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Interactive Effects of apoE4 Genotype and Cerebrovascular Risk on Neuropsychological Performance and Structural Brain Changes

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Abstract

Objective—To determine if the presence of the apoE4 allele, a known risk factor for Alzheimer's disease, interacts with cerebrovascular risk factors to produce a disproportionate impairment in neuropsychological performance and alterations in structural morphometry as measured by magnetic resonance imaging.

Methods—1,995 participants from the community based Framingham Offspring Cohort participants (mean age 61; 1,063 women) underwent neuropsychological testing and structural magnetic resonance imaging in 1999-2002.

Multivariate linear regression was used to estimate the relationships between Framingham Stroke Risk Profile scores, neuropsychological variables and magnetic resonance imaging measures; interaction terms were included to examine modification of these relationships by the presence of the apoE4 allele. All analyses were cross sectional.

Results—We found significant interactions between the presence of the apoE4 allele and the top sex-specific quartile of the Stroke Risk Profile and their effects on verbal memory ($p < 0.001$), verbal organization ($p < 0.001$), non-verbal memory ($p = 0.015$), as well as set shifting and complex attention ($p = 0.005$). Systolic blood pressure was the only individual risk factor significantly linked to these cognitive measures. With the exception of lateral ventricular volume, there were no significant

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interactions between presence of apoE4, the top sex-specific quartile of the Stroke Risk Profile and any of the magnetic resonance imaging variables.

Conclusion—The apoE4 allele exacerbates the effects of cerebrovascular risk factors on neuropsychological function. This relationship appears to be driven by systolic blood pressure, suggesting that treatment of high systolic blood pressure could potentially reduce risk of cognitive impairment among those already at increased risk for Alzheimer's disease.

INTRODUCTION

Emerging literature indicates that cerebrovascular disease (CVD) risk factors are associated with neuropsychological (NP) deficits. Factors most strongly correlated with cognitive decline among the elderly include diabetes mellitus (DM), [1-7] obesity [8-11] and hypertension (HTN) [8,9,12-14]. Additionally, research demonstrates that careful regulation and treatment of CVD risk factors is associated with improved neuropsychological performance [12,15-18].

Previous research from the Framingham Heart Study (FHS) has demonstrated a correlation between stroke risk (as reflected in Framingham Stroke Risk Profile [FSRP] scores) and both cognition and morphology. Elias et. al. (2004) [19] found that among participants who were free of dementia and stroke at the time of examination, higher stroke risk was associated with reduced neuropsychological performance in multiple cognitive domains including concentration, abstract reasoning, visual spatial memory, and visual organization. Other findings from the FHS demonstrated relationships between stroke risk factors and morphology, including a strong positive association with white matter hyperintensity [20], as well as an inverse relationship between total cerebral brain volume and FSRP scores [21]. Further, other studies examined the impact on NP performance of various risk factors such as the e4 allele of the gene coding apolipoprotein E (apoE4), HTN, DM and obesity independently [8,22-25] as well as the combined impact of different factors (e.g. obesity and HTN) [9,12,22-24].

In addition to research demonstrating cognitive and morphological implications of cerebrovascular risk factors, previous research strongly suggests that apoE4 significantly impacts the rate of volume loss over time in the hippocampus and is a major risk factor for Alzheimer's disease (AD) [25-28]. This loss of hippocampal volume is associated with memory decline [29] and is in and of itself a possible early marker of incipient dementia in older adults [30].

However, significant questions remain regarding the dynamics and interrelationships between CVD risk factors and genetic markers known to increase the risk for progressive dementing disorders. For example, consider that while extensive research has demonstrated a relationship between apoE4 and the development of AD [27,31-34], the development of AD is attributable to more than simply the presence of apoE4 [35]. Additional research indicates a synergistic relationship between apoE4 and CVD risk factors. For example, Zlokovic (1996) reported that neurovascular dysfunction and the subsequent attenuation of the blood brain barrier's ability to regulate the Amyloid B peptide may exacerbate the effects of apoE4 [36,37]. Also, recent research suggests that the presence of apoE4 increases fasting glucose levels, which may heighten the risk for neurovascular and cognitive decline [38]. Further, related studies [39, 40] have identified a link between atherosclerosis and apoE4. These investigations suggest that microvascular disease (MVD) not only exacerbates the effects of apoE4, but apoE4 itself may also heighten the risk for developing MVD. Additional research suggests that the progression of vascular deterioration, may, in turn, be influenced by the presence of cerebral amyloid angiopathy (CAA) [8]. Finally, research also suggests that a rare apoE genotype (apoE2/2) may serve as a protective factor against Alzheimer's-related cognitive decline [35,41].

