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Brain tissue volumes by APOE genotype and leisure activity - The AGES-Reykjavik Study

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Abstract

This study investigates the association of the *APOE* $\epsilon 4$ allele and leisure activity with brain tissue volumes, including white matter hyperintensities (WMH), in a population-based cohort of 4,303 non-demented individuals, aged 66–96 years. *APOE* $\epsilon 4$ carriers were shown to have greater WMH and cerebrospinal fluid (CSF) volumes than non-carriers but smaller gray matter (GM) volumes. There was no significant difference in white matter (WM) and total brain parenchymal (TBP) volumes between *APOE* $\epsilon 4$ carriers and non-carriers. Tests for linear trend showed that individuals with the lowest leisure activity levels had greater WMH- and CSF volumes, smaller TBP-, WM- and GM volumes than those with the highest levels of participation. The significant positive trend of the leisure activity with the brain tissue volumes was observed in the *APOE* $\epsilon 4$ carriers as well as in non-carriers after adjustment for demographic and health factors. These cross-sectional data suggest leisure activity is associated with tissue volumes in the brain irrespective of the *APOE* $\epsilon 4$ risk allele status.

Keywords

APOE; Leisure activities; brain volumes; MRI; AGES-Reykjavik study

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Disclosure statement

There are no actual or potential conflicts of interest.

All participants signed an informed consent form, and the AGES-Reykjavik Study was approved by the Icelandic National Bioethics Committee (VSN: 00-063), the Data Protection Authority and the institutional review board of the National Institute on Aging.

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1. Introduction

The brain undergoes structural changes with aging and begins decreasing in volume early in adulthood (Fotenos et al., 2005). The volume loss seems to be accelerated in those with cognitive impairment (den Heijer et al., 2010; Driscoll et al., 2009), and demented individuals have smaller brain volumes than clinically normal persons (Ikram et al., 2008). Brain structure has also been associated with physical function in the form of gait speed, where brain atrophy and white matter hyperintensity (WMH) was associated with lower speed (Rosano et al., 2010). WMHs in the brain increase with age (DeCarli et al., 2005) and have been implicated in cognitive decline and dementia (DeBette and Markus, 2010).

The Apolipoprotein E (*APOE*) $\epsilon 4$ allele has been associated with structural changes in the brains of patients with Alzheimer's disease (Agosta et al., 2009; Filippini et al., 2009b; Schuff et al., 2009). However, studies on the association between *APOE* genotype and brain structure in the general population have provided inconsistent results. Most studies on healthy individuals have not been able to show a statistically significant association of the *APOE* genotype with whole brain volumes (Filippini et al., 2009a; Honea et al., 2009; Vemuri et al., 2010) or regional brain volume (Adamson et al., 2008; Cherbuin et al., 2008; Filippini et al., 2010). In contrast differences in total brain volumes between *APOE* $\epsilon 4$ carriers and non-carriers have been shown in healthy adults (Carmelli et al., 2000; DeCarli et al., 1999) and Chen et al. (2007) found the *APOE* $\epsilon 4$ allele to have a dose-dependent effect on whole brain volume in individuals with normal cognition. The association between *APOE* genotype and white matter lesions is also controversial. Nevertheless, a recent longitudinal study has demonstrated a greater WMH load in $\epsilon 4$ homozygotes in a large population-based cohort (Godin et al., 2009).

Participation in leisure activity has been associated with reduced rates of hippocampal atrophy (Valenzuela et al., 2008), but Foubert-Samier et al. (2010) did not find a relationship to whole brain volume. It has been suggested that leisure activities can reduce the risk of developing dementia (Akbaraly et al., 2009; Carlson et al., 2008; Verghese et al., 2003), and Saczynski et al. (2008) showed that high leisure activity participation is associated with better cognitive performance in an aging cohort. Although leisure activity has been shown to influence cognitive health in old age, the effects on brain structure are poorly understood.

In this study, the Age Gene/Environment Susceptibility Reykjavik Study (AGES-Reykjavik), we investigated the influence of *APOE* $\epsilon 4$ allele on brain volumes and WMHs in a population-based cohort. We also tested whether leisure activity engagement modified the *APOE* effect on brain volume. We hypothesized that smaller brain volumes and greater WMH are associated with the *APOE* $\epsilon 4$ allele and lower levels of leisure activity participation.

