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Executive Function Performance and Change in Aging is Predicted by *Apolipoprotein E*, Intensified by *Catechol-O-methyltransferase* and *Brain-derived neurotrophic factor*, and Moderated by Age and Lifestyle

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Abstract

Recent studies have reported several genetic, health, and aging interaction effects in predicting cognitive performance and change. We used an accelerated longitudinal design to examine interactions among genetic, lifestyle, and aging for executive function (EF) in non-demented older adults (n=634; age range=53–95 years). The polymorphisms were *Apolipoprotein E* (*APOE*), *Catechol-O-methyl transferase* (*COMT*), and *Brain-derived neurotrophic factor* (*BDNF*). We tested (a) independent and additive effects of *APOE*, *COMT*, and *BDNF* and (b) *APOE* effect modification for *COMT*+ *BDNF*, on EF performance and 9-year change as separated by age and lifestyle activities. First, *APOE* ε4+ carriers had poorer EF performance and steeper 9-year decline. Second, *APOE* ε4+ carriers with (a) *BDNF* Met/Met genotype and (b) increasing allelic risk in the *COMT*+ *BDNF* risk panel had poorer EF performance; these effects were moderated by lifestyle activities (composite of everyday social, physical, cognitive activities). Examining *APOE* effect modification for *COMT*+ *BDNF* risk panel effects with other moderating factors may help identify complex neurobiological and genetic underpinnings of polygenic phenotypes such as EF in aging.

Keywords

Aging; Executive Function; *Apolipoprotein E*; *Catechol-O-methyl transferase*; *Brain-derived neurotrophic factor*; Victoria Longitudinal Study

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Disclosure Statement

All authors confirm that there is no actual or potential conflict of interest. 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.

1. Introduction

Research on biological and genetic markers of non-demented cognitive aging is in a transitional phase. Single candidate biomarker or gene association studies have produced encouraging but inconsistent associations with such prominent cognitive aging phenotypes as memory and executive functions (EF) (Harris & Deary, 2011; Laukka et al., 2013). Several recent observations provide promising and converging research directions for genetic marker research in non-demented aging. These observations include: (a) single gene-related individual differences in cognitive ability may increase in aging (Das et al., 2014; Deary et al., 2010); (b) genetic associations with cognitive phenotypes may be magnified as neurological resources decline (Belsky et al., 2009; Lindenberger et al, 2008); (c) cognitive phenotypes may be profitably measured with multiple indicators as they change over time (McFall et al., 2015a; Raz et al., 2009), and (d) biomarker predictors may be measured in terms of neurobiologically reasonable interactions, panels, or composites (Sapkota et al., 2015). Accordingly, some recent research has focused on identifying sets of genetic and other factors that may tap into underlying neurobiological mechanisms and thereby complement, modify, or intensify effects on cognitive changes with aging (McFall et al., 2015b). These changes may be differential, including patterns consistent with maintenance (McFall et al., 2015a; Nyberg et al., 2012), non-demented decline (Harris & Deary, 2011; Raz et al., 2009), and impairment (Dixon et al., 2014). Although the relevant research designs are sometimes complex, they afford the opportunity for examining interactions among concordant genetic variants and non-genetic biological and environmental risk factors as they predict longitudinal variations in cognitive trajectories and clinical outcomes (Thibeau et al., 2016). The present study contributes to this effort by including two typical cognitive aging polymorphisms, one prominent Alzheimer's disease (AD) genetic risk variant, age, and environmental (lifestyle) factors— all in the context of longitudinal change in cognitive performance.