The findings of the studies reviewed above underscore the importance of investigating not only the independent influence of CVD and genetic risk factors, but also the dynamics of the interaction between those factors that may produce differential risk for cognitive decline and structural brain alterations. The current study investigates the degree to which the relationship between CVD risk factors and neuropsychological performance as well as volumetric measures of brain structure is modified by the presence of the apoE4 allele.

METHODS

The Framingham Offspring Cohort is comprised of community dwelling participants and was enrolled in 1971 (n = 5,124). Participants from the Offspring Cohort have returned for health examinations every four to eight years through the present. Attendees of the 7th examination (1998-2001), were invited to undergo magnetic resonance imaging (MRI) of the brain and neuropsychological assessment and were eligible for this study if they were free of dementia, clinical stroke and other neurological disease that could alter MRI measures or cognitive performance, and had undergone apoE genotyping and both the MRI and NP assessments. These 1,995 (mean age 61; 1,063 women) participants comprise the sample for this cross sectional study. Our institutional review board approved the study protocol and all participants provided written informed consent.

Participants were stratified by apoE status, with apoE2/4's excluded in the interest of eliminating from analyses those participants carrying both protective (i.e. apoE2) [35,41] and risk-enhancing (i.e. apoE4) [27,31-33] genetic markers.

The MRI variables, which have previously been described [42], were as follows: total brain volume, white matter hyperintensities, frontal brain volume, temporal horn volume, lateral ventricular volume; each was expressed as a percentage of total cranial volume and log-transformed as necessary to normalized its distribution. Hippocampal volume was measured in a subset of 907 participants using previously reported methods [42].

The cognitive domains included: Long term verbal memory (as measured by Wechsler Memory Scale (WMS) Logical Memory-delayed recall [D.R.]); verbal organization (as measured by WMS Paired Associates-D.R.); nonverbal memory (as measured by WMS Visual Reproductions-D.R.); verbal concept formation and abstraction (as measured by WAIS-R Similarities); and nonverbal organizational ability, (as measured by the Hooper Visual Organization Test); processing speed (as measured by Trail Making Test-A); and corrected set shifting and complex attention (as measured by Trail Making Test-B) [43] Note, scores for Trails-B were calculated by subtracting Trails-A times scores from Trails-B time scores (Trails-B minus Trails-A). Each neuropsychological measure was log-transformed as necessary, adjusted for age and education within gender, and then standardized within gender. The neuropsychological measures listed above were administered by trained psychometricians as part of a standardized 40 minute battery. The Framingham Stroke Risk Profile (FSRP) score is a validated, widely-used composite measure of vascular risk factors that predicts the 10-year probability of a stroke [44]; our primary analyses used the top sex-specific quartile of FSRP (Q4-FSRP) as a measure of CVD risk. The FSRP is composed of the following components: age, cigarette smoking status, systolic blood pressure in mm Hg, use of antihypertensive medication, diabetes as determined by blood glucose and medication use, history of cardiovascular disease, left ventricular hypertrophy by electrocardiogram and atrial fibrillation.

Although our primary measure was Q4-FSRP we were also interested in examining specific cardiovascular risk factors whose effects were most modified by the presence of the apoE4 allele. We selected risk factors based upon the frequency with which previous investigations have associated them with variations in neuroanatomy and neuropsychological deficits:

systolic blood pressure [8,9,12,13], glucose [3,8,12] and diabetes status [2-7]. Multivariable linear regression was used to estimate the relationships between FSRP, MRI and NP variables; interaction terms were included to examine modification of these relationships by the presence of the apoE4 allele. All models were adjusted for age and sex. Models that analyzed NP variables were additionally adjusted for education. We used a cutoff of $p < 0.10$ to determine significant interaction; all other analyses were performed using 5% levels of significance.