2. Methods

Data are from the AGES-Reykjavik Study. The Reykjavik Study cohort originally comprised a random sample of men and women born in 1907–1935 and living in Reykjavik in 1967 (Jonsdottir et al., 1998). Between 2002 and 2006, the AGES-Reykjavik Study re-examined 5,764 survivors from the original Reykjavik Study cohort. AGES-Reykjavik is an

epidemiological study focusing on four biological systems: vascular, neurocognitive, musculoskeletal and body composition; it was initiated with the aim of investigating the contribution of genetic and environmental risk factors and their interactions to disorders of importance in old age. All participants signed an informed consent form, and the AGES-Reykjavik Study was approved by the Icelandic National Bioethics Committee (VSN: 00-063), the Data Protection Authority and the institutional review board of the National Institute on Aging. A more detailed description of the AGES-Reykjavik Study and collection of data can be found elsewhere (Harris et al., 2007). Of the total AGES-Reykjavik Study cohort, 5,232 participants had complete data before magnetic resonance imaging (MRI) of the brain.

2.1. Apolipoprotein E genotype

APOE genotyping was carried out using the MADGE (microplate array diagonal gel electrophoresis) system (Gudnason et al., 1993). Persons with $\epsilon 2/4$, $\epsilon 3/4$ and $\epsilon 4/4$ genotype were grouped together as $\epsilon 4$ carriers ($\epsilon 4+$), and persons with genotypes $\epsilon 2/2$, $\epsilon 2/3$ and $\epsilon 3/3$ were grouped together as non-carriers ($\epsilon 4-$).

2.2. Magnetic resonance imaging

MR images including T1-, PD-, T2-weighted and FLAIR images were acquired on a 1.5T system in the AGES-Reykjavik Study. Brain tissue volumes, including gray matter (GM), white matter (WM), cerebral spinal fluid (CSF) and white matter hyperintensities (WMH), were generated separately, using the multi-spectral MR images and a high-throughput automatic image analysis pipeline, which is based on the MNI pipeline and optimized for use in the AGES-Reykjavik Study (AGES-RS/MNI pipeline) (Zijdenbos et al., 2002). The key processing stages were as follows: stereotaxic registration was achieved following signal non-uniformity correction by an affine transformation of the T1-weighted images to the ICBM152 template. Inter-sequence registration was performed by registering images from the individual (T2/PD, FLAIR) sequences to the T1-weighted images in order to accurately align all image volumes acquired during an acquisition session. Linear signal intensity normalization was then applied to correct for signal intensity variations across images in the different sequences. Finally, tissue classification was achieved with an artificial neural network classifier. The absolute volumes of the four tissue types were subsequently calculated and converted to native space volumes using the scale factor obtained from the stereotaxic registration transformation. Total brain parenchymal (TBP) volume was computed as the sum of GM-, WM-, and WMH volumes. The intracranial (IC) volume was computed as the sum of TBP- and CSF volumes.

2.3. Leisure activity

The leisure activities, ascertained by questionnaire, were doing crossword puzzles; playing board or card games; using the computer; writing letters or poems; doing artwork, carpentry or sewing; attending a performance or movie; attending religious services or meetings; attending a class, lecture or public meeting; and participating in community, church or social clubs. The frequency of participation was reported for the past 12 months and recoded to the median number of days per month for each category, i.e., 30 points for daily participation, 14 points for participation at least once a week, 1.5 points for participation at least once a

month, 0.5 points for participation less than once a month, and 0 points for reports of never participating in an activity. Summary scores were created by adding all responses for each individual, and the sample was then categorized into quartiles (1 = lowest leisure activity participation, 4 = highest) according to leisure activity levels (Saczynski et al., 2008).

