principal peptide involved in vascular homeostasis in the brain RAS (McKinley et al. 2003). The hemodynamic mechanisms of AngII are primarily mediated through activation of the type 1 angiotensin receptor (AT₁; Saavedra 2005) localized to brain regions involved in autonomic function (Ando et al. 2004). Increased brain RAS activity is associated with increased AT₁ expression in cerebral arteries and microvessels promoting endothelial dysfunction, vascular inflammation, and blood–brain barrier permeability (Nishimura 2001; Ando et al. 2004; Saavedra et al. 2006). This AT₁-induced pathophysiological cascade is characteristic of aging phenotypes causing progressive changes in cerebral circulation and white matter microstructure (Nation et al. 2010; Saavedra et al. 2011).

Activation of the peripheral RAS also has indirect pathological implications for brain aging by stimulating visceral adipocyte growth and vascular rigidity (Zieman et al. 2005; Tchkonina et al. 2010). Adipose tissue is a secretory organ that regulates vascular tone through AT₁-mediated production of AngII (Tchkonina et al. 2010). Adipocytes expand during normal aging, promoting visceral obesity and dysfunctional elevations of circulating AngII (Pacholczyk et al. 2013). Chronic increases in AngII production mechanically damage the vascular wall (Zieman et al. 2005), resulting in arterial stiffness and blood pressure variability (Thalmann and Meier 2007; Natale et al. 2009). Arterial stiffness and elevated body mass are both significant predictors of white matter abnormalities and risk for ischemic stroke in older individuals (Safar et al. 2000; Kuo et al. 2010; Strazzullo et al. 2010; Verstynen et al. 2012), suggesting that abnormal activation of the peripheral RAS may influence cerebrovascular mechanisms of age-related white matter degeneration.

Cerebrovascular disease is a consequence of vascular aging that can be visualized in the subcortical white matter as hyperintense signals on T2-weighted MRI (Paul et al. 2005). Although subcortical hyperintensities (SH) are associated with an aged vascular system and

are common in older populations (Söderlund et al. 2003), the severity and cognitive impact of SH is variable among older individuals (Schmidt et al. 2011). The established relationship between AngII and vascular pathology suggests that predisposing risk factors for increased AT₁ expression may influence SH severity, especially in older patients.

Polymorphisms in the AT₁ gene have been identified as risk factors for cerebrovascular pathology (Duncan et al. 2001). Most notably, the A1166C polymorphism has been implicated as an independent risk factor for vascular phenotypes such as hypertension and ischemic stroke. A1166C has also been associated with white matter lesion severity in elderly populations both with and without depression (Taylor et al. 2009, 2013). Despite these identified relationships, an independent association between A1166C and white matter integrity has not been defined. In addition, the cognitive impact of A1166C in healthy older adults remains unknown.

The present study examined the impact of the A1166C polymorphism (rs5186) on SH and cognition in healthy adults between the ages of 51–85. Cognitive performance was assessed using subtest scores from the repeatable battery for the assessment of neuropsychological status (RBANS). Body mass index (BMI) and pulse pressure (PP) were also individually calculated to serve as noninvasive measures of body composition and arterial stiffness, respectively. Genetic status was evaluated using a dominant statistical model (CC + CA (risk) vs. AA). We hypothesized that individuals with at least one risk allele of A1166C would demonstrate greater SH volume and decreased cognitive performance compared with those with the homozygous AA genotype. We further postulated that differences in SH and cognition would be moderated by vascular factors such as PP and BMI between groups.