RESULTS

Table 1 presents the clinical characteristics of the sample overall, and broken out by apoE4 status. Significant results in tables 2a-4b include results that are presented in the form of beta weights. These beta weights are derived from linear regressions representing the effect on standardized neuropsychological and MRI variables, and represent differences in adjusted means between those in the top quartile and those in the lower three quartiles. With respect to analyses of systolic blood pressure, the betas are the effect of a one unit change in systolic blood pressure on standardized MRI.

Q4-FSRP was significantly associated with poorer performance on WMS Visual Reproductions-D.R. and Trail Making Test-B (i.e., nonverbal memory and set shifting/complex attention). Q4-FSRP was not significantly associated with the other neuropsychological measures (Table 2a). Additional examination of the relationship between FSRP and morphometry revealed findings consistent with previous FHS investigations [19, 21]. Specifically, we found that Q4-FSRP was significantly associated with lower total brain volume, frontal lobe volume and temporal lobe volume, and higher white matter hyperintensities volume, temporal horn volume, and lateral ventricular volume (Table 2b). Q4-FSRP was also associated with lower hippocampal volume; this association was not significant.

ApoE4 status was found to significantly modify several of the relationships between Q4-FSRP and neuropsychological performance (Table 2a). In particular, the interactions between Q4-FSRP and apoE4 status were significant for Logical Memory-D.R. ($p < 0.001$), Paired Associates-D.R. ($p < 0.001$), Visual Reproductions-D.R. ($p = 0.015$), and Trail Making Test-B ($p = 0.005$). In each case, the negative relationship between stroke risk and neuropsychological performance was significant only for individuals who possess the E4 allele.

ApoE4 status did not modify the relationships between Q4-FSRP and total brain volume, white matter hyperintensities, frontal lobe volume, temporal lobe volume, or temporal horn volume. However, the positive relationships between Q4-FSRP and each of temporal horn volume and lateral ventricular volume were steeper and only significant among those with the apoE4 allele (see Table 2b). There was a significant interaction [$p = 0.012$] between the presence of the apoE4 allele and Q4-FSRP in their effects on lateral ventricular volume.

Finally, in addition to the interaction of apoE4 and the composite FSRP, we were interested in the *specific* cerebrovascular risk factors whose effects are most exacerbated by the presence of apoE4. We found that apoE4 significantly modified the effect of systolic blood pressure (SBP) on Paired Associates-D. R., Logical Memory-D. R., Visual Reproductions-D. R. and Trail Making Test-B, but not for any brain structure (Tables 3a & b.) We did not find a significant modifying effect of apoE4 on DM for any cognitive measure, but did find a modifying effect of apoE4 on white matter hyperintensities (Table 4a and 4b).

COMMENT

This study demonstrates that the presence of the apoE4 allele can exacerbate neuropsychological deficits associated with CVD risk as indexed by FSRP. It appears that SBP is driving this effect since it was the only risk factor whose impact on neuropsychological

performance was significantly modified by the presence of the apoE4 allele. This suggests that the presence of the apoE4 allele in combination with high SBP may produce synergistic effects with respect to functional ability. This interaction may significantly exacerbate the progression and acceleration of cognitive decline in those with high SBP, although more research is needed in this area.

Although we confirmed previous Framingham Heart Study findings that Q4-FSRP was significantly associated with MRI measures, the lack of significant FSRP and apoE interactions on brain structures may be because the specific imaging techniques used were not optimal for detecting the neural changes resulting from apoE4/CVD risk factor interaction. It could be that the neural changes associated with the alterations in neuropsychological performance are associated with changes in the neural integrity of the white matter. This could be addressed in a future study examining white matter with Diffusion Tensor Imaging. In contrast to our expectations, the effect of DM was only significantly modified by the presence of apoE4 for the white matter hyperintensities MRI variable (tables 4a and 4b). It is possible that other factors associated with the development of AD such as family history or lifestyle might be more important moderators of DM's effect on the brain and neuropsychological function.