2.4. Covariates

Analyses were adjusted for demographic and health factors associated with brain volume or white matter lesions. The demographic factors included were age, gender, BMI (weight (kg)/height² (m²)) and education (primary, secondary, college and university). The following health factors were used as covariates: coronary heart disease (CHD), depression, hypertension, mild cognitive impairment (MCI), smoking status and type 2 diabetes. The definition of prevalent coronary heart disease was based on adjudicated hospital records. The presence of depression was assessed using the MINI International Neuropsychiatric Interview (Sheehan et al., 1998). Participants were eligible for the MINI Interview if they had a score ≥ 6 on the 15-item Geriatric Depression Scale (GDS) (Valdimarsdóttir et al., 2000), or if they reported anxiety, a doctor's diagnosis of depression or use of antidepressant medications. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or self-reported physician's diagnosis of hypertension or use of antihypertensive medication. MCI and dementia was diagnosed by a team of specialists, including a neurologist, neuroradiologist and geriatrician, using results from cognitive testing, a neurology exam and proxy interview. Smoking status was assessed by questionnaire and assigned as ever vs. never smoker. Diabetes was defined as a fasting blood glucose level ≥ 7.0 mmol/l, the use of diabetic medication or self-reported physician's diagnosis of diabetes.

2.5. Analytical sample

Of the 5,232 participants, 739 did not have MRI data; in addition, 191 individuals were diagnosed with dementia and excluded, resulting in an analytic group of 4,303 individuals. Dementia was ascertained by use of a three-step process that has been described elsewhere (Harris et al., 2007). Compared with the analytical sample, the excluded group was significantly older (78.1 vs. 76.1 years, $p < 0.01$), included fewer women (51% vs. 59%, $p = 0.001$), had higher BMI (27.3 vs. 27.0 kg/m², age-adjusted $p = 0.001$), had higher prevalence of coronary heart disease (19.8% vs. 14.3%, age-adjusted $p < 0.0001$), hypertension (84.0% vs. 80.3%, age-adjusted $p < 0.0001$), included a higher percentage of ever smokers (60.4% vs. 57.0%, age-adjusted $p = 0.005$), had higher prevalence of diabetes (15.7% vs. 11.0%, age-adjusted $p < 0.0001$) and *APOE* $\epsilon 4$ carriers (33.3% vs. 27.4%, $p = 0.0003$). The education level along with prevalence of MCI and depression did not differ between the two groups when adjusted for age.

2.6. Data analysis

All brain volumes were corrected for IC volume, and WMHs were log transformed for analysis. The association of brain volume with *APOE* genotype and leisure activity participation was assessed using a general linear model for univariate and multivariate response. Three models were tested; the first model tested the relationship between *APOE* genotype and brain volumes, adjusting for age and gender. In the second model, the leisure

quartile scores were added in order to establish the association between leisure activity and brain volumes. The interaction of *APOE* genotype and leisure activity was tested in order to investigate whether the association of leisure to brain volume differed between carriers of the $\epsilon 4$ allele and non-carriers. In the third model BMI, education, coronary heart disease, depression, hypertension, MCI, smoking status and type 2 diabetes were added. Finally, the volumes of the four brain tissue types were analyzed together in a multivariate regression model, using the same multiple variable adjustment as in the third model above, to compare profiles of change in brain tissue volumes with respect to quartiles of leisure activity. The multivariate analysis test criteria were based on Wilk's lambda and the accompanying F statistic. All statistical calculations were performed using SAS Enterprise Guide 4.3.

3. Results

3.1. Participant characteristics

The general characteristics of the study population are provided in Table 1. The carriers of the *APOE* $\epsilon 4$ risk allele are significantly younger, have higher cholesterol levels and lower BMI than non-carriers.

3.2. *APOE* genotype

After adjusting for age and gender, there is a significant difference in brain tissue volumes between *APOE* genotypes (Table 2). Compared to non-carriers, carriers of the $\epsilon 4$ risk allele have smaller GM- (0.49 %, $p=0.03$), larger CSF- (0.89 %, $p=0.03$) and larger WMH volume (6.9 %, $p=0.01$) than $\epsilon 4$ non-carriers. There is no statistically significant difference in WM- ($p=0.22$) and TBP volume ($p=0.08$) between genotypes.