Methods

Participants

Data were obtained from 49 healthy men ($n=16$) and women ($n=33$) enrolled in a longitudinal study of cognitive aging. Recruitment involved local print and radio advertisements and the Research Participant Registry of the Washington University Institute of Clinical and Translational Sciences (ICTS). All English-speaking adults above the age of 50 qualified for pre-enrollment

screening. Information regarding medical and psychiatric conditions was obtained through phone screening. Individuals who reported a medical condition capable of influencing cognition (e.g., multiple sclerosis, thyroid disease, etc.) or severe psychiatric diagnosis (e.g., all axes I and II disorders with the exception of treated depression) were excluded from the study. Individuals were also excluded if they reported a history of treatment-dependent diabetes, learning disabilities, current or past substance abuse, or significant head injury (i.e., loss of consciousness, >5 min). Those who demonstrated contraindications for MRI (e.g., claustrophobia) were also excluded from the present study. Dementia was evaluated using the Mini-Mental Status Examination (MMSE). Those scoring ≤ 24 on the MMSE were excluded from all analyses. All individuals were able to independently perform basic daily activities according to the Lawton and Brody Activities of Daily Living scale (Lawton and Brody 1969). A physician evaluated all imaging scans to exclude individuals with gross radiological abnormalities.

Informed consent was obtained from all individuals prior to participation. All individuals were financially compensated for participation, and the research protocol was approved by the local IRB.

Neuropsychological testing

The RBANS (Randolph 1998) measures performance in cognitive domains of immediate memory, visuospatial skills, language, attention, and delayed memory, and has been validated as a sensitive measure of cognition in nonclinical populations (Duff et al. 2003; Gontkovsky et al. 2004). Each cognitive domain consists of raw subtest scores that are converted into age-adjusted composite index scores. Raw subtest scores from each domain were the primary outcome measures used to evaluate cognitive function in this cohort.

Neuroimaging acquisition

MRI acquisition was completed using a head-only Magnetom Allegra 3 T MRI (Siemens Medical Solutions, Erlangen, Germany) at Washington University in St. Louis, MO. The Allegra has high-performance gradients (maximum strength of 40 mT/m in a 100- μ s rise time and slew rate of 400 T/m/s) to minimize scan times. Quality control was obtained through consistent use of scanner hardware, vendor

operating software, and acquisition protocols. Quality Assurance tests were performed daily to ensure data fidelity. Imaging parameters were designed to optimize whole-brain coverage and a high signal-to-noise ratio. Subject head movement was restrained using specialized foam pads and RF coil. An initial 15-s scout scan composed of three orthogonal planes was used to confirm head positioning. Whole-brain structural scans were obtained using a T2-weighted fluid-attenuated inversion-recovery (FLAIR) TSE sequence (Hajnal et al. 1992). FLAIR images were obtained in the following parameters: a transverse plane with TR=10,000 ms, TE=98 ms, TI=2,150 ms; field of view (FOV)=256 $\times$ 180 mm, matrix size=256 (frequency) $\times$ 164 (left–right phase encoding), 3.0 mm slice thickness, 39 slices acquired via 2D multislice mode with no slice gaps, $N_{av}=1$, voxel size=1.0 $\times$ 1.1 $\times$ 3.0 mm³, and 130 Hz pixel⁻¹ bandwidth. FLAIR was used to evaluate SH particularly in regions proximal to the ventricles. A detailed description of imaging acquisitions can be found in Paul et al. (2011). Standard shimming was applied.

SH quantification

SH was quantified in the FLAIR images of each subject using a semiautomated method in MANGO (Research Imaging Institute (RII), University of Texas Health Science Center—San Antonio (UTHSCSA)) following several standardized steps. First, nonbrain tissues for each image were removed using FSL BET (brain extraction tools; Oxford Centre for Functional MRI of the Brain (FMRIB)) tools run directly through MANGO's plugin interface. Second, the images were corrected for inhomogeneity artifacts using FSL BET method using the default parameters. Third, images underwent an automated thresh-holding process using the range of voxel intensities associated with SH. This process yielded a region of interest (ROI) label map that included SH voxels that were visually inspected by a trained rater who manually removed any spurious results and/or manually traced any SH missed by the automated thresholding method. It should be noted that the raters were blinded to any participant demographic information with high intra- and inter-rater reliability ($r=0.96$ and $r=0.94$ respectively). Manual edits were monitored in a prospective fashion for consistency throughout the study. Finally, total SH volume was quantified by summing the voxels across each slice and multiplying by a

correction factor derived from scan parameters to yield a volumetric measure in cubic millimeter.

