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Interaction of APOE e4 and poor glycemic control predicts white matter hyperintensity growth from 73 to 76

Simon R. Cox[a,b,c,*], Stuart J. Ritchie[a,b], David Alexander Dickie[c,d], Alison Pattie[a,b], Natalie A. Royle[a,c,d,e], Janie Corley[a,b], Benjamin S. Aribisala[a,c,d,e], Sarah E. Harris[a,f], Maria Valdés Hernández[a,c,d], Alan J. Gow[a,g], Susana Muñoz Maniega[a,c,d], John M. Starr[a,h], Mark E. Bastin[a,c,d], Joanna M. Wardlaw[a,c,d,1], Ian J. Deary[a,b,1]

[a] *Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK*
[b] *Department of Psychology, University of Edinburgh, Edinburgh, UK*
[c] *Scottish Imaging Network, a Platform for Scientific Excellence (SINAPSE) Collaboration, Edinburgh, UK*
[d] *Brain Research Imaging Centre, Neuroimaging Sciences, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK*
[e] *Department of Computer Science, Lagos State University, Lagos, Nigeria*
[f] *Centre for Genomic and Experimental Medicine, MRC Institute of Genetics & Molecular Medicine, University of Edinburgh, Edinburgh, UK*
[g] *Department of Psychology, School of Life Sciences, Heriot-Watt University, Edinburgh, UK*
[h] *Alzheimer Scotland Dementia Research Centre, University of Edinburgh, UK*

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We examined whether apolipoprotein E (*APOE*) status interacts with vascular risk factors (VRFs) to predict the progression of white matter hyperintensities (WMHs) on brain MRI scans over a specific period of life in older age when the risk of dementia increases. At age 73 years, baseline VRFs were assessed via self-reported history of diabetes, hypertension, smoking, and hypercholesterolemia, and via objective measures of blood HbA1c, body mass index, diastolic and systolic blood pressure, and blood high-density lipoprotein to total cholesterol (HDL) ratio. *APOE* e4 allele was coded as either present or absent. WMH progression was measured on MRI over 3 years in 434 older adults, in a same-year-of-birth cohort. *APOE* e4 carriers with either a self-reported diagnosis of diabetes ($\beta = 0.160$, $p = 0.002$) or higher glycated hemoglobin levels ($\beta = 0.114$, $p = 0.014$) exhibited greater WMH progression, and the former survived correction for multiple testing. All other *APOE*-VRF interactions were nonsignificant ($\beta_{interaction} < 0.056$, $p > 0.228$). The results suggest that carrying the *APOE* "risk" e4 allele increases the risk of greater age-related WMH progression over the early part of the eighth decade of life, when combined with poorer glycemic control. The interaction effect was robust to co-occurring VRFs, suggesting a possible target for mitigating brain and cognitive aging at this age.

1. Introduction

Brain white matter hyperintensities (WMHs) are a prevalent MRI feature of healthy and pathologic states in older age and are associated with important life outcomes (Debette and Markus, 2010; Kloppenborg et al., 2014; Lee et al., 2016; Longstreth et al., 1996) and vascular risk factors (VRFs) such as hypertension, diabetes, smoking, obesity, and hypercholesterolemia (de Leeuw et al., 2004; Dufouil et al., 2001; Prins and Scheltens, 2015; Wang et al., 2015; Wardlaw et al., 2014). Compared with cross-sectional WMH volumetric measures, WMH progression shows a stronger relation with important age-related functional changes (Prins and Scheltens, 2015; van Dijk et al., 2008), and it is possible that different VRFs are relevant at different ages (Zhang et al., 2015). Hence, longitudinal studies with a narrow age range are essential to identify the most pertinent VRFs at specific periods in life.

Alongside evidence of VRF-WMH associations, WMH heritability is estimated at 55%–80% (Atwood et al., 2004; Carmelli et al., 1998; Turner et al., 2004). Variation in the apolipoprotein E (*APOE*) gene (which delivers essential lipids to neurons and is linked to accelerated neurodegeneration Bu, 2009; Mahley and Rall, 2000), is a plausible candidate to explain some of this heritability. Possession of the e4 "risk" allele is associated with more WMHs

* Corresponding author at: Department of Psychology, 7 George Square, Edinburgh EH8 9JZ, UK. Tel.: 0131 650 8493; fax: 0131 651 1771.
E-mail address: simon.cox@ed.ac.uk (S.R. Cox).
[1] These authors contributed equally to the manuscript.

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and poorer white matter microstructure in older adults (Brickman et al., 2014; Heise et al., 2011) and greater cognitive decline (Bangen et al., 2013; Schiepers et al., 2012; Wisdom et al., 2011). However, *APOE* was not associated with cross-sectional WMH load in 2 large studies (Fornage et al., 2011; Paternoster et al., 2009). Discrepancies between heritability estimates of complex disease and the risk explained by the common genetic variants might be due to interactions with VRFs (Manolio et al., 2009). Prior examinations of *APOE*-VRF interactions involved cross-sectional white matter measures across participants of a broad age range, yielding inconsistent results (de Leeuw et al., 2004; Foley et al., 2014; Wang et al., 2015).

The current study is the first, to our knowledge, to test the interactions between *APOE* e4 status and VRFs on longitudinal WMH progression.