3.3. Leisure

There is a significant difference in mean brain volumes between groups with varying levels of leisure activity (Table 3). The association between larger brain volumes and a higher level of participation in leisure activities remained strong after correcting for potential confounding variables, including age, gender, BMI, education, prevalent CHD, depression, hypertension, MCI, smoking status, type 2 diabetes and *APOE* genotype. Compared with the group in the highest leisure activity quartile, the groups in lower activity quartiles have significantly smaller TBP-, GM- and WM volume, and greater CSF- and WMH volume. The differences in TBP volume relative to the fourth leisure quartile are 0.30%, 0.38% and 1.15%, respectively. For GM the difference in volume is 0.60%, 0.90% and 1.67%, respectively for leisure activity groups, and for WM the volume reduction is 0.10%, 0.00% and 1.20%, respectively. The increase in CSF volume was 0.77%, 0.80% and 2.79 % and for WMH volume 3.23%, 8.45 and 12.04%, respectively. Tests for linear trend were significant for all volumes. In the multivariate analysis the associations between each brain volume type and leisure were in agreement with the univariate results. The association was strongest with GM, then CSF, WM and WMH, in that order. The trend in both GM and WM was positive and parallel with respect to quartiles of increasing leisure activity, while the trend in both CSF and WMH was negative and parallel. With respect to quartiles of leisure, divergence between the average of GM and WM versus the average of CSF and WMH was statistically

significant ($p < 0.0001$). Analyses were conducted after excluding participants with MCI, and linear trend remained significant for all volumes (data not shown).

3.4. APOE and leisure interaction

The analysis of the relationship between brain volumes and leisure activity was repeated according to *APOE* genotype, and the results are shown in Figure 1. The trend of brain volume differences between levels of leisure activity participation is the same in both *APOE* groups. Although carriers of the $\epsilon 4$ allele have worse brain volume profiles than non-carriers (Table 2), the difference in volume between leisure activity quartiles is not statistically different between *APOE* groups. Tests for interaction between leisure and *APOE* genotype were not significant for any volume (data not shown).

4. Discussion

These results show that *APOE* $\epsilon 4$ carriers have worse brain volume profiles than non-carriers, independent of age and gender, suggesting a positive association of leisure activity with tissue volumes in the brain regardless of the *APOE* $\epsilon 4$ risk allele status.

4.1. APOE

Relationships have been established between *APOE* genotypes and brain volumes, where correlations with cognitive function are shown (Honea et al., 2009; Vemuri et al., 2010). Our results are in agreement with recent studies (Agosta et al., 2009; Honea et al., 2009; Liu et al., 2010; Schuff et al., 2009; Vemuri et al., 2010) showing that *APOE* $\epsilon 4$ risk allele carriers have worse brain profiles than non-carriers. Most studies focus on smaller regions of the brain, and there is limited and inconsistent documentation on the effect of *APOE* on whole brain volume (Carmelli et al., 2000; Yasuda et al., 1998). The small cohort size in these studies can possibly explain the lack of association between *APOE* genotypes and whole brain volume.

4.2. Leisure and brain volumes

Despite the consistency of epidemiological evidence linking leisure activity with dementia and cognitive function (Akbaraly et al., 2009; Niti et al., 2008; Wilson et al., 2007), the underlying mechanisms are not clear. Wilson and colleagues (2007) studied the neuropathological basis of the connection between dementia and levels of cognitive activity participation and found no connection between dementia-specific brain pathology and levels of activity engagement. Although studies on healthy elderly people have shown that there is not a relationship between leisure and whole brain volume (Foubert-Samier et al., 2010; Valenzuela et al., 2008), a recent study focusing on this connection found an association between high levels of mental activity and reduced rate of hippocampal atrophy (Valenzuela et al., 2008). Other studies have shown activity-related structural differences in the brain in relation to learning (Draganski and May, 2008; Filippi et al., 2010). These studies had small cohort sizes and could detect small regional changes in brain volume. The results presented here with the large AGES-Reykjavik cohort show an association of increased leisure activity with greater GM- and WM volume and decreased WMHs and atrophy of the brain. The connection between WMH and cognitive function has been established in our cohort

(Saczynski et al., 2008) and a positive influence of leisure activity demonstrated. The effect of leisure activity on other brain volumes can possibly play a role in the effect on cognitive function as well. Furthermore, the connection between levels of leisure participation and cognition may be explained by different brain volumes.

