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Risk-reducing *Apolipoprotein E* and *Clusterin* genotypes protect against the consequences of poor vascular health on executive function performance and change in nondemented older adults

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ABSTRACT

We examined independent and cumulative effects of 2 Alzheimer's-related genetic polymorphisms, *Apolipoprotein E* (*APOE*) and *Clusterin* (*CLU*), in relation to the deleterious effects of poor vascular health (pulse pressure [PP]) on executive function (EF) performance and change in nondemented older adults. Using a sample (n = 593; age range = 53–95 years) from the Victoria Longitudinal Study, we applied latent growth modeling to test the effect of PP, as moderated by *APOE* and *CLU*, on an EF latent variable. EF was affected by higher levels of PP but differentially less so for carriers of low-risk alleles (*APOE* ε2+; *CLU* TT) than for moderate- or high-risk alleles (*APOE* ε2−; *CLU* C+). The cumulative genetic risk of *APOE* plus *CLU* provided similar moderation of PP level effects on EF. Future research may focus on how *APOE* and *CLU* might provide different but complementary contributions to predicting EF level and change. Vascular health risk in synergistic association with risk-related polymorphisms can elucidate the neurobiological underpinnings of cognitive trajectories in nondemented aging.

1. Introduction

Biomarkers associated with the risk of developing Alzheimer's disease (AD) may affect cognition long before clinical symptoms of AD occur (Anstey et al., 2015). AD-related risk or protection factors derive from genetic, biological, health, lifestyle, and other domains. Such factors may operate independently or interactively to predict the level and slope of neurocognitive performance. Among key AD risk genes, *Apoliprotein E* (*APOE*) and *Clusterin* (*CLU*) have also been prominently implicated in differential cognitive decline in nondemented aging (Small et al., 2004; Thambisetty et al., 2013). Independently, these genes present relatively low penetrance and consequently low-effect sizes, but together, they may account for substantial cognitive risk (Barral et al., 2012; McFall et al., 2015a) especially within the context of other AD and vascular health risk factors (Josefsson et al., 2012; McFall et al., 2014, 2015b). One important vascular health factor is pulse pressure (PP), a proxy measure of arterial stiffness. Higher levels of PP are associated with decreased vascular health (Steppan et al., 2011), poorer cognitive outcomes (Al Hazzouri and Yaffe, 2014; McFall et al., 2014; Raz et al., 2011), and risk of dementia or AD (Peters et al., 2013; Qiu et al., 2003). This study examines the independent and additive effects of genetic variants within the *APOE* and *CLU* genes in interaction with a key vascular risk factor (i.e., PP) on executive function (EF) level and 9-year change in nondemented older adults.

APOE (rs429358 and rs7412) has 3 isoforms (ε2, ε3, and ε4) that exert varying levels of risk on cognitive decline and AD. The isoforms differentially regulate amyloid beta (Aβ) aggregation and clearance, glucose metabolism, neuroinflammation, lipid transport, mitochondrial function, and neuronal signaling (Bennet et al., 2007; Castellano et al., 2011; Corder et al., 1993; Liu et al., 2013). In general, the ε2 allele has been associated with reduced risk of cognitive decline and AD (Suri et al., 2013). The ε3 allele, the most common, is generally considered neutral (Corbo and Scacchi, 1999). Finally, the ε4 allele is an established risk factor for cognitive decline and AD, alone or in combination with biomarker risk (Bangen et al., 2013; Corder et al., 1993; Schiepers et al., 2012). The *CLU* (rs11136000) single nucleotide polymorphism (SNP) is involved in Aβ clearance, apoptosis, brain atrophy, and disease progression. *CLU* allelic risk carriers (C+) show decreased white matter integrity and 1.16 greater odds of developing sporadic AD than low-risk homozygotes (TT; Bertram et al., 2007). *APOE* and *CLU* both have similar molten globule structures (Morrow et al., 2002) and may influence each other in specific brain regions (Wu et al., 2012). Together, *APOE* and *CLU* may co-influence physiological and pathologic risk by contributing to AD

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pathology through their similar involvement in the reduced clearance of Aβ peptides which, in turn, lead to neuronal loss and cognitive decline (Lambert and Amouyel, 2011; Wu et al., 2012).

Although these AD genetic risk factors are generally not modifiable, vascular health is a prominent, changing, and potentially modifiable influence on brain and cognitive aging. PP, represented by the difference between systolic and diastolic blood pressure, is a measure related to arterial stiffness and is considered a better indicator of declining vascular health than either mean arterial pressure or systolic blood pressure. PP typically shows a steep linear age-related increase (toward worse health) in older adults (Raz et al., 2011). PP is an independent marker of (1) cardiovascular disease and mortality (Bérard et al., 2013; Singer et al., 2014); (2) cognitive decline (Al Hazzouri and Yaffe, 2014; McFall et al., 2014; Singer et al., 2014; Waldstein et al., 2008); (3) mild cognitive impairment (Yaneva-Sirakova et al., 2012); (4) AD biomarkers (Nation et al., 2013); and (5) dementia and AD risk (Peters et al., 2013; Qiu et al., 2003). Increases in systolic blood pressure or PP have been associated with neuropathology such as brain atrophy, lesions, and white matter hyperintensities (Jochemsen et al., 2015; Tsao et al., 2013; van Sloten et al., 2015), especially in prefrontal structures, leading to decreases in EF performance (McFall et al., 2014; Raz et al., 2003).

