HHS Public Access

Author manuscript

J Alzheimers Dis. Author manuscript; available in PMC 2018 April 01.

Published in final edited form as:

J Alzheimers Dis. 2018 ; 62(2): 887–900. doi:10.3233/JAD-170909.

A Network of Genetic Effects on Non-Demented Cognitive Aging: Alzheimer's Genetic Risk (*CLU* + *CR1* + *PICALM*) Intensifies Cognitive Aging Genetic Risk (*COMT* + *BDNF*) Selectively for *APOE* ε4 Carriers

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Abstract

Background—Trajectories of complex neurocognitive phenotypes in preclinical aging may be produced differentially through selective and interactive combinations of genetic risk.

Objective—We organize three possible combinations into a "network" of genetic risk indices derived from polymorphisms associated with normal and impaired cognitive aging, as well as Alzheimer's disease (AD). Specifically, we assemble and examine three genetic clusters relevant to non-demented cognitive trajectories: (1) *Apolipoprotein E* (*APOE*), (2) a Cognitive Aging Genetic Risk Score (CA-GRS; *Catechol-O-methyltransferase* + *Brain-derived neurotrophic factor*), and (3) an AD-Genetic Risk Score (AD-GRS; *Clusterin* + *Complement receptor 1* + *Phosphatidylinositol-binding clathrin assembly protein*).

Method—We use an accelerated longitudinal design (n = 634; age range = 55–95 years) to test whether AD-GRS (low versus high) moderates the effect of increasing CA-GRS risk on executive function (EF) performance and change as stratified by *APOE* status (ε4+ versus ε4-).

Results—*APOE* ε4 carriers with high AD-GRS had poorer EF performance at the centering age (75 years) and steeper 9-year decline with increasing CA-GRS but this association was not present in *APOE* ε4 carriers with low AD-GRS.

Conclusions—*APOE* ε4 carriers with high AD-GRS are at elevated risk of cognitive decline when they also possess higher CA-GRS risk. Genetic risk from both common cognitive aging and AD-related indices may interact in intensification networks to differential predict (1) level and trajectories of EF decline and (2) potential selective vulnerability for transitions into impairment and dementia.

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Conflict of Interest/Disclosure Statement

The authors have no conflict of interest to report.

All research has been approved continuously by relevant institutional review boards. Certificates are available and on file in the University of Alberta Research Services Office and the US National Institutes of Health. All participants have completed and signed informed consent forms.

Keywords

Alzheimer's disease; Cognitive Aging; Genetic Risk; *Apolipoprotein E*; Executive Function; Victoria Longitudinal Study

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease that accounts for approximately 60–80% of dementia cases worldwide [1–3]. The AD pathophysiological process includes the build-up of amyloid plaques and neurofibrillary tangles, which start years before the onset of clinical symptoms that lead to diagnosis [3,4]. Current theoretical models of AD suggest that the accumulation of amyloid-β (Aβ) peptide triggers a pathological cascade that leads to increased cerebrospinal tau production, brain atrophy, and cognitive impairment [5]. Primary clinical characteristics include memory loss, decline in global cognition, and early impairments in executive function (EF) [6]. Although age is a prominent factor in the incidence and prevalence of sporadic AD [7], studies have shown that genetic risk factors play a critical role in AD development [8]. Single AD risk genes may operate through (1) interactive effects with other AD genetic polymorphisms [9], (2) panel effects with other polymorphisms of similar structure and function [10], (3) aggregated or magnified associations with genetic risk for exacerbated but non-demented cognitive decline [11], and (4) networks of panels that reflect coordinated functions or canonical pathways [12]. Arguably, network-based approaches may lead to early identification of individual non-demented adults with elevated genetic risk for accelerated cognitive decline, Mild Cognitive Impairment (MCI) or AD, thus promoting timely and effective prevention programs [13]. In the present study, we examine a network approach assembling three clusters of genetic risk: (1) a prominent and commonly examined AD risk gene (i.e., *Apolipoprotein* (*APOE*; rs7412, rs429358)), (2) three AD risk genetic polymorphisms with different functions in the central nervous system (i.e., *Clusterin* (*CLU*; rs11136000), *Complement receptor 1* (*CR1*; rs6656401), and *Phosphatidylinositol-binding clathrin assembly protein* (*PICALM*; rs3851179)), and (3) two commonly studied polymorphisms relevant to EF trajectories in non-demented aging (i.e., *Catechol-O-methyltransferase* (*COMT*; rs4680) and *Brain-derived neurotrophic factor* (*BDNF*; rs6265)). As we focus on testing a network of genetic risk for preclinical aging, we examine these three clusters for interactive predictions of longitudinal cognitive trajectories in non-demented older adults. We have selected the EF domain, which involves cognitive processes such as planning, goal-directed actions, and problem solving [14,15]. Recent studies have shown that changes in EF performance and decline can be detected prior to clinical diagnosis making EF an important and promising early marker for MCI and AD [16].