We focus on the cognitive domain of EF, which represents everyday goal-oriented performance (de Frias et al; 2006; de Frias et al., 2009; Luszcz, 2011). Some recent genetic studies of EF in non-demented aging have concentrated on two commonly examined dopaminergic- and neurotrophic-related variants (Das et al., 2014; Harris et al., 2006; Nagel et al., 2008; Sapkota et al., 2015) that may interact through basal ganglia-thalamocortical loops (Alexander et al., 1986). The single nucleotide polymorphisms (SNPs) identified for dopaminergic and neurotrophic-related factors include *catechol-O-methyltransferase* (*COMT*; rs4680) (Papenberg et al., 2014; Papenberg et al., 2015b; Wishart et al., 2011) and *brain-derived neurotrophic factor* (*BDNF*; rs6265) (Ghisletta et al., 2014; Nagel et al., 2008), respectively. In an earlier cross-sectional study, we observed synergistic associations between these two polymorphisms as they predicted concurrent EF performance (Sapkota et al., 2015). *COMT* and *BDNF* were selected because of the neurobiological and cognitive relationship of both genes (Nagel et al., 2008). *COMT* and *BDNF* have shown to influence the prefrontal and medial temporal lobe regions (Bertolini et al., 2006), which are both activated during EF tasks (Cabeza et al., 2003). Perhaps the most commonly considered polymorphism in cognitive and neurodegenerative aging is *Apolipoprotein E* (*APOE*; rs7412; rs429358). The *APOE* ε4 allele has been consistently linked to normal cognitive decline (Caselli et al., 2001; Laukka et al., 2013; Luciano et al., 2009; Wisdom et al., 2011), Mild Cognitive Impairment (MCI) (Brainerd et al., 2011; Dixon et al., 2014), and dementia (Barral et al., 2012). The role of *APOE* in cognitive aging may be pivotal in that it interacts with other genetic variants, as well as with health, lifestyle (e.g., physical activity), and neurobiological risk factors (McFall et al., 2016). In the present study, we extend our earlier cross-sectional report by assembling new 3-wave longitudinal data to test specific dynamic synergies among genetic markers (*APOE* plus *COMT* and *BDNF*) as moderated by age and lifestyle behaviors. Interactively, these factors are expected to shed light on mechanisms associated with EF change in brain aging. Specifically, we examine independent and additive effects of *APOE*, *COMT*, and *BDNF*. In addition, we test for an *APOE* moderation effect for *COMT* and *BDNF*, and *APOE* effect modification for *COMT* + *BDNF*. An *APOE* moderation would be observed when the *APOE* genotype interacts or influences the effect of *COMT* or *BDNF* on EF performance. An *APOE* effect modification would be observed if there is, as expected, a differing relationship of (*COMT* + *BDNF*) on executive functioning in the context of *APOE* stratification (i.e., ε4+ versus ε4- groups). According to the brain-resource modulation hypothesis (Lindenberger et al., 2008; Papenberg et al., 2015a), genetic effects may be magnified in late adulthood, as compared with earlier adulthood. Therefore, our dynamic synergistic analyses involves both the overall sample ($n = 634$; age range = 53–95 years) and as stratified by age group. Furthermore, some research has shown that lifestyle activity engagement (e.g., physical, cognitive, and social activities) can affect EF performance (Erickson, et al., 2008). For this reason, we test the moderating effects of a lifestyle activity composite on the synergistic associations of the genetic variants and potential magnification by chronological age on longitudinal trajectories of EF performance in a 40-year band of non-demented aging.

Our approach to predicting EF performance and change includes examining independent and additive associations for *APOE*, *COMT*, and *BDNF* genetic risk as moderated by age and lifestyle risk factors. The additive (gene + gene) model tests panels of risk, whereby an additional allelic risk may amplify the vulnerability already present with one risk allele (Sapkota et al., 2015; Verhaaren et al., 2013). The four main steps are as follows. First, we examine independent effects of *APOE*, *COMT*, and *BDNF* as moderated by age group and lifestyle activities. Second, we test *APOE* moderation for *COMT* and *BDNF* on EF performance and 9-year change. Third, we test whether a set of additive effects (i.e., *APOE* + *COMT*, *APOE* + *BDNF*, *COMT* + *BDNF*) separately and as moderated by age group and lifestyle activities influence EF performance and decline. Fourth, we test whether an additive effect for *COMT* + *BDNF* is modified by *APOE*. We now summarize the three polymorphisms as related to cognitive functioning in aging.

APOE is the most commonly studied genetic risk factor for AD and MCI (Brainerd et al., 2011; Dixon et al., 2014; Verghese et al., 2011). It is differentiated by three isoforms: ε2, ε3, and ε4. Carriers of the ε4 allele have a higher risk of AD development (Wisdom et al., 2011). In contrast, the ε2 allele has been found to be protective in numerous studies (Corder et al., 1994; de-Almada et al., 2012; McFall et al., 2015a; Panza et al., 2000). *APOE* is involved in transporting cholesterol to neurons, which is crucial for synaptic formation and axonal growth important in learning, memory, and neuronal injury repair. In addition, the *APOE* genotype presents an allelic dosage effect whereby the ε4/ε4 allele is associated with the highest risk followed by ε3/ε3 and ε2/ε2 (Liu et al., 2013). *APOE* ε4 allelic risk has been linked to lower dendritic spine density in the hippocampus and increased neuro-inflammation (Fotuhi et al., 2009; Liu et al., 2013). Current reports focus on synergistic associations of *APOE* with other biological (Das et al., 2014; Sapkota et al., 2015) and vascular-health (i.e., pulse pressure (McFall et al., 2015a)) risk factors.