EFs are a collection of cognitive control processes involved in higher order thinking such as strategic planning, goal-directed behavior, and problem solving (Luszcz, 2011). Performance scores on cognitive tests representing each component can be combined quantitatively to produce latent EF variable(s). Two characteristics of EF associated with aging should be noted. First, with normal and impaired aging, EF latent structure exhibits dedifferentiation or consolidation into a single factor, although differentiation may continue for exceptional brain aging (de Frias et al., 2006, 2009). Second, EF performance generally declines with nondemented aging, but considerable variability in timing and trajectories across individuals is observed. Notably, below average or steeply declining EF performance in older adults is associated with development of cognitive impairment (de Frias et al., 2009; Nathan et al., 2001) or AD (Bäckman et al., 2005; Grober et al., 2008; Rapp and Reischies, 2005). Neurobiological, health, and lifestyle markers may contribute independently to differential EF performance and decline, but also interactively with genetic or other biomarkers (Lindenberger et al., 2008; McFall et al., 2013; Papenberg et al., 2014). Identifying specific factors, moderating influences, and synergistic combinations that contribute to variability in EF trajectories is an important avenue of research in neurocognitive aging.

Single-gene risk associated with typical cognitive decline is often difficult to detect. However, in the cumulative or interactive presence of other genetic or biomedical factors, associations may become evident. Increasingly, researchers are investigating cumulative or interactive effects (from genetic, biological, or health domains) to better understand mechanisms associated with variability in trajectories of nondemented and impaired neurocognitive aging (Ferencz et al., 2014; McFall et al., 2015a; Sapkota et al., 2015; Sleegers et al., 2015). We examine EF performance and change in older adults as related to interactive and cumulative risk with selected genetic polymorphisms and vascular health. We address 2 specific research questions. Research question (RQ)1: Do *APOE* or *CLU* low-risk (protective) alleles reduce the negative effects of poor vascular health (higher PP) on EF performance and change in nondemented older adults (e.g., *APOE* × PP)? RQ2: Does the combination of *APOE* and *CLU* clarify the negative effects of poor vascular health (higher PP) on EF performance and change in nondemented older adults beyond that of *APOE* or *CLU* alone? We expected genetic low-risk (protective) alleles of *APOE* and *CLU*, both independently and in combination, to reduce the deleterious effects of higher PP on EF performance and 9-year change.

2. Material and methods

2.1. Participants

Participants were community-dwelling adults (initially aged 53–95 years) drawn from the Victoria Longitudinal Study (VLS). The VLS is a longitudinal sequential study designed to examine human aging in relation to biomedical, genetic, health, cognitive, and neuropsychological aspects (Dixon and de Frias, 2004). The VLS and all present data collection procedures were in full and certified compliance with prevailing human research ethics guidelines and boards. Informed written consent was provided by all participants. Using standard procedures (e.g., Dixon et al., 2012; Small et al., 2011), we assembled longitudinal data consisting of 3 samples and all available waves (up to 3) since the early 2000s. The EF tasks required for this study were installed in the VLS neuropsychological battery at this point. Therefore, the first included wave for each sample was the first exposure to the EF tasks. This study assembled (1) sample 1 (S1) waves 6, 7, and 8; (2) sample 2 (S2) waves 4 and 5; and (3) sample 3 (S3) waves 1, 2, and 3. For terminological efficiency, the respective earliest wave of each sample became wave 1 (W1 or baseline), and the respective second and third wave became wave 2 (W2) and wave 3 (W3). The mean intervals between the waves of data collection were approximately 4.5 years (W1–W2; W2–W3). Although we used the 3 waves to organize the demographic information (Table 1), it is important to note that wave was not used as the metric of longitudinal change in the analyses. Specifically, age was used as the metric of change for this study. Statistically, using age in this manner permits us to account for variability associated with age as well as, or better than, if it were used as a covariate in the statistical models. Moreover, testing genetic-health interactions on EF across multiple linked longitudinal periods of up to 9 years (M = 8.9) allowed us to produce an accelerated longitudinal design covering a 40-year band of aging (i.e., 53–95 years).

Given the necessity for both genetic and longitudinal data in this study, these factors defined the initial opportunity in sample recruitment. VLS genotyping occurred in the 2009–2011 period and was limited by funding arrangement to about 700 continuing VLS participants. After initial evaluations, the eligible source sample consisted of 695 participants. Several exclusionary criteria were then applied to this source sample: (1) a diagnosis of Alzheimer's disease or any other dementia; (2) a mini-mental status examination (MMSE; Folstein et al., 1975) score of less than 24; (3) a self-report of "severe" for potential comorbid conditions (e.g., epilepsy, head injury, and depression); (4) a self-report of "severe" or "moderate" for potential comorbid diseases such as neurologic conditions (e.g., stroke, Parkinson's disease); and (5) insufficient EF data. The final study sample consisted of n = 593 adults. One participant (female) contributed data to W2 only. At W1, there were 592 adults, including 398 females and 194 males (M age = 70.3 years, SD = 8.66, range 53.2–95.2). At W2, there were 495 adults, including 332 females and 163 males (M age = 74.5 years, SD = 8.53, range 57.3–94.5). At W3, there were 319 adults, including 222 females and 97 males (M age = 76.2 years, SD = 8.22, range 62.4–95.6). The design stipulated that although S1 and S3 participants could contribute data to all 3 waves, S2 participants contributed data to W1 and W2 (the required data from the third wave are not yet available). The retention rates for each available and defined 2-wave interval are as follows (1) S1 W1–W2 = 88%; (2) S1 W2–W3 = 80%; (3) S2 W1-W2 = 82%; (4) S3 W1-W2 = 84%; and (5) S3 W2-W3 = 90%. Structural equation modeling estimates