Consistent with our previous studies, we found that, overall, Q4-FSRP was associated with poorer performance on Visual Reproductions-D.R. and Trail Making Test-B; but was not associated with the other NP measures. One possible contributing factor may be that that increased stroke risk factors are more likely to lead to attenuated executive functions (associated with lower frontal lobe volume and reflected in performance on Trail Making Test-B) as well as reduced ability in the domain of non-verbal organization, as reflected in poor performance on the complex visual designs. This relationship is highlighted further by the our findings that the interactions between Q4-FSRP and apoE4 status were significant for our memory measures, e.g., Logical Memory-D.R., Paired Associates-D.R., Visual Reproductions-D.R., and executive function e.g., Trail Making Test-B. In each of these interactions, the negative relationship between stroke risk and neuropsychological performance was significant only for individuals in possession of the E4 allele. These findings suggest that the presence of apoE4 leads to synergistic effects, greatly increasing the negative consequences of some stroke risk factors.

Many previous investigations have demonstrated that CVD risk factors can lead to subtle morphometric changes, especially to frontal subcortical structures. We believe that examining the interaction of the relationship between various CVD and genetic risk factors for dementia suggests that a strict dichotomy between microvascular disease and AD is inappropriate. The findings of this investigation, combined with the work of previous studies, suggest that the factors underlying the clinical presentations of vascular cognitive impairment and AD are interrelated, complex and dynamic. Effective treatment strategies for treating or preventing either disease should therefore address both the factors traditionally associated with vascular cognitive impairment (e.g., blood pressure, cholesterol, glucose levels and atherosclerosis) as well as those traditionally associated with Alzheimer's disease (i.e. apoE4).

Strengths/Limitations

The strengths of our study are the large community-based sample, the availability of multiple CVD and neuroanatomical measures and the use of a comprehensive, standardized battery of neuropsychological tests in all participants.

Our study also has several limitations. We do not have repeated measures of brain MRI and neuropsychological testing, and hence cannot determine if the neuroanatomical and physiological alterations preceded or followed the onset of neuropsychological decline.

Additionally, our participants are of predominantly European decent, which restricts the generalizability of our results to other ethnicities/races.

While the issues discussed above reflect limitations of our investigation, we view this research as one in a series of steps towards a more comprehensive understanding of the factors that increase risk for cognitive decline amongst geriatric populations. We hope that understanding the factors that increase the risk for cognitive decline will facilitate improved treatments and encourage preventative health behaviors, allowing geriatric populations to extend functional independence.

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References

1. Biessels GJ, Koffeman A, Scheltens P. Diabetes and cognitive impairment. Clinical diagnosis and brain imaging in patients attending a memory clinic. *J Neurol* 2006;253(4):477–82. [PubMed: 16283097]
2. Musen G, et al. Effects of type 1 diabetes on gray matter density as measured by voxel-based morphometry. *Diabetes* 2006;55(2):326–333. [PubMed: 16443764]
3. Yaffe K, et al. Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. *Neurology* 2004;63(4):658–63. [PubMed: 15326238]
4. Kuo HK, et al. Cognitive function in normal-weight, overweight, and obese older adults: an analysis of the Advanced Cognitive Training for Independent and Vital Elderly cohort. *J Am Geriatr Soc* 2006;54(1):97–103. [PubMed: 16420204]
5. Munshi M, et al. Cognitive dysfunction is associated with poor diabetes control in older adults. *Diabetes Care* 2006;29(8):1794–9. [PubMed: 16873782]
6. Pasquier F, et al. Diabetes mellitus and dementia. *Diabetes Metab* 2006;32:403–414. [PubMed: 17110895]
7. Knopman D, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. *Neurology* 2001;56(1):42–8. [PubMed: 11148234]
8. Jellinger KA. The enigma of vascular cognitive disorder and vascular dementia. *Acta Neuropathol* 2007;113(4):349–88. [PubMed: 17285295]
9. Wolf PA, et al. Relation of obesity to cognitive function: importance of central obesity and synergistic influence of concomitant hypertension. The Framingham Heart Study. *Curr Alzheimer Res* 2007;4(2):111–6. [PubMed: 17430232]
10. Jeong SK, et al. Interactive effect of obesity indexes on cognition. *Dement Geriatr Cogn Disord* 2005;19(2-3):91–6. [PubMed: 15591798]
11. Gustafson D. Adiposity indices and dementia. *Lancet Neurol* 2006;5(8):713–20. [PubMed: 16857578]
12. Duron E, Hanon O. Vascular risk factors, cognitive decline, and dementia. *Vasc Health Risk Manag* 2008;4(2):363–81. [PubMed: 18561512]
13. Skoog I, Gustafson D. Update on hypertension and Alzheimer's disease. *Neurol Res* 2006;28(6):605–11. [PubMed: 16945211]
14. Honig LS, Kukull W, Mayeux R. Atherosclerosis and AD: analysis of data from the US National Alzheimer's Coordinating Center. *Neurology* 2005;64(3):494–500. [PubMed: 15699381]
15. Xu G, et al. Cognitive performance after carotid angioplasty and stenting with brain protection devices. *Neurol Res* 2007;29(3):251–5. [PubMed: 17178010]
16. Mlekusch W, et al. Improvement of neurocognitive function after protected carotid artery stenting. *Catheter Cardiovasc Interv* 2008;71(1):114–9. [PubMed: 18098213]