The COMT enzyme regulates dopamine (DA) levels primarily in prefrontal cortex (Bilder et al., 2004; Chen et al., 2004; Papenberg et al., 2014). Multiple dopaminergic pathways in the prefrontal cortex (Raz et al., 2009) have been associated with EF processes (Bäckman et al., 2010). Because of lower enzymatic activity, the *COMT* polymorphism at codon 158 on chromosome 22q11 results in greater DA levels for *COMT* homozygotes for the Met allele as compared to Val allele homozygotes (Das et al., 2014; Egan et al., 2003). Carriers of the Val allele may thus be at higher risk for brain and cognitive deficits, including executive functioning (Das et al., 2014; Nagel et al., 2008; Sapkota et al., 2015; Wishart et al., 2011) and reduced white matter integrity (Papenberg et al., 2015b).

The *BDNF* (rs6265) Val66Met polymorphism located at 11p13 (Houlihan et al., 2009) is involved in BDNF secretion. BDNF is mostly present in hippocampus and prefrontal cortex, and may play an important role in memory (Miyajima et al., 2008), EF (Egan et al., 2003; Nagel et al., 2008; Sapkota et al., 2015), and cognitive plasticity (Poo, 2001). The *BDNF* Met allele is considered to be the higher risk allele as it is linked to lower levels of BDNF in the hippocampus and prefrontal cortex. However, *BDNF*-cognition association studies have reported an inconsistent pattern of results. For example, a meta-analysis examined 23 publications with a combined total of 7095 individuals and did not observe significant associations with any of the five most commonly studied phenotypes: general cognition, memory, EF, visual processing, and verbal fluency (Mandelman & Grigorenko, 2012). This meta-analysis was not focused on aging, and several known moderators of brain aging may affect observed *BDNF*-cognition associations in older adults. These include younger age and an active lifestyle. In aging, the latter may increase BDNF expression in the brain resulting in greater synaptic plasticity (Cotman & Berchtold, 2002) and reduced cognitive impairment (Erickson et al., 2012). This augmented effect in younger and higher lifestyle activities older adult groups may then lead to large detectable differences in cognitive performance and change, particularly for those with higher genetic risk combinations (Ward et al., 2014).

As applied to this study, a genetic magnification perspective suggests that more than one “copy” of a neurobiological aging risk factor may exacerbate the deleterious effects on phenotypes such as cognitive performance and change in aging. The sources of risk may be multimodal, including additional genetic risk, advanced biological aging, and low lifestyle activity. This study is a major longitudinal and predictor-related extension of an earlier cross-sectional report, which focused on determining the optimal operations for combining these variants (additive or multiplicative) in terms of examining synergistic effects of *COMT* and *BDNF* on EF in non-demented older adults (Sapkota et al., 2015). We adopt the additive operation combined with tests of moderation and effect modification by *APOE* and potential magnification by chronological age and lifestyle activities. We test magnification effects on longitudinal data across a 40-year band of aging. In addition, using a procedure established earlier (McFall et al., 2014), we measure EF as a single latent and invariant variable indicated by four standardized neuropsychological tests.

1.1. Research Questions

We examined two general research questions. For both, we predicted EF performance and 9-year change. Both general research questions were divided into two parts to represent the fact that two different ways of testing gene-cognition associations were stratified by age group, lifestyle activities, and *APOE* genotype. In general research question 1, we tested independent associations of *APOE*, *COMT*, and *BDNF*. In general research question 2, we tested additive associations of all possible dual-gene additive panels (i.e., *APOE* + *COMT*, *APOE* + *BDNF*, *COMT* + *BDNF*) as separated by age and lifestyle activities. Both research questions were divided into two corresponding parts. In parts 1a and 2a, we examined all three genotypes. In part 1b, we tested *APOE* moderation effect of *COMT* and *BDNF* (research question 1b) as separated by age and lifestyle activities. In part 2b, we tested *APOE* effect modification for *COMT* + *BDNF* (research question 2b) as separated by age and lifestyle activities. In part a (1a and 2a) the three genes were tested as separated by age group and lifestyle. In part b (1b and 2b) we added a test of further moderation and effect modification by *APOE* genotype. Based on our previous cross-sectional study, we expected to observe *APOE* moderation and effect modification for *COMT* and *BDNF* genotypes on EF performance and change.

1.1.1. Research question 1a (RQ1a)—Do higher allelic risk carriers for *APOE* (ε4+), *COMT* (Val/Val; Val/Met), and *BDNF* (Met/Met; Met/Val) show poorer performance and steeper decline in EF than their lower-risk counterparts? We test this question independently, by age group (younger versus older), and by lifestyle activities (higher versus lower activities)? We expected higher allelic risk carriers to have poorer EF performance and steeper decline overall. We also expected worse performance and exacerbated decline in the older group or the lower lifestyle activities group than in the younger or the higher lifestyle activities groups.