The *APOE* gene located on chromosome 19q13.2 has three isoforms, ε2, ε3, and ε4 [17]. The ε4 allele is consistently associated with increased risk for sporadic AD [18–20] and also observed in recent AD genome wide association studies (GWAS) [21,22]. The ε2 allele is shown to have a protective effect and the ε3 allele is considered neutral [17]. Approximately 40% of AD patients across major ethnic groups are carriers of at least one copy of the ε4 allele [17,23]. *APOE* is involved in regulating cholesterol levels which plays an important

role in Aβ metabolism, aggregation, and deposition, leading to increased senile plaques and cerebral amyloid angiopathy in brains of *APOE* ε4 carriers diagnosed with AD. In healthy older adults, *APOE* ε4 homozygotes are associated with higher amyloid pathology, greater medial temporal lobe atrophy, elevated resting-state activity in the default mode network, neuroinflammation [17] and accelerated decline on cognitive tests [24,25].

Recent studies have identified additional single nucleotide polymorphisms (SNPs) that may play an important role in AD development [26]. A meta-analysis conducted by the AD Genetics Consortium confirmed that *CLU*, *CR1*, and *PICALM* [9,21,22] are associated with high AD risk susceptibility in independent samples [9]. These three SNPs have been further replicated for association with late-onset AD in European [27], North American [28], and Chinese [29] populations. The three SNPs represent varying functions in the brain where *CLU* is mainly involved with cholesterol metabolism, *CR1* is associated with immune response, and *PICALM* with endocytosis [30]. We now summarize the three polymorphisms as related to risk for cognitive decline and AD.

CLU is located on chromosome 8p21.1 and differentially regulates lipid transport, Aβ clearance, brain atrophy, and apoptosis [30]. AD patients show higher CLU levels implying that CLU acts in response to poor neuronal functions [31]. In such cases, CLU may (1) act as an anti-apoptotic signal, (2) provide oxidative stress protection, (3) defend activated complement proteins as a result of inflammation, and (4) bind to partially unfolded proteins to prevent aggregation [31]. *CLU* allelic risk carriers (C+) are at 1.16 greater odds of developing AD compared to their low risk homozygotes (T/T) [32]. In healthy young adults, *CLU* allelic risk had lower white matter integrity than their counterparts [33] which may indicate an increased risk for developing dementia in old age. CLU is also similar in structure with the molten globule structure of APOE and they may influence each other in frontal lobe regions [10,34,35].

CR1 gene is located on chromosome 1q32. CR1 is a multifunctional glycoprotein expressed on many cells including dendritic cells [36]. The protein is involved in a number of functions including regulation of the complement cascade and clearance of immune complexes. In relation to AD, CR1 acts as a receptor for the Aβ-42 peptide removal from the brain and the circulatory system [22]. Thus, the *CR1* SNP may be responsible for modifying the rate of Aβ-42 clearance in AD patients [37].

The *PICALM* gene is located on chromosome 11q14 is involved in the production of Aβ peptide and linked to the formation of amyloid plaques and Aβ metabolism [38]. The PICALM protein is involved in clathrin-mediated endocytosis. A recent study replicated GWAS findings with 2816 AD and 2706 control subjects in a European population [22] and confirmed that the T allele was associated with AD risk. *PICALM* risk (T/T) homozygotes have been associated with decreased cerebrospinal fluid Aβ-42 levels and therefore increased Aβ-42 levels in the brain [39]. A meta-analysis reported that *PICALM* interacts with *APOE* such that *APOE* ε4 risk carriers with the *PICALM* risk genotype are at increased AD risk [9]. Similarly, a recent study reported interaction effects for *PICALM* rs3851179 risk and *APOE* ε4+ leading to changes in brain atrophy and cognitive performance in AD [40].

The three AD-related SNPs have also independently been associated with accelerated cognitive decline in healthy older adults. Specifically, a faster rate of memory decline in older adults was observed for *PICALM* risk carriers [41], *CLU* risk carriers who eventually converted to MCI or AD [42], and *CR1* risk carriers as mediated by amyloid plaque burden [43]. Although identified and confirmed in large GWAS and examined in single candidate gene association studies with normal cognitive performance [42,43], the neurobiological underpinnings for the synergistic effect of *CLU*, *CR1*, and *PICALM* on cognitive trajectories in non-demented aging has not yet been studied. *CLU*, *CR1*, and *PICALM* broadly represent three distinct processes (cholesterol metabolism, immune response, endocytosis) in the brain [30] and all been linked to Aβ metabolism and production, and cognitive decline in older adults at risk for dementia.

Complex neurocognitive phenotypes observed in non-demented older adults may be a result of select combinations of genes associated with AD and those linked with cognitively normal aging. Network-based approach incorporating interactions between cognitive aging and AD genes may provide insight into specific AD disease mechanism and molecular interactions in preclinical decline [12]. Although inconsistent in their independent effects, select combinations of *COMT* and *BDNF* polymorphisms have been shown to play a magnifying role in predicting the extent of neurocognitive deficits observed among groups of non-demented older adults [44–46]. *COMT* homozygotes and carriers of the risk allele (G/G, G/A) have lower dopamine levels in the prefrontal cortex [47]. *BDNF* homozygotes and carriers of the risk allele (A/A, A/G) secrete lower levels of neurotrophic factors, particularly in the hippocampus [48]. In two previous studies [11,49], we established an additive (*COMT* + *BDNF*) Cognitive Aging Genetic Risk Score (CA-GRS). We observed a significant additive effect (and no interactive associations) between *COMT* and *BDNF*, where higher CA-GRS was associated with poorer EF decline. This implies additive pathways for cognitive aging SNPs (i.e., *COMT* and *BDNF*) where eliminating one risk factor does not reduce the risk associated with the other allelic risk. The CA-GRS effect was further modified by *APOE* genotype, where *APOE* ε4 carriers displayed poorer EF performance with increasing CA-GRS. EF risk associated with increasing CA-GRS may be especially magnified for older adults who are carriers of a notable genetic risk allele for cognitive impairment and AD [11].