17. Yu F, et al. Improving cognition and function through exercise intervention in Alzheimer's disease. *J Nurs Scholarsh* 2006;38(4):358–65. [PubMed: 17181084]
18. Ploughman M. Exercise is brain food: the effects of physical activity on cognitive function. *Dev Neurorehabil* 2008;11(3):236–40. [PubMed: 18781504]
19. Elias MF, et al. Framingham stroke risk profile and lowered cognitive performance. *Stroke* 2004;35(2):404–9. [PubMed: 14726556]
20. Jeerakathil T, et al. Stroke risk profile predicts white matter hyperintensity volume: the Framingham Study. *Stroke* 2004;35(8):1857–61. [PubMed: 15218158]
21. Seshadri S, et al. Stroke risk profile, brain volume, and cognitive function: the Framingham Offspring Study. *Neurology* 2004;63(9):1591–9. [PubMed: 15534241]
22. Nakamura Y, et al. Associations of obesity measures with metabolic risk factors in a community-based population in Japan. *Circ J* 2007;71(5):776–81. [PubMed: 17457008]
23. Yaffe K. Metabolic syndrome and cognitive decline. *Curr Alzheimer Res* 2007;4(2):123–6. [PubMed: 17430234]
24. Yaffe K, et al. The metabolic syndrome and development of cognitive impairment among older women. *Arch Neurol* 2009;66(3):324–8. [PubMed: 19273750]
25. Corder EH, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993;261(5123):921–3. [PubMed: 8346443]
26. Saunders AM, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* 1993;43(8):1467–72. [PubMed: 8350998]
27. Raber J, Huang Y, Wesson Ashford J. ApoE genotype accounts for the vast majority of AD risk and AD pathology. *Neurobiology of Aging* 2004;25:641–650. [PubMed: 15172743]
28. Riley KP, et al. Cognitive function and apolipoprotein E in very old adults: findings from the Nun Study. *Journal of Gerontology B: Psychol Sci Soc Sci* 2000;55(2):S69–75.
29. Jak AJ, et al. Differential cross-sectional and longitudinal impact of APOE genotype on hippocampal volumes in nondemented older adults. *Dement Geriatr Cogn Disord* 2007;23(6):382–9. [PubMed: 17389798]
30. Zhang Y, et al. Diffusion tensor imaging of cingulum fibers in mild cognitive impairment and Alzheimer disease. *Neurology* 2007;68(1):13–9. [PubMed: 17200485]
31. Grossman H, Bergmann C, Parker S. Dementia: a brief review. *Mt Sinai J Med* 2006;73(7):985–92. [PubMed: 17195884]
32. Myers RH, et al. Apolipoprotein E epsilon4 association with dementia in a population-based study: The Framingham study. *Neurology* 1996;46(3):673–7. [PubMed: 8618665]
33. Altamura C, et al. What is the relationship among atherosclerosis markers, apolipoprotein E polymorphism and dementia? *Eur J Neurol* 2007;14(6):679–82. [PubMed: 17539949]
34. Agosta F, et al. Apolipoprotein E epsilon4 is associated with disease-specific effects on brain atrophy in Alzheimer's disease and frontotemporal dementia. *Proc Natl Acad Sci U S A* 2009;106(6):2018–22. [PubMed: 19164761]
35. Qiu C, et al. Risk and protective effects of the APOE gene towards Alzheimer's disease in the Kungsholmen project: variation by age and sex. *Journal of Neurology, Neurosurgery and Psychiatry* 2004;75:828–833.
36. Donahue JE, Johanson CE. Apolipoprotein E, amyloid-beta, and blood-brain barrier permeability in Alzheimer disease. *J Neuropathol Exp Neurol* 2008;67(4):261–70. [PubMed: 18379441]
37. Zlokovic BV. Cerebrovascular transport of Alzheimer's amyloid beta and apolipoproteins J and E: possible anti-amyloidogenic role of the blood-brain barrier. *Life Sci* 1996;59(18):1483–97. [PubMed: 8890929]
38. Scuteri A, et al. apoE4 allele and the natural history of cardiovascular risk factors. *Am J Physiol Endocrinol Metab* 2005;289(2):E322–7. [PubMed: 15769795]
39. Eichner JE, et al. Relation of apolipoprotein E phenotype to myocardial infarction and mortality from coronary artery disease. *Am J Cardiol* 1993;71(2):160–5. [PubMed: 8421977]
40. Davignon J, et al. Apolipoprotein E and atherosclerosis: insight from animal and human studies. *Clin Chim Acta* 1999;286(1-2):115–43. [PubMed: 10511288]