1.1.2. Research question 1b (RQ1b)—Does *APOE* status (ε4+ versus ε4-) moderate EF performance for *COMT* and *BDNF* higher allelic risk carriers such that *COMT* and *BDNF* higher allelic risk carriers in the *APOE* ε4+ group have poorer EF performance and steeper decline than those in the *APOE* ε4- group? We also examined whether this effect was magnified in the older age group or lower lifestyle activities groups than in the younger age group or higher lifestyle activities groups?

1.1.3. Research question 2a (RQ2a)—Is the additive (gene + gene) risk effect for each combination (i.e., *APOE* + *COMT*, *APOE* + *BDNF*, *COMT* + *BDNF*) associated with exacerbated EF deficits or decline? Is this exacerbation overall, by age group, or by lifestyle activities? We expected that the cumulative effect of higher allelic risk would produce poorer EF performance and steeper decline than would the lower-risk combinations, especially in the older age and lower lifestyle activities group.

1.1.4. Research question 2b (RQ2b)—Do *APOE* ε4+ carriers have poorer EF performance and steeper decline with increasing allelic risk in the *COMT* + *BDNF* risk panel compared to the *APOE* ε4-group? Is this effect larger in the older than in the younger age group or in the lower than in the higher lifestyle activities group? We expected *APOE* ε4+ carriers in the older group and in the lower lifestyle activities group to have poorer EF performance and steeper decline with increasing risk in the *COMT* + *BDNF* risk panel compared to those in the *APOE* ε4- group.

2. Method

2.1. 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. We use the term longitudinal sequential to describe a complex design that includes the following characteristics: (a) more than one age-based sample is followed over time, and (b) these similar age-based samples are staggered in historical time, reflecting the fact that they represent different but overlapping birth cohorts (Baltes et al., 1977). In the VLS, three such samples (from the 1980s, 1990s, and 2000s) are included (Dixon & de Frias, 2004). General information on recruitment, methodological, and VLS characteristics are available elsewhere (Dixon & de Frias, 2004; Dolcos et al., 2012). All volunteers in the VLS were initially healthy, 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. The present sample reflects the implementation of exclusionary criteria affecting individuals with (a) diagnosis of dementia, (b) anti-psychotic medication, (c) Mini Mental State Exam (MMSE) scores less than 24, (d) uncontrolled hypertension, (e) insulin-controlled diabetes, and (f) history of serious head injury (e.g., hospitalized). Participants were screened for dementia and MMSE at each wave. 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; Supplementary Table 1). We followed an accelerated longitudinal design by assembling three partial samples (S; S1, S2, S3) from the VLS. We note that the term "acceleration" refers not to a quickening in the rate of change but to a methodological adjustment whereby change trajectories are presented and analyzed according to an age (rather than a wave) metric and thus includes a broader band of aging (Galbraith et al., 2014; McArdle & Hamagami, 1991). 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 ($n = 634$) refers to S1W6, S2W4, and S3W1, (b) W2 ($n = 518$) refers to S1W7, S2W5, S3W2, and (c) W3 ($n = 294$) refers to S3W3 (see Table 1). As noted, with these data, we link a series of shorter individual longitudinal trajectories across the full available 40-year band of aging. 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 for: (a) S1: W1-W2 was 83%, (b) S2: W1-W2 was 77%, (c) S3: W1-W2 was 84%, (d) S3: W2-W3 was 88%, and (e) S3: W1-W3 was 74%.

2.2 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 PCR-RFLP strategy to analyze the allele status for *BDNF* (rs6265), *COMT* (rs4680), and *APOE* (rs7412, rs429358). Genotyping was successful for the targeted SNPs for all present participants. Supplementary Table 1 shows participant characteristics by genotype for *BDNF*, *COMT*, and *APOE*. The genotype frequencies did not differ significantly from Hardy-Weinberg equilibrium: *BDNF* rs6265 ($\chi^2 = 0.837$, $p = 0.36$), *COMT* rs4680 ($\chi^2 = 2.786$, $p = 0.10$), and *APOE* rs7412, rs429358 ($\chi^2 = 0.545$, $p = 0.909$). We included all three allelic combinations for *COMT* and *BDNF* (Met/Met, Met/Val, and Val/Val). Both SNPs were coded from 1 to 3 (3 = highest risk). For evaluating moderation and effect modification by *APOE*, we deleted all ε2/ε4 carriers ($n = 30$) and then compared patterns between ε4+ carriers and ε4- group. The *APOE* ε4- group was coded as 1 (lower risk) and *APOE* ε4+ group as 2 (higher risk).