There are several different methods that can be used to control for head size. The present study utilized a ratio approach to standardize SH volume to each participant, where total SH volume was divided by total intracranial volume derived from FreeSurfer v4.2.0 (Martinos Center, Harvard University, Boston, MA, USA). Descriptions of postprocessing techniques are included in a previous study of the same participants (Paul et al. 2011). The ratio approach corrects for head size on an individual basis (Sanfilipo et al. 2004) and has been utilized in previous studies of SH (Jefferson et al. 2007; Haley et al. 2007; Lane et al. 2011; Opherk et al. 2014). Previous research comparing this approach with other standardization techniques has revealed minimal to no differences in results, with no statistically superior standardization measure (Bigler et al. 2004; Tate et al. 2011).

Genotyping

Saliva samples were collected during the initial neuropsychological evaluation using the Oragene DNA collection kit (DNA Genotek, Ottawa, Canada) and shipped to Genetic Repositories Australia at Neuroscience Research Australia for processing. Genomic DNA was extracted from saliva samples using the Autopure LS nucleic acid purification system (QIAGEN, Hilden, Germany).

AGTR1 A1166C (rs5186) was determined using iPLEX Gold™ primer extension followed by mass spectrometry analysis on the Sequenom MassARRAY system (Sequenom, San Diego, CA) by the Australian Genome Research Facility (<http://www.agrf.org.au/>). Genotype frequencies in the sample ($n=49$) were AA=31, AC=16, and CC=2. The distribution did not differ from Hardy-Weinberg equilibrium.

Statistical analysis

Individuals were grouped according to a dominant statistical model (CC + CA ($n=18$) vs. AA ($n=31$) genotype) where those with at least one C allele were denoted “at risk.” Differences in demographic variables such as age, sex, ethnicity, and years of education were analyzed between groups using independent samples *t* tests and Chi-square analyses. Indication of hypertension (defined as systolic pressure ≥ 140 or diastolic pressure

≥ 90 averaged across three time points during the cognitive evaluation) was also examined between groups.

Using SPSS 21, a univariate analysis of variance (ANOVA) was completed to examine differences in SH volume between groups, with genetic status serving as the independent variable and SH volume as the dependent variable. Cognitive performance was analyzed using a separate multivariate analysis of variance (MANOVA) with genetic status serving as the independent variable and RBANS subtest scores serving as the dependent variables. RBANS indices were grouped in the same MANOVA to limit the probability of a type 1 error. Correlational analyses were also computed for SH volume and RBANS subtest scores.

Results

No significant differences were observed on demographic measures between groups with the exception of ethnicity ($p<0.05$; Table 1). Given this difference, a one-way ANOVA was computed to examine the impact of ethnicity on SH volume. Results revealed no significant differences in SH as a function of ethnicity and therefore ethnicity was not included as a covariate in the primary analyses. Hypertension did not differ significantly between genetic groups (Table 1).

Results from the ANOVA revealed significantly larger SH volume for individuals with at least one C allele compared with those with the AA genotype ($F(1, 47)=6.237$, $p<0.05$, partial $\eta^2=0.117$; Table 2). To determine if differences in SH volume were influenced by vascular factors commonly associated with SH, two separate regression analyses were computed among at risk individuals (C allele carriers) with PP (defined as average systolic pressure–average diastolic pressure) and BMI serving as the independent variables and SH serving as the dependent variable in each analysis. Neither PP nor BMI significantly contributed to SH volume among those with CC/CA genotypes (PP $F(1, 16)=0.309$, $p=0.586$; BMI $F(1, 16)=0.802$; $p=0.384$; Table 2).