Recent genetic reports on AD and cognitive impairment have involved (1) single candidate genes, (2) genetic risk scores, and (3) network of molecular and pathway analysis of genetic variants. AD genetic network based approaches focus on using large molecular networks [50] to identify and understand specific AD-related biological functions. For example, recent network approaches include (1) co-expression networks (gene-gene correlations), (2) genetic integration (protein-protein interactions), (3) tissue specificity (network for tissues associated with AD), (4) robustness (strength in patterns of gene co-expressions in specific regions) [51,52], (5) network-based stratification (protein-protein interaction to stratify patients and identify disease molecules within the network), (6) analysis of directed networks (predicts specific signals), and (7) disease state-specific networks (networks that are only significant in specific disease states) [12,51,52]. The present network analysis represents a combination of three genetic risk clusters integrated by elements of both network-based stratification and disease state-specific network approaches. Specifically, we

examine the interaction between an Alzheimer's disease-Genetic Risk Score (AD-GRS) and a CA-GRS as modified by *APOE* genotype. The target phenotype is EF performance (level and trajectories) in non-demented older adults. We examine select group of cognitive aging and AD risk alleles that may work in synergy to magnify cognitive decline in non-demented older adults. To date, previous work with additive risk panels [53,54] have been examined independently and lack integration with complex interactive networks between additive panels commonly linked to AD independently, in risk panels, and mechanisms related to cognitive impairment.

Genetic risk scores for AD and cognitive impairment risk have included varying number and types of polymorphisms. AD genetic risk scores have been associated with increased risk of late life cognitive impairment [55], AD risk [56], greater risk of conversion from MCI to AD [54,57,58], and discriminating an AD group from controls [59]. Research on genetic risk approaches have used several procedures for calculating risk scores. For example, prior studies have used an explained variance-weighted genetic risk score [60], an odds ratio weighted risk score [53,54], large number of SNPs to create a polygenic risk score [61,62], weighted sum of the top risk scores [56], and an additive allelic risk score [11,53,63].

Although previous studies have focused on a variety of methods to create AD genetic risk scores, the results have been incomplete with potential biases [12]. Previous reports have not examined interactive and modification effects with AD and cognitive aging genetic risk scores to predict non-demented cognitive change. In the present study, we focus on predicting actual trajectories of non-demented cognitive change, not the outcome of AD diagnosis. AD genetic risk is one important component, but not the only source, of genetic prediction of preclinical cognitive decline or impairment. We therefore design a test of a "network" approach that combines not only AD risk genes but also brain/cognitive decline risk genes that, in combination or interaction, may magnify cognitive decline and impairment in non-demented older adults. Accordingly, we examine interactions between sets (or panels) of genotypes that could intensify their effects on cognitive trajectories. Specifically, we select three components: (1) a genetic cognitive aging risk panel (*COMT + BDNF*), (2) a targeted set of relatively well-known AD risk genes for an AD genetic risk panel (*CLU + CR1 + PICALM*) and (3) the best-known and predominant AD risk gene (*APOE*) as modifier. We then test the interactions among these three genetic risk components, with *APOE* playing the special role of modifier. Regarding *APOE*, we elected to stratify *APOE* ε4− and ε4+ because AD and cognitive aging genes may differentially influence the mechanisms in these two groups. We select these specific genetic risk factors as previous research has accumulated considerable information on associated mechanisms (often as independent or candidate gene predictors) so that we could both (1) provide a strong test of potential genetic network effects and (2) propose mechanisms that underlie them and promote future research with this approach and on these mechanisms. In our own previous research [11], we have been investigating all of the genes (and their possible mechanisms and interactions) we examine in this research report, building to the point that we can now examine whether their influence on non-demented cognitive trajectories can be modelled as a network largely influenced by selected sets of AD-related and cognitive-aging-related risk genes.

In designing the present study, we acknowledged and adapted several important methodological and mechanistic contributions from both candidate gene approaches and basic gene x gene interaction approaches. Our network approach included a sequence of interactions between two clusters of aging and AD genetic risk, as modified by *APOE*, in the context of predicting differential cognitive trajectories over a 40-year band of aging. Specifically, we examined a sequence of interactions between two additive panels of genetic risk factors for AD (*CLU* + *CR1* + *PICALM*) and accelerated cognitive decline (*COMT* + *BDNF*) as modified by *APOE* ε4 status. The sequence represents a network of genetic effects in cognitively normal older adults. To our knowledge, the present study is the first to examine a genetic network approach to examine (1) synergistic associations between clusters of AD (AD-GRS) and cognitive aging (CA-GRS) genes (2) as modified by *APOE* genotype (ε4− vs ε4+) (3) to predict EF trajectories (4) in non-demented older adults. We expect to observe that *APOE* ε4 carriers with interactive associations of higher CA-GRS and higher AD-GRS show poorer EF performance and steeper 9-year decline than their counterparts with lower CA-GRS and lower AD-GRS, and those who are in the *APOE* ε4− group.