2. Materials and methods

2.1. Participants

Members of the Lothian Birth Cohort 1936 were initially 1091 older adults, most of whom took part in the Scottish Mental Survey 1947 when aged 11 years and were living in the Edinburgh and Lothian areas of Scotland at the start of Wave 1 of testing (at ~70 years of age in 2004–2007; Deary et al., 2007, 2012). All were White Caucasian and reported no diagnosis of dementia at baseline. 488 participants attended brain MRI scans at both Waves 2 and 3 (mean ages 72.65 and 76.36 years). Of these, 434 provided blood for genotyping at Wave 1 and VRF data at Wave 2. The Multi-Centre Research Ethics Committee for Scotland (MREC/01/0/56), the Scotland A Research Ethics Committee (07/MRE00/58) and the Lothian Research Ethics Committee (LREC/2003/2/29) approved use of the human subjects in this study; all participants provided written informed consent and these have been kept on file.

2.2. APOE status

Genotyping on the 2 polymorphic sites (rs7412 and rs429358) that account for the e2, e3, and e4 alleles (Wenham et al., 1991) was performed on genomic DNA, isolated from whole blood, using TaqMan technology by the Wellcome Trust Clinical Research Facility Genetics Core, Western General Hospital, Edinburgh. An exact test (Web Reference 1) confirmed that the APOE genotypes were in Hardy-Weinberg equilibrium ($p = 0.657$).

2.3. Vascular risk factors

The World Heart Federation, UK National Health Service, Framingham Heart Study, and the British Heart Foundation (Web References 2-5) overlap in their identification of diabetes, hypertension, smoking, high body mass index (BMI), and hypercholesterolemia as important VRFs and are pertinent to WMH burden in older age (de Leeuw et al., 2004; Dufouil et al., 2001; Prins and Scheltens, 2015; Wang et al., 2015; Wardlaw et al., 2014). VRFs were assessed during a cognitive and physical testing appointment at age 73 years. During a medical interview, diagnosis of diabetes, hypertension, smoking (current, ex, or never), and hypercholesterolemia were reported. Objective VRFs were BMI (weight kg/height m^2), pulse pressure (difference between average systolic and diastolic blood pressure, taken over 6 consecutive measurements, 3 sitting and 3 standing, from an Omron 705IT monitor), blood glycated hemoglobin (HbA1c using a Menarini HA8160 analyser), and the ratio of high-density lipoprotein to total cholesterol (HDL ratio; Milián et al., 2009).

2.4. MRI acquisition and processing

Whole brain MRI was performed on each participant at ages 73 and 76 years using the same scanning protocol in the same scanner (GE Signa Horizon 1.5 T HDx; Milwaukee, WI, USA). T1-, T2-, T2*-, and FLAIR-weighted sequences were coregistered at a resolution of $1 \times 1 \times 2$ mm. A semi-automated multispectral fusion method (Valdés Hernández et al., 2010) combined these sequences to measure the intracranial and WMH volumes. WMHs were explicitly defined as punctate, focal, or diffuse lesions in all subcortical regions (Wardlaw et al., 2013). All segmented images were visually examined for accuracy on anonymized scans to correct errors and ensure that infarcts (including lacunar infarcts, n = 3 at baseline in this sample) and enlarged perivascular spaces were excluded from WMH masks. Full details are available in an open-access protocol (Wardlaw et al., 2011).

2.5. Statistical analysis

WMH volumes at age 73 and 76 years were expressed as a proportion of intracranial and corrected for age in days on the date of image acquisition. Residuals of the regression between log WMH volume at Waves 2 (IV) and 3 (DV) were derived to index WMH volume change (ΔWMH) over a mean of 3.71 (SD = 0.27) years. Using the "sem" function in the "lavaan" package (v.0.5–22) in R v3.2.2, we used ΔWMH as the dependent variable in models with VRFs and *APOE* status (e4 allele present or absent) as predictors, alongside an interaction term (APOE e4 status × VRF), for each VRF. We used full information maximum likelihood estimation to reduce bias due to missingness, under the assumption of "missing at random" (Rubin, 1976), including the following "auxiliary" variables (previously used to model dropout in this cohort; Ritchie et al., 2016): age 11 IQ, years of education, father's and own social class, Scottish Index of Multiple Deprivation at recruitment, forced expiratory volume over 1 second, 6-meter walk, hand grip strength (best of 6; 3 with each hand), a binary variable indicating a self-reported diagnosis of dementia or MMSE score <24 at any wave of testing (n = 22). In instances where interaction terms were significant, coincident VRFs were inserted as covariates. Standardized βs, corrected for false discovery rate (FDR) are reported throughout. Variance inflation factors (VIFs) among VRFs was ascertained using "vif" in the "usdm" package for R. In a supplementary, a posteriori analysis, we further explored interactions between *APOE* status and both HbA1c and diabetes. We split *APOE* e4 and e2/3 groups by diabetes diagnosis or high/low HbA1c level (median split at 5.59 DCCT), visualized, and tested (*t*-tests) group differences in WMH progression.

3. Results

Participant characteristics are shown in Table S1, and density plots of the raw and corrected measures of WMH change are shown in Fig. 1. There was a significant increase in corrected WMH volume in under 4 years ($t(865.34) = 3.685$, $p < 0.001$) in the total sample. Associations among the VRFs were modest (Table S2) and showed low variance inflation factor (all <1.87). Exploratory factor analysis provided no basis to extract 1 ($\chi^2 = 164.8$, $p = 8.85 \times 10^{-25}$; 18.4% of the variance) or 2 ($\chi^2 = 59.96$, $p = 5.33 \times 10^{-8}$; 27.9% of the variance) factors of general vascular risk. A total of 136 participants were *APOE* e4 carriers, who were not significantly different to non-e4 carriers in terms of age, cross-sectional WMH volume at either wave, male:female ratio, MMSE score at Wave 2, or VRF status. *APOE* e4 carriers did, however, show a significantly lower MMSE score at Wave 3 ($p = 0.020$, Table S1).

Effects of VRFs on WMH volume change—without reference to *APOE*—have previously been reported in this sample (Dickie et al.,