2.3. 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 (de Frias et al., 2006; McFall et al., 2014; Sapkota et al., 2015).

2.3.1 Hayling Sentence Completion (Inhibition)—This test (Burgess & Shallice, 1997) 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).

2.3.2. Stroop (Inhibition)—This test (Taylor et al., 1997) 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.

2.3.3. Brixton Spatial Anticipation (Shifting)—This test (Burgess & Shallice, 1997) 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).

2.3.4. Color Trails (Shifting)—This test (D'Elia et al., 1996) 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.

2.4. Lifestyle Activities Composite

The 67-item version of the VLS Activity Lifestyle Questionnaire (VLS-ALQ) was used to determine the level or frequency of participation in everyday activities. Based on previous research (e.g., Small et al., 2012; Thibeau et al., 2016) the following four activity domains were selected for this study: (a) social, such as visiting friends (7 items); (b) physical activity, such as gardening (4 items); (c) integrative information processing, such playing a musical instrument (12 items); and (d) novel information processing, such as completing jigsaw puzzles (27 items). The frequency of participation is rated on a 9-point scale (never, less than once a year to two or three times a week, and daily). The lifestyle activities composite was calculated by summing the scores across all four domains.

2.5. Statistical Analysis

Structural equation modeling (SEM) was used to analyze both parts of the two research questions with Mplus Version 7 (Muthén & Muthén, 1998–2015). All missing values for cognitive measures were assumed to be missing at random and handled using maximum likelihood. Missing predictor variables were handled using list-wise deletion in Mplus. Only two participants with missing measures on all four EF tasks were lost. Although we used the three waves to organize the demographic information (Supplementary Table 1), it is important to note that age rather than wave was used as the metric of longitudinal change in the analyses. Statistically, using age in this manner permitted us to account for variability associated with age as well or better than if it is used as a covariate in the statistical models.

2.5.1. Analyses for research questions—Older adults who were 70 years and older were in the old-old (OO) group and those below 70 years were in the young-old (YO) group. In the YO group, age was centered at 63 years and in the OO group, age was centered at 77 years, based on the mean age in each group. The lifestyle activities composite was split into low and high clusters of activity participation at the overall group mean ($M = 133$). As noted, age (as a continuous variable) was incorporated as the metric of change. Sex and education (continuous) were used as covariates in all 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. We now turn to analyses for each research question.

For RQ1a, EF intercept and slope regression pathways were examined for *APOE*, *COMT*, and *BDNF* independently, and as separated by age group (YO and OO) and lifestyle activities composite (low and high).

For RQ1b, EF intercept and slope regression pathways were examined for *COMT* and *BDNF* as separated by *APOE* status (ε4+ versus ε4-). Next, we tested this regression model as further separated by age group (YO and OO) and lifestyle activities (low and high).

For RQ2a, EF intercept and slope regression pathways were examined separately for all additive genetic combinations. Specifically, for the additive models we tested (a) *APOE* + *COMT*, (b) *APOE* + *BDNF*, and (c) *COMT* + *BDNF*. We tested all three models independently, and as separated by age group (YO and OO) and lifestyle activities (low and high).

For RQ2b, EF intercept and slope regression pathways were examined for *COMT* + *BDNF* additive model as separated by *APOE* status (ε4+ versus ε4-). Next, we tested this regression model as further separated by age group (YO and OO) and lifestyle activities (low and high).

3. Results

First, we established several foundational results through preliminary analyses. The one-factor parsimonious model of EF provided the best fit to the data and was used as the final confirmatory factor analysis model (see supplementary material (text) and Supplementary Table 2). Unstandardized regression coefficients for the EF latent variable were examined to determine differences and changes in performance. Demonstrating longitudinal invariance of the latent variable, we obtained partial scalar longitudinal invariance across all three waves (χ^2 (*df*) = 84.60 (49), *p* = .001; *RMSEA* (90% CI) = .034 (.021−.044); *CFI* = .977; and *SRMR* = .084) (Supplementary Table 2). We computed EF factor scores, which were used in all succeeding models for testing RQ1 and RQ2. The best latent-growth model was obtained with the random intercept and random slope model (Supplementary Table 3).

For RQ1a, we observed four significant independent effects of *APOE* on EF performance and change. First, overall, *APOE* higher risk carriers (ε4+) performed worse than their lower-risk (ε4-) counterparts at age 75 (β = −0.206; SE = 0.098; *p* = .036) (Supplementary Figure 1