Cognitive performance did not differ significantly between genetic groups (Wilks' $\Lambda=0.756$ $F(12, 36)=0.966^a$, $p=0.497$) and was not significantly associated with SH in this cohort with the exception of figure recall (Table 3).

Table 1 Demographic variables

Genotype	Age (M, SD)	Education ^a (M, SD)	Gender (M, F)	Race (<i>n</i>)		
				C	AA	H
CC/CA	64.50 (6.92)	15.89 (2.65)	(6,12)	17	0	1
AA	61.97 (7.75)	15.65 (2.60)	(10,21)	23	8	0

C Caucasian, AA African American, H Hispanic

^a Education refers to the highest level of completed education measured in years. Trade school credits and continuing education completed beyond a terminal degree were not included

Discussion

The present study examined the impact of the *AGTR1* A1166C polymorphism on SH and cognition among otherwise healthy older adults. Results revealed significantly greater SH volume among individuals with at least one C allele that was not influenced by PP or BMI in this sample. By contrast, genetic status was not significantly associated with cognitive performance in any domain. These results suggest that the C1166 variant of *AGTR1* may represent a biomarker of risk for decreased brain integrity independent of vascular phenotypes.

Previous studies have demonstrated similar relationships between A1166C and white matter integrity in older populations. Taylor et al. (2009) reported significant increases in white matter lesion volume over a 2-year period in older adult men with the C1166 variant. A similar study from this group reported a modest association between the C1166 variant and enhanced lesion severity spanning multiple white matter tracts among nondemented elders both with and without depression

(Taylor et al. 2013). The results of the present study extend those of Taylor et al. (2009, 2013) by demonstrating enhanced SH volume in a sample of clinically healthy (e.g., no evidence of clinical depression or dementia) older men and women. Furthermore, no studies have examined the functional relationship between A1166C, SH, and cognition in a healthy population. In contrast to our hypotheses, neither genetic status nor SH volume significantly influenced cognitive performance in domains of memory, attention, language, or visuospatial abilities.

The absence of consistent association between cognitive performance and genetic status or SH volume in this study may have resulted from the selection of the neuropsychological battery. The RBANS does not contain a measure of executive function, which is often impacted by subcortical ischemic vascular disease (Putzke et al. 1998; Gunning-Dixon and Raz 2000; Saxby et al. 2003; Cook et al. 2004; Kramer et al.

Table 2 Vascular factors by genetic status

Genotype	AA	CC/CA
Hypertension ^a (%)	12.9	27.8
Pulse pressure ^b	50.28±9.93	46.85±11.17
BMI	25.53±3.49	24.51±4.38
SH volume (mm ³)	2,539.77±904.04*	3,486.67±1,756.06*

**p*<0.05

^a Blood pressure was obtained at three time points during the initial neuropsychological evaluation and averaged separately for systolic and diastolic pressure. Using these values, individuals were considered hypertensive based on a mean systolic pressure ≥140 or a mean diastolic pressure ≥90

^b Pulse pressure was determined by subtracting total diastolic pressure from total systolic pressure

Table 3 Relationships between genetic status, SH, and cognitive performance

RBANS subtest	CC/CA (M, SD)	AA (M, SD)	SH (<i>r</i>)
List learning	27.89 (2.56)	28.58 (4.54)	−0.218
Story memory	18.89 (3.38)	17.68 (3.54)	−0.152
Figure copy	17.11 (1.68)	16.03 (2.47)	0.074
Line orientation	18.44 (1.89)	17.42 (2.78)	0.135
Picture naming	9.83 (0.38)	9.71 (0.59)	0.030
Semantic fluency	22.11 (4.66)	22.87 (4.27)	−0.126
Digit span	12.17 (1.72)	11.42 (2.31)	−0.077
Coding	48.33 (8.38)	47.61 (5.57)	−0.230
List recognition	18.83 (1.79)	18.87 (1.38)	−0.110
List recall	5.83 (1.92)	5.68 (2.44)	−0.093
Figure recall	12.94 (3.21)	12.97 (2.96)	0.074*
Story recall	9.89 (1.37)	9.29 (1.97)	−0.077