Method

Participants

We used data from the Victoria Longitudinal Study (VLS), a large-scale, longitudinal sequential study examining biomedical, health, genetic, lifestyle, cognitive and other aspects of aging. General information on recruitment, methodological, and VLS characteristics are available elsewhere [64]. All volunteers in the VLS were cognitively normal (non-demented) and relatively healthy, with no reported brain-related serious conditions. They were enrolled through advertisements, and received a small honorarium for their participation. The VLS and all present data collection procedures are in full and certified compliance with prevailing human/institutional research ethics guidelines. Written informed consent was obtained from all participants. Approximately 99.2% of participants were White, not of Hispanic Origin. All had complete access to Canadian national health care. At baseline, all recruited VLS participants are cognitively normal (no dementia) and followed over time as they develop impairment or dementia. For the present study, we ensured a non-demented sample by applying a set of exclusionary criteria (including diagnosis of AD or neuropsychiatric disorder or Mini Mental State Exam (MMSE) score < 24). The present sample reflects the implementation of exclusionary criteria affecting individuals with (a) diagnosis of dementia, (b) anti-psychotic medication, (c) MMSE scores less than 24, (d) uncontrolled hypertension, (e) insulin-controlled diabetes, and (f) history of serious head injury (e.g., hospitalized). Accordingly, 634 participants (age range = 53–95 years, mean age = 70.58, SD = 8.65), including 423 females and 211 males with genetic data were included at baseline (Table 1). We followed an accelerated longitudinal design by assembling three partial samples (S; S1, S2, S3) from the VLS. The present Wave 1 (W1) and Wave 2 (W2) included participants from all three samples and Wave 3 (W3) included participants from S3. Specifically, throughout this report (a) W1 (n = 632) refers to S1W6, S2W4, and S3W1, (b) W2 (n = 517) refers to S1W7, S2W5, S3W2, and (c) W3 (n = 293) refers to S3W3. The average interval

was 4.4 years between W1 and W2, and 4.5 years between W2 and W3. The retention rates for each wave interval ranged between 74% and 88%.

DNA Extraction and Genotyping

Saliva was collected according to standard procedures from Oragene DNA Genotek and stored at room temperature in Oragene® disks until DNA extraction. DNA was manually extracted from 0.8 ml of saliva sample mix using the manufacturer's protocol with adjusted reagent volumes. Genotyping was carried out by using a polymerase chain reaction-restriction fragment length polymorphism strategy to analyze the allele status for *CLU* (rs11136000), *CR1* (rs6656401), *PICALM* (rs3851179), *BDNF* (rs6265), *COMT* (rs4680), and *APOE* (rs7412, rs429358). Genotyping was successful for the targeted SNPs for all present participants. The genotype frequencies did not differ significantly from Hardy-Weinberg equilibrium for: *BDNF* ($\chi^2 = 0.868$, $p = 0.35$), *COMT* ($\chi^2 = 2.909$, $p = 0.08$), *APOE* ($\chi^2 = 0.189$, $p = 0.66$), and *CLU* ($\chi^2 = 0.710$, $p = 0.40$). We note that the *CR1* ($\chi^2 = 6.219$, $p = 0.01$) and *PICALM* ($\chi^2 = 36.955$, $p = 0.00$) genotype frequencies were not in Hardy-Weinberg equilibrium.

Executive Function Measures

Two dimensions of EF (inhibition, shifting) were each measured by two standard and frequently used tests for cognitive, clinical, and neurobiological studies in older adults [14,49,65,66].

Hayling Sentence Completion (Inhibition)—This test [67] consists of two sections, each comprising 15 sentences. The standardized scores are based on errors from the second of two sections and the speed of each response from both sections, which are then combined to obtain the final score (1 = very low to 10 = very high).

Stroop (Inhibition)—This test [68] consists of the standard three parts (Parts A, B and C), with the measures based on latencies. The score is the standardized Stroop interference index ([Part C− Part A]/Part A), with a lower index reflecting better performance.

Brixton Spatial Anticipation (Shifting)—This test [67] consists of 10 different circles, one being blue, whereas the rest are colorless. Participants are asked to guess where the blue colored circle will appear on subsequent pages. The total number of incorrect guesses are measured and the final scores are calculated (1 = very low to 10 = very high).

Color Trails (Shifting)—This test [69] comprises two different sections in which participants connect different attributes, such as numbered and colored circles. Latency scores in the second of two sections were computed and used in the final analyses. Lower scores reflected better performance.

Statistical Analyses

Structural equation modeling (SEM) was used for all analyses with Mplus Version 7 [70]. All missing values for cognitive measures were assumed to be missing at random and estimated using maximum likelihood. Cases with missing predictor values were removed

using list-wise deletion in Mplus 7. Age was centered at 75 years because aging related changes in many cognitive domains are not visible until 75 years [71]. Only two participants with missing measures on all four EF tasks were lost due to list-wise deletion. Preliminary analyses were examined to obtain EF factor scores and the best latent growth model (see supplementary materials).