41. Berlau DJ, et al. Dissociation of neuropathologic findings and cognition: case report of an apolipoprotein E epsilon2/epsilon2 genotype. *Arch Neurol* 2007;64(8):1193–6. [PubMed: 17698712]
42. DeCarli C, et al. Memory impairment, but not cerebrovascular disease, predicts progression of MCI to dementia. *Neurology* 2004;63(2):220–7. [PubMed: 15277612]
43. Spreen, O.; Sherman, MS.; Strauss, E. *A Compendium of Neuropsychological Tests*. Vol. 533. Oxford University Press; New York: 2006.
44. Wolf PA, et al. Probability of stroke: a risk profile from the Framingham Study. *Stroke* 1991;22(3): 312–8. [PubMed: 2003301]

Table 1
Participant Characteristics

Variables	Overall	apoE4 present (3/4, 4/4)	apoE4 absent (2/2, 2/3, 3/3)
N	1995	426	1569
Framingham 10-y stroke risk, %	6.4 ± 7.3	6.2 ± 7.5	6.5 ± 7.2
Stroke Risk Profile Components			
Age [mean ± sd]	61 ± 9	61 ± 9	61 ± 9
Male (%)	47%	46%	47%
Mean Systolic Blood Pressure	126 ± 18	125 ± 19	126 ± 18
Diabetes Mellitus (%)	11%	12%	11%
Stage 1+ Hypertension (%)	41%	43%	41%
History of AF (%)	3.4%	2.8%	3.5%
History of CVD (%)	9%	11%	9%
Current Smoking (%)	12%	9%	13%
Neuroanatomical Measures ^{††}			
Total brain volume [mean ± sd]	79 ± 3	79 ± 4	79 ± 3
White matter hyperintensities [med (range)]	0.05 (0-4.77)	0.05 (0-1.84)	0.05 (0-4.77)
Frontal Lobe volume [mean ± sd]	36 ± 3	37 ± 3	36 ± 3
Temporal Lobe volume [mean ± sd]	11 ± 1	10 ± 1	11 ± 1
Temporal horn volume [med (range)]	0.04 (0-0.55)	0.04 (0-0.55)	0.04 (0-0.38)
Lateral ventricular volume [mean ± sd]	1.8 ± 1.2	1.8 ± 1.1	1.8 ± 1.2
Hippocampal volume [mean ± sd]	0.32 ± 0.05	0.32 ± 0.05	0.32 ± 0.04
Neuropsychological Measures			
Logical memory- delayed recall (D. R.) [mean ± sd]	10.5 ± 3.6	10.3 ± 4.0	10.6 ± 3.6
Paired associates- D. R.[mean ± sd]	8.3 ± 1.5	8.3 ± 1.6	8.3 ± 1.5
Visual Reproduction-D.R. [mean ± sd]	8.2 ± 3.4	8.2 ± 3.4	8.2 ± 3.4
Trails A [med (range)] (minutes)	0.5 (0.2-5.0)	0.5 (0.2-5.0)	0.5 (0.2-2.4)
Trails B - Trails A [med (range)] (minutes)	0.7 (-1.5-4.6)	0.7 (-1.5-4.5)	0.7 (-0.4-4.6)
Similarities [mean ± sd]	16.8 ± 3.6	17.1 ± 3.6	16.7 ± 3.6
Hooper Visual Organization Test [med (range)]	26 (3-30)	26 (3-30)	26 (6-30)