**p*<0.001

2007; Paul et al. 2005; Haley et al. 2007). Although neuropsychological status has not been examined in the context of A1166C, it is possible that group differences would be evident on cognitive measures inclusive of executive function. In addition, SH may not have reached a threshold to influence cognition in this sample of well-educated, generally healthy individuals. There is currently no standard threshold to determine the degree of SH necessary to produce cognitive changes, and therefore the relevance of SH in healthy populations may be limited to “risk” in the absence of cognitive decline. This is especially true in samples with high cognitive reserve and may have contributed to the findings in the present study (mean level of education $\approx$ 16 years). Similarly, the age distribution of participants ($M_{\text{age}} \approx$ 63 years) may have been too young to observe genetic relationships to cognitive effects, as previous studies have indicated that the phenotypic expression of chronic vascular disease is typically evident in older cohorts ($\geq$ 80 years) (Gorelick et al. 2011).

The physiological mechanism by which A1166C influences SH is currently unclear. Several studies have postulated that A1166C is merely a marker of cardiovascular risk, as it is located in a noncoding 3'-untranslated region (UTR) of the *AGTR1* gene (Ceolotto et al. 2010). However, the A1166C polymorphism is located in a *cis*-regulatory site that influences posttranscriptional protein expression through complementary base pairing with microRNA (miRNA; Sethupathy et al. 2007). Interestingly, only the A1166 variant is recognized by a specific miRNA known as miR-155, causing downregulation of receptor expression (Sethupathy et al. 2007; Ceolotto et al. 2010). Recent evidence suggests that the interaction between miRNA and SNP expression may be due to the combination of modified miRNA sequence and 3'UTR secondary structure disruption, thus altering accessibility of the recognition site and implicating a potential role for SNPs in linkage disequilibrium with A1166C (Haas et al. 2012). It is possible that these interdependent anomalies lead to abrogated receptor downregulation in C1166 carriers, resulting in chronic elevations in AT_1 expression and progressive vascular complications characteristic of this polymorphism.

A few limitations are present in this study. First, the cell sizes of each group were limited and may have reduced power to detect significant group differences in cognitive performance. The relatively young age range of this sample may have also influenced the lack

of significant cognitive effects in this study. Second, although validated as a sensitive measure in nonclinical populations (Duff et al. 2003, 2006; Gontkovsky et al. 2004), the RBANS may not provide optimal sensitivity in healthy populations with high cognitive reserve, particularly compared with more demanding neuropsychological batteries, including an executive component. Finally, it is worth noting that our measure of SH was not region-specific, and therefore we cannot determine if the cognitive domains of interest reflect lesion location. Future studies employing more advanced techniques of white matter lesion fiber tractography may provide useful information regarding the functional correlates of SH and genetic status on domain-specific cognitive performance.

In summary, the present study provides seminal evidence that the *AGTR1* A1166C polymorphism is significantly associated with decreased white matter integrity in a sample of healthy older individuals void of major cardiovascular conditions. Cognitive performance was not significantly influenced by genetic status or current degree of SH, though it is unclear if enhanced SH in C1166 carriers represents a prodromal marker for subsequent cognitive impairment. Longitudinal studies are needed to evaluate the age-related influence of A1166C on SH progression, and if an observed increase in SH contributes to decreased cognitive performance that is accelerated by genetic status. Further research is also needed to clarify the physiological manifestations of A1166C in the context of normal aging. Understanding these mechanisms will allow for the initiation and development of preventative techniques and behavioral intervention strategies that reduce negative outcomes associated with A1166C among otherwise healthy individuals.

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Conflict of interest There are no actual or potential conflicts of interest for any of the authors on this manuscript.

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