The *APOE* ε4− group was coded as 0 (lower risk) and *APOE* ε4+ group as 1 (higher risk). All ε2/ε4 carriers (n = 30) were deleted [10,11]. *APOE* ε4− and ε4+ groups were separated and examined for effect modification by *APOE*. The AD-GRS [53,54,72] was calculated in three steps. First, we dichotomized *CLU* (risk: C/C, C/T; no risk: T/T), *CR1* (risk: A/A, A/G; no risk: G/G), and *PICALM* (risk: T/T, T/C; no risk: C/C) into no risk (0) and risk (1) groups. Second, we summed across *CLU*, *CR1*, and *PICALM* to obtain a score for each adult ranging from 0–3. Third, we performed a median split [53] for this score and grouped the *CLU* + *CR1* + *PICALM* allelic risk score by low (0–1 risk allele) and high (2–3 risk allele) genetic risk. The CA-GRS was calculated using all three allelic combinations (A/A, A/G, and G/G) of *COMT* and *BDNF*. Both SNPs were coded from 1 to 3 (3 = highest risk) and summed across *COMT* and *BDNF* to obtain the CA-GRS ranging from 2–6.

EF was regressed on CA-GRS as moderated by low and high AD-GRS. This analysis was performed twice, for the *APOE* ε4− group and the *APOE* ε4+ group. We expected that sex differences may modify the effects of genetic risk on EF performance and decline [73]. Therefore, sex was included as a covariate in both group analyses. We accounted for variability associated with age by directly incorporating age as the metric of change in our analyses. For model fit statistics and significant results, we examined the regression estimate and $p < .05$, and −2 log likelihood (−2LL), Akaike information criteria (AIC), and Bayesian information criteria (BIC) values with lower values indicating better model fit (see Table 2).

Results

In our preliminary analyses and results (see supplementary materials) for the EF factor analysis and growth modeling, we established that the one-factor parsimonious model of EF provided the best fit to the data [74] and met partial scalar longitudinal invariance (see Supplementary Table 1). To obtain partial scalar invariance, we first need to meet configural invariance (all four indicators load on to the EF factor) and metric invariance (unstandardized EF factor loadings at all three waves are equal to each other). Partial scalar invariance is obtained when two out of the four EF indicator intercept were constrained to be equal across all three waves. The best latent growth model was obtained with the random intercept and random slope model (see Supplementary Table 2). This model shows that adults vary in their EF intercept (at age 75 years) and EF slope over time (9 years). In the present study, we extended our previous findings [11] and observed two novel genetic network associations with cognitive aging and AD genes. We observed that poorer EF performance at age 75 years with increasing CA-GRS in *APOE* ε4 carriers is (1) moderated by AD-GRS and (2) significant EF decline over 9 years is observed only when AD-GRS is included in this complex genetic network (Figure 1). Specifically, *APOE* ε4 carriers in the high AD-GRS group showed poorer EF performance at age 75 years ($\beta = -0.396$; SE = 0.151; $p = .009$) and steeper 9-year decline ($\beta = -0.015$; SE = 0.007; $p = .045$) with

increasing CA-GRS (Figure 1B). Poorer EF performance at age 75 years or steeper 9-year decline was not observed in: (1) *APOE* ε4 carriers with low AD-GRS (Figure 1A); (2) the *APOE* ε4− group with high AD-GRS (Figure 1D); and (3) the *APOE* ε4− group with low AD-GRS (Figure 1C). We did not observe that sex (as a covariate) influenced the CA-GRS and AD-GRS interactive association on EF performance and change in either the *APOE* ε4− or *APOE* ε4+ group. CA-GRS effect on EF performance and change was selective and only present in *APOE* ε4 carriers with high AD-GRS.

Discussion

We examined a network approach to test AD and cognitive aging genetic effects on cognitive trajectories in preclinical aging. We tested interactive and effect modification of cognitive aging genetic risk factors [11] and clinically pertinent clusters of AD genetic risk factors [30] associated with lipid transport, inflammation, and endocytosis important in neuronal and synaptic changes in the brain. Specifically, whether an AD-GRS interacts with a CA-GRS as stratified by *APOE* risk status to differentially predict EF performance and change across a 40-year age band in non-demented older adults. We observed that the cumulative effect of high allelic risk in the AD-GRS magnifies the risk associated with increasing CA-GRS selectively for *APOE* ε4 carriers. This is the first study to show interactive effect of select AD and cognitive aging SNPs on EF trajectories as modified by *APOE* ε4 status. This finding advances the field on genetic and neurocognitive associations in preclinical aging by showing that network-related genetic associations may (1) lead to early detection of older adults most vulnerable or at high risk of cognitive impairment or dementia and (2) promote our understanding of the underlying genetic and molecular networks involved in preclinical cognitive impairment and potential risk of AD disease pathogenesis.