The relationship between *APOE* genotype and pattern of brain activation in healthy individuals observed using functional brain imaging techniques (Filippini et al., 2009a; Lind et al., 2006; Wishart et al., 2006) and positron emission tomography (Thambisetty et al., 2010) verifies *APOE* involvement in normal brain function. To our knowledge, no previous study has reported the influence of the *APOE* genotype and leisure activity on brain volumes in such a large population-based sample. Despite the *APOE* risk allele carriers having worse brain profiles than non-carriers, leisure activity has the same beneficial effect in both groups. A study on older Chinese adults shows that individuals carrying the $\epsilon 4$ allele are more susceptible to the effects of leisure activity participation in preventing dementia (Niti et al., 2008). In our study leisure activity has a similar effect on brain volume regardless of *APOE* genotype status. We cannot exclude the difference in developing dementia in our cohort as shown in the Chinese study, but this would need further investigation. However, the frequency of *APOE* $\epsilon 4$ carriers is much lower in this Chinese study than in the Icelandic population (18% vs. 27%), and the overall study cohort was smaller (1,635 vs. 4,303 individuals), which could partly explain the difference.

In the cohort analyzed here, the mean annual decline in total brain volume is 0.39% according to model 3, and other studies have shown similar change (DeCarli et al., 2005; Fotenos et al., 2005). For specific tissue types of the brain, the annual decline is 0.47% for GM and 0.52% for WM, and the annual increase in CSF and WMH volumes is 1.04% and 4.77%, respectively. Compared to these values, individuals with the highest level of leisure activity had larger brain tissue volumes and less WMHs, equivalent to approximately 3 years of brain aging, compared with those with the lowest level of leisure activity.

This study has a number of strengths, including its large population-based cohort; comprehensive characterization of potential confounding factors, precise and stringently quality-controlled MRI, along with an automated brain segmentation method giving very accurate volumetric measurements.

4.3. Limitations

These findings should be interpreted with limitations in mind due to the cross-sectional nature of the study and must be replicated in longitudinal studies. Excluded individuals due to MRI contraindications limited the group, and the analytic sample of the cohort represents a healthier population. We cannot rule out the possibility that the findings are due to epiphenomena. Participation in leisure activities may be related to a certain lifestyle that is known to affect the brain, like a lifestyle of reduced stress, social integration and physical exercise (McEwen and Gianaros, 2010).

The function and anatomy of the brain is more complex than can be measured at whole brain level. Cognition is presumably dependent on different neuronal activity in different structures of the brain. The compensatory mechanisms for brain pathology at neuronal level

can change the reliability of brain volume values to predict cognitive function, and there are different thresholds for neuronal damage between individuals (Stern, 2009). However, brain volumes can perhaps give some idea of brain function and be an indicator of age-related atrophy of the brain. More detailed information in regions of interest, such as the hippocampus and amygdala, could give further understanding of the changes in brain volume found here.

The presence of preclinical dementia might explain the reduced participation in leisure activities and the difference in brain profiles as dementia is associated with lower brain volumes and more WMH (Aggarwal et al., 2010; den Heijer et al., 2010; Driscoll et al., 2009; Fotenos et al., 2005). In our analysis we corrected for MCI, and the effect of leisure activity was still significant. Exclusion of individuals with MCI from the analysis did not change the outcome. However, due to our three-stage process of clinical determination, we cannot discern whether we have managed to detect all preclinical cases.

4.4. Conclusion

Carriers of the *APOE* $\epsilon 4$ risk allele have worse brain profiles than non-carriers. Participating in leisure activity is associated with brain tissue volume loss and WMH load and affects age-related decline and pathology of the brain. The protective effect of leisure is not attenuated in *APOE* $\epsilon 4$ carriers. We are unable to establish a causal relation due to the cross-sectional nature of the study. The results presented here call for further investigation and warrant focused interventions of increased leisure activity in late life to prevent cognitive decline and dementia and hopefully increase quality of life.

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Figure 1.