^{††} neuroanatomical measures were analyzed as a percentage of total cranial volume; the units listed are percentages. For white matter hyperintensities and temporal horn volume, variables were log transformed.

Table 2AModerating effect of apoE4 status on the relationship between *stroke risk* and cognitive ability

	Overall (beta±se)	P-value for interaction with apoE4	With no apoE4 (2/2, 2/3, 3/3) (beta±se)	apoE4 present (3/4, 4/4) (beta±se)
Logical memory- D. R. [†]	-0.047 ± 0.054	<0.001	0.073 ± 0.060	-0.477 ± 0.121 ***
Paired associates-D. R.	-0.058 ± 0.055	<0.001	0.052 ± 0.061	-0.453 ± 0.123 ***
Visual Reproductions - D. R.	-0.121 ± 0.054 *	0.015	-0.051 ± 0.061	-0.371 ± 0.116 **
Trails A	-0.087 ± 0.055	ns	-0.049 ± 0.059	-0.227 ± 0.137
Trails B - Trails A	-0.113 ± 0.054 *	0.005	-0.033 ± 0.056	-0.403 ± 0.139 **
Similarities	-0.084 ± 0.054	ns	-0.051 ± 0.061	-0.204 ± 0.119
Hooper Visual Organization Test	-0.019 ± 0.055	ns	-0.012 ± 0.062	-0.042 ± 0.119

[†]D.R.=Delayed Recall*
p<0.05**
p<0.01***
p<0.001

Table 2BModerating effect of apoE4 status on the relationship between *stroke risk* and brain volume

	Overall (beta±se)	P-value for interaction with apoE4	With no apoE4 (2/2, 2/3, 3/3) (beta±se)	apoE4 present (3/4, 4/4) (beta±se)
Total brain volume	-0.338±0.057***	ns	-0.353 ± 0.064***	-0.276 ± 0.132*
White matter hyperintensities	0.208 ± 0.060***	ns	0.200 ± 0.069**	0.222 ± 0.126
Frontal Lobe volume	-0.198 ± 0.060***	ns	-0.188 ± 0.068**	-0.233 ± 0.127
Temporal Lobe volume	-0.193 ± 0.066**	ns	-0.174 ± 0.075*	-0.240 ± 0.138
Temporal horn volume	0.155 ± 0.062*	Ns	0.120 ± 0.070	0.270 ± 0.135*
Lateral ventricular volume	0.205 ± 0.060***	0.012	0.124 ± 0.068	0.490 ± 0.124***
Hippocampal volume	-0.159 ± 0.094	ns	-0.141 ± 0.102	-0.195 ± 0.227

Table 3AModerating effect of apoE4 status on the relationship between *systolic blood pressure* and cognitive ability

	Overall (beta±se)	P-value for interaction with apoE4	apoE4 absent (2/2, 2/3, 3/3) (beta±se)	apoE4 present (3/4, 4/4) (beta±se)
Logical memory- D. R. [†]	-0.020 ± 0.022	0.001	0.019 ± 0.025	-0.153 ± 0.049**
Paired associates- D. R.	-0.008 ± 0.022	0.032	0.018 ± 0.025	-0.096 ± 0.049
Visual Reproductions - D. R.	0.002 ± 0.022	0.069	0.024 ± 0.025	-0.072 ± 0.046
Trails A	-0.005 ± 0.022	ns	-0.006 ± 0.024	-0.001 ± 0.055
Trails B - Trails A	0.014 ± 0.022	0.072	0.034 ± 0.023	-0.061 ± 0.056
Similarities	0.016 ± 0.022	ns	0.016 ± 0.025	0.016 ± 0.047
Hooper Visual Organization Test	0.021 ± 0.022	ns	0.014 ± 0.025	0.047 ± 0.047