In a previous cognitive aging genetic risk panel study [11], we established a CA-GRS using *COMT* and *BDNF.* Both have been implicated in normal cognitive aging [46] and are thought to influence each other through basal ganglia-thalamocortical loops [75]. We observed poorer EF performance at centering age 75 and no significant 9-year change with increasing CA-GRS in *APOE* ε4 carriers. In the present study, we extended these results by identifying a complex interactive genetic network with AD-GRS and CA-GRS as modified by *APOE* ε4 genotype to predict EF performance and change. Our key finding is that the effect of *APOE* ε4 allelic risk on EF trajectories in non-demented aging is exacerbated via interactive effects of high AD-GRS and high CA-GRS. Specifically, *APOE* ε4 carriers in the high AD-GRS group had poorer EF performance at age 75 years and significantly steeper 9-year decline with increasing CA-GRS (Figure 1B). Compared to the high AD-GRS group, *APOE* ε4 carriers with low AD-GRS had poorer EF performance and were declining overall irrespective of their CA-GRS (Figure 1A). Whereas *APOE* ε4− group with high or low AD-GRS (Figure 1C–1D) did not show the same vulnerable pattern of poorer EF performance and steeper 9-year decline with increasing CA-GRS. Future studies focusing on the molecular underpinnings of cognitive decline and impairment should consider interactive effects of cognitive aging genes in conjunction with AD genes to detect subtle changes and intricate genetic networks effects in preclinical phenotypes.

Recent studies are starting to combine omics data into multi-scale models to examine networks associated with AD-related risk factors [12]. A recent study applied a systems biology approach to examine common pathways and molecular networks among AD related genes. Three inter-connected pathway modules (neuronal and metabolic; cell growth/survival and neuroendocrine; immunological cluster) were identified [50]. Identifying genes involved in the same pathways will contribute to our understanding of how select clusters of genes operate to influence neurocognitive phenotypes associated with cognitive impairment and AD. Although the molecular pathways underlying the genetic network in our study require detailed mechanistic studies, we propose a potential process through which the three genetic combinations (*APOE*, AD-GRS, CA-GRS) may work together to magnify cognitive decline in *APOE* ε4 carriers with the high AD-GRS and high CA-GRS. First, *APOE* ε4 carriers may have decreased synaptic function, axonal growth, Aβ clearance, hippocampal dendrites, cholesterol metabolism, and mitochondrial function. They also may show greater medial temporal lobe atrophy, mostly around the hippocampus, accelerated loss in cortical thickness and hippocampal volume that is correlated with cognitive decline [17]. Second, increases in CA-GRS (*COMT* + *BDNF* allelic risk panel) are associated with lower dopamine levels in the prefrontal cortex [47] or lower neurotrophic factors [48] in the hippocampus that may influence each other through the basal ganglia thalamocortical loops [75]. This implies that higher CA-GRS may lead to poorer EF performance and steeper decline in non-demented aging [11] due to lower dopamine levels or lower neurotrophic factors.

Third, the additive effect of all three polymorphisms in the AD-GRS (*CLU* + *CR1* + *PICALM* allelic risk panel) and their respective pathologies may lead to magnified risk for reductions in amyloid clearance and increases in brain atrophy, both of which are typically observed in older adults with cognitive impairment or dementia. Briefly, CLU is involved in cholesterol transport and binds to Aβ. The CR1 protein plays a role in inflammation especially in AD patients. PICALM influences neurotransmitter release at presynaptic terminals [30,76]. Furthermore, CLU protein levels are also higher in the frontal cortex and hippocampus of postmortem AD patients [77]. For example, older adults with low AD-GRS may be at a decreased risk of amyloid deposition, and lower dopamine levels (*COMT* risk allele in the CA-GRS) may not lead to poorer EF performance in the *APOE* ε4− group. Whereas, in the *APOE* ε4+ group, lower dopamine levels may result in steeper EF decline with risk intensification from high AD-GRS. Fourth, APOE and CLU show similar physiological and functional properties (e.g., molten globule structures and differences in CLU levels in the frontal cortex among *APOE* ε4 carriers versus non-carriers) [34] and this may partially explain the moderation observed among *APOE* ε4 carriers for low and high AD-GRS. In addition, reduced APOE levels in the hippocampus and frontal cortex and increased CLU levels are associated with increasing *APOE* ε4 allele dose [78].

In the present study, we observed a network-based interactive effect between two sets of genetic risk scores (CA-GRS and AD-GRS) on EF trajectories selectively for *APOE* ε4 carriers. *APOE* isoforms have previously been associated with the timing, location, and amount of amyloid beta deposition and clearance in the brain parenchyma and vasculature which may trigger a chain of pathological events resulting in AD [79]. Overall, poor central nervous system functioning (for *APOE* ε4 carriers) as moderated by rate of amyloid

clearance, efficient synaptic transmission, and amount of brain atrophy (*CLU* + *CR1*+ *PICALM*), may change the influence of lower dopamine levels or neurotrophic factors (*COMT* + *BDNF*) on EF performance in non-demented aging. Future research may use this and similar network approaches (e.g., [12]) to (1) test other dementia and cognitive aging polymorphisms using varying combinations of interactive, additive, and effect modifications, (2) extend the networks to include other modalities of AD biomarkers (e.g., molecular, brain), and (3) replicate our findings to identify subpopulations of specific risk profiles that may be targeted for precision clinical interventions to delay cognitive impairment. In addition, this work suggests that some future AD clinical trials may benefit from including not only *APOE* [80], the most prominent AD genetic risk factor, but also a selected subset of other AD risk genes (such as *CLU*, *CR1*, and *PICALM*) to (1) improve precision in the determination of risk for cognitive decline and dementia and (2) promote efficient and effective evaluation of intervention outcomes.