Least squares mean brain volume for each leisure activity quartile according to *APOE* $\epsilon 4+$ and $\epsilon 4-$ groups, adjusted for age, gender, BMI, education, prevalent CHD, depression, hypertension, MCI, smoking status and type 2 diabetes. Leisure quartile 4 represents the highest level of leisure activity participation and quartile 1 the lowest. Brain gray matter (GM), white matter (WM), cerebral spinal fluid (CSF) and white matter hyperintensities (WMH) are presented as percentages of intracranial volume (ICV). Error bars represent 95% confidence intervals.

Table 1

General characteristics of the cohort

	<i>APOE</i> $\epsilon\epsilon$ - n=3125	<i>APOE</i> $\epsilon\epsilon$ + n=1178	p-value
Age, mean (SD)	76.3 (5.4)	75.7 (5.3)	**
Females, % (N)	59 (1845)	57.1 (673)	ns
Cholesterol, mM, mean (SD)	5.6 (1.1)	5.8 (1.2)	$\dagger$
BMI, kg/m ² , mean (SD)	27.2 (4.4)	26.5 (4.2)	$\dagger$
Primary education, % (N)	23.7 (741)	20.5 (241)	ns
CHD, % (N)	14.1 (440)	14.9 (176)	ns
Depression, % (N)	4.3 (133)	4.5 (53)	ns
Hypertension, % (N)	80.3 (2509)	80.1 (944)	ns
MCI, % (N)	9.6 (300)	9.5 (112)	ns
Ever smoker, % (N)	57.2 (1787)	56.6 (667)	ns
Type 2 diabetes, % (N)	11.6 (361)	9.6 (113)	ns

BMI: Body mass index; CHD: Coronary heart disease; MCI: Mild cognitive impairment.

**
 $P < 0.01$; $\dagger P < 0.0001$; ns, nonsignificant

Table 2
Differences in brain volume between carriers and non-carriers of the *APOE ε4* genotype

Brain volumes	<i>APOE ε4</i> -			<i>APOE ε4</i> +			p-value
	LSM	95% CI		LSM	95% CI	% difference	
GM	44.92	44.82 to 45.02		44.70	44.54 to 44.87	0.49	0.03
WM	25.61	25.55 to 25.67		25.54	25.44 to 25.64	0.29	0.22
CSF	27.69	27.57 to 27.81		27.94	27.75 to 28.14	0.89	0.03
WMH	0.886	0.860 to 0.913		0.952	0.907 to 1.000	6.94	0.01
TBP	71.92	71.80 to 72.04		71.72	71.53 to 71.91	0.28	0.08

Least squares mean (LSM) brain gray matter (GM), white matter (WM), cerebral spinal fluid (CSF), white matter hyperintensities (WMH) and total brain parenchymal (TBP) volume as percentages of intracranial volume, assessed using a general linear model adjusted for age and gender.

CI: confidence interval.

Table 3

Mean percent difference in brain volume according to leisure activity quartiles

Brain volume	Leisure quartile							
	1		2		3		4	
	% difference	95% CI	% difference	95% CI	% difference	95% CI		Test for trend
GM	-1.67	-2.38 to -0.96	-0.90	-1.59 to -0.20	-0.60	-1.30 to 0.10	Referent	<.0001
WM	-1.20	-1.95 to -0.44	0.00	-0.74 to 0.75	-0.10	-0.85 to 0.65	Referent	0.0002
CSF	2.79	1.41 to 4.19	0.80	-0.53 to 2.14	0.77	-0.56 to 2.11	Referent	<.0001
WMH	12.0	1.74 to 23.4	8.45	-1.31 to 19.2	6.36	-3.23 to 16.9	Referent	0.0025
TBP	-1.15	-1.67 to -0.63	-0.38	-0.89 to 0.14	-0.30	-0.81 to 0.22	Referent	<.0001

Difference in least squares mean brain gray matter (GM), white matter (WM), cerebral spinal fluid (CSF), white matter hyperintensities (WMH) and total brain parenchymal (TBP) is relative to the fourth leisure quartile. Quartile 4 represents the highest level of leisure activity participation and quartile 1 the lowest. Model 3: adjusted for age, gender, BMI, education, prevalent CHD, depression, hypertension, MCI, smoking status, type 2 diabetes and *APOE* genotype. CI: confidence interval.