[†]D.R.=Delayed Recall*
p<0.05**
p<0.01***
p<0.001

Table 3BModerating effect of apoE4 status on the relationship between *systolic blood pressure* and brain volume

	Overall (beta±se)	P-value for interaction with apoE4	apoE4 absent (2/2, 2/3, 3/3) (beta±se)	apoE4 present (3/4, 4/4) (beta±se)
Total brain volume	-0.040 ± 0.020*	ns	-0.047 ± 0.022*	-0.013 ± 0.044
White matter hyperintensities	0.022 ± 0.021	ns	0.031 ± 0.024	-0.006 ± 0.042
Frontal Lobe volume	-0.042 ± 0.020*	ns	-0.049 ± 0.023*	-0.017 ± 0.042
Temporal Lobe volume	-0.011 ± 0.023	ns	-0.009 ± 0.026	-0.011 ± 0.045
Temporal horn volume	0.054 ± 0.022*	ns	0.052 ± 0.025*	0.059 ± 0.045
Lateral ventricular volume	0.060 ± 0.021**	ns	0.052 ± 0.024*	0.082 ± 0.042*
Hippocampal volume	0.024 ± 0.033	ns	0.024 ± 0.037	0.036 ± 0.075

Table 4AModerating effect of apoE4 status on the relationship between *Diabetes diagnosis* and cognitive ability

	Overall (beta±se)	P-value for interaction with apoE4	apoE4 absent (2/2, 2/3, 3/3) (beta±se)	apoE4 present (3/4, 4/4) (beta±se)
Logical memory- D. R. [†]	-0.016 ± 0.070	ns	0.010 ± 0.079	-0.089 ± 0.155
Paired associates- D. R.	0.021 ± 0.071	ns	0.074 ± 0.080	-0.151 ± 0.156
Visual Reproductions - D. R.	-0.165 ± 0.070*	ns	-0.135 ± 0.080	-0.259 ± 0.146
Trails A	-0.174 ± 0.070*	ns	-0.153 ± 0.076	-0.240 ± 0.171
Trails B minus Trails A	-0.126 ± 0.069	ns	-0.117 ± 0.074	-0.148 ± 0.174
Similarities	-0.092 ± 0.070	ns	-0.130 ± 0.079	0.029 ± 0.148
Hooper Visual Organization Test	-0.049 ± 0.071	ns	0.001 ± 0.080	-0.216 ± 0.148

[†]D.R.=Delayed Recall

Table 4BModerating effect of apoE4 status on the relationship between *Diabetes diagnosis* and brain volume

	Overall (beta±se)	P-value for interaction with apoE4	apoE4 absent (2/2, 2/3, 3/3) (beta±se)	apoE4 present (3/4, 4/4) (beta±se)
Total brain volume	-0.335 ± 0.058***	ns	-0.354 ± 0.065***	-0.288 ± 0.128*
White matter hyperintensities	0.049 ± 0.061	0.061	-0.013 ± 0.070	0.258 ± 0.123*
Frontal Lobe volume	-0.354 ± 0.060***	ns	-0.388 ± 0.068***	-0.256 ± 0.124*
Temporal Lobe volume	-0.061 ± 0.066	ns	-0.077 ± 0.076	-0.037 ± 0.135
Temporal horn volume	0.186 ± 0.063**	ns	0.172 ± 0.072**	0.233 ± 0.133
Lateral ventricular volume	0.197 ± 0.062**	ns	0.211 ± 0.072**	0.165 ± 0.123
Hippocampal volume	-0.178 ± 0.104	ns	-0.182 ± 0.116	-0.253 ± 0.238

*
p<0.05**
p<0.01***
p<0.001