We note several limitations of the present study. First, at present the VLS database does not include all SNPs linked with either AD or cognitive aging. Some recent and important ones are not available (e.g., *Bridging Integrator 1*, *Triggering Receptor Expressed on Myeloid Cells 2*). Future studies may benefit from genetic risk scores (AD-GRS and CA-GRS) that include contributions from additional SNPs. Second, the subset of VLS data we assembled did not feature full representation of three waves for all participants. Some were in data collection samples that have not been completed. However, we used maximum likelihood to estimate missing EF factor scores. Maximum likelihood uses all available data to identify and generate population parameter estimates that have the highest probability (log likelihood) [81]. In addition, some other features of the design were corresponding strengths, including the sample size (n = 634) and the coverage of a 40-year band of non-demented aging. Third, we focused on EF, to the exclusion of other important domains of cognition. Although this was reasonable, given the domain-specificity of many genetic-cognition associations in aging, future studies should validate this approach and these results with other cognitive domains (i.e., episodic memory, speed). Fourth, the present network approach is based on genetic markers, but could be extended to multi-modal biomarkers, such as cerebrospinal fluid-based and neuroimaging markers in similar designs. Fifth, although sex as covariate did not influence our models, future studies should consider examining sex differences for differential patterns in other complex multimodal network associations with preclinical phenotypes [82]. We note two additional strengths. First, the longitudinal design and analyses featured age as the metric of change. This allowed us to incorporate chronological age directly into our analyses [11] to account for EF variability associated with age. This approach is better than if age were included as a covariate and allowed us to examine EF change across a 40-year band of aging. Second, we used four standard neuropsychological tests that contributed to one EF latent variable. The latent modeling approach is representative of the overall EF construct and accounts for measurement error commonly present with single cognitive tests.

APOE ε4 carriers who were at additional AD risk (due to higher scores on the AD-GRS) and also had higher risk for cognitive decline (indicated by the CA-GRS) performed selectively worse on an EF latent variable at the intercept (age 75) and produced steeper 9-year longitudinal decline. This result was interpreted as both biologically feasible and

selective, in that it did not appear for other tested networks of genetic risk. SNPs identified in AD GWAS studies may (1) work via select clusters of additive risk scores (AD-GRS), (2) in interaction with cognitive aging risk scores (CA-GRS), and (3) as stratified by *APOE* ε4 status to alter preclinical cognitive aging. Future research should examine the underlying molecular pathways involved in this or similar complex genetic networks as they predict cognitive trajectories and outcomes in non-demented aging. Such network analyses may lead to precision approaches for early detection and individualized intervention programs to identify older adults at higher and lower risk for accelerated decline or dementia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The present research is supported by grants to Roger A. Dixon from (a) the National Institutes of Health (National Institute on Aging; R01 AG008235), (b) Alberta Health Services (University Hospital Foundation) (to David Westaway, Jack Jhamandas, and Roger Dixon), and (c) the Canadian Consortium on Neurodegeneration in Aging (CCNA) (with funding from the Canadian Institutes of Health Research and partners, including SANOFI-AVENTIS R&D). RAD is also supported by the Canada Research Chairs program. SS is also supported by the CCNA/ Alzheimer Society of Canada Postdoctoral Fellowship. The funding sources did not have a role in the study design, data collection, statistical analysis, results interpretation, report writing, or submission decisions. SS is now at Sunnybrook Health Sciences Centre.

We thank the volunteer participants and the VLS staff for their many contributions. More information about the VLS may be found at: http://www.ualberta.ca/~vlslab/.

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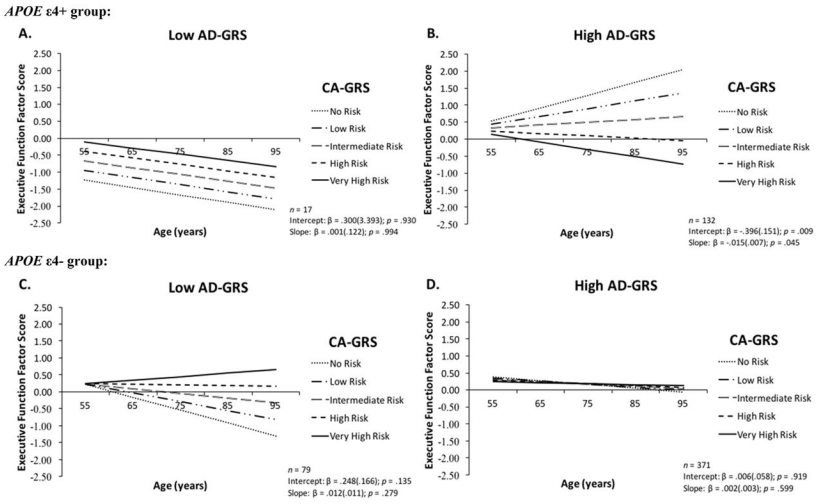

Figure 1.

Increasing risk associated with Cognitive Aging-Genetic Risk Score [CA-GRS: *Catechol-O-methyltransferase* + *Brain-derived neurotrophic factor*] was magnified by high Alzheimer's disease-Genetic Risk Score [AD-GRS: *Clusterin* + *Complement receptor 1* + *Phosphatidylinositol-binding clathrin assembly protein*] selectively in *Apolipoprotein E* (*APOE*) ε4 carriers. (A) *APOE* ε4 risk carriers with low AD-GRS showed overall poorer EF performance and same rate of 9-year decline regardless of CA-GRS; (B) *APOE* ε4 risk carriers with high AD-GRS showed poorer EF performance at age 75 years and steeper 9-year decline with increasing CA-GRS; (C) *APOE* ε4− group with low AD-GRS did not show poorer EF performance at age 75 years or steeper 9-year decline with higher CA-GRS; (D) *APOE* ε4− group with high AD-GRS showed similar EF performance at age 75 years and 9-year decline for all levels in the CA-GRS.

Table 1

Participant characteristics by genotype.

	COMT				***BDNF***				***APOE***		
	A/A	**A/G**	**G/G**	***p*-value**	**G/G**	**A/G**	**A/A**	***p*-value**	**ε4-**	**ε4+**	***p*-value**
n	146	336	150	--	416	189	27	--	453	149	--
Age (years)	70.15 (8.86)	70.82 (8.69)	70.40 (8.39)	0.709	70.30 (8.82)	71.45 (8.52)	68.54 (6.32)	0.145	70.89 (8.84)	69.86 (8.27)	0.212
Education (years)	14.92 (3.11)	15.36 (2.80)	15.36 (3.15)	0.294	15.29 (2.96)	15.13 (2.99)	15.72 (2.70)	0.585	15.19 (2.97)	15.55 (3.07)	0.208
Sex (F/M)	101/45	225/111	96/54	0.637	276/140	128/61	18/9	0.946	304/149	93/56	0.295
MMSE	28.72 (1.20)	28.72 (1.20)	28.56 (1.32)	0.390	28.62 (1.28)	28.74 (1.15)	29.15 (0.77)	0.071	28.66 (1.24)	28.68 (1.25)	0.914
	CLU			***CR1***			***PICALM***			**Total**	
	T/T	C+	*p*-value	G/G	A+	*p*-value	C/C	T+	*p*-value		
n	103	527	--	213	417	--	151	478	--	632	
Age (years)	70.65 (8.11)	70.55 (8.75)	0.982	70.30 (8.90)	70.70 (8.52)	0.854	69.42 (8.69)	70.95 (8.59)	0.129	70.56 (8.65)	
Education (years)	14.92 (2.80)	15.33 (2.98)	0.182	15.41 (3.02)	15.19 (2.92)	0.282	15.52 (2.93)	15.18 (2.97)	0.310	15.26 (2.96)	
Sex (F/M)	65/38	355/172	0.428	137/76	283/134	0.408	96/55	323/155	0.314	422/210	
MMSE	28.71 (1.12)	28.68 (1.25)	0.387	28.76 (1.27)	28.65 (1.20)	0.222	28.69 (1.24)	28.68 (1.22)	0.356	28.68 (1.23)	

Abbreviations: n = total number; *COMT = Catechol-O-methyl transferase; BDNF = Brain-derived neurotrophic factor; APOE = Apolipoprotein E; CLU = Clusterin; CR1 = Complement receptor 1; PICALM = Phosphatidylinositol-binding clathrin assembly protein; p* < .05; MMSE = Mini-Mental State Exam; Standard deviations are in parentheses.

Table 2

Cognitive Aging-Genetic Risk Score (CA-GRS) effect model estimates for low and high Alzheimer's disease-Genetic Risk Score (AD-GRS) as separated by *APOE* ε4− and ε4+ groups.

	Intercept			Slope			Model Fit Statistics				
	β	SE	*p*	β	SE	*p*	H0 value	Free Parameters	−2LL	AIC	BIC
***APOE* ε4− group**							−1432.04	32	2864.08	2928.08	3059.58
Low AD-GRS: CA-GRS	0.248	0.166	0.135	0.012	0.011	0.279					
Low AD-GRS: Sex	0.031	0.284	0.912	−0.004	0.017	0.797					
High AD-GRS: CA-GRS	0.006	0.058	0.919	0.002	0.003	0.599					
High AD-GRS: Sex	−0.207	0.118	0.080	−0.011	0.006	0.050					
***APOE* ε4+ group**							−490.72	32	981.44	1045.43	1141.56
Low AD-GRS: CA-GRS	0.300	3.393	0.930	0.001	0.122	0.994					
Low AD-GRS: Sex	0.792	2.495	0.751	0.017	0.114	0.883					
High AD-GRS: CA-GRS	−0.396	0.151	0.009	−0.015	0.007	0.045					
High AD-GRS: Sex	0.058	0.239	0.808	0.002	0.012	0.853					

Abbreviations: Est. = regression estimate; SE = standard error; H0 = log likelihood; −2LL = −2 log likelihood; AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; *COMT = Catechol-O-methyltransferase; BDNF = Brain-derived neurotrophic factor; APOE = Apolipoprotein E; CLU = Clusterin; CR1 = Complement receptor 1; PICALM = Phosphatidylinositol-binding clathrin assembly protein.* CA-GRS = *COMT* + *BDNF*; AD-GRS = *CLU* + *CR1* + *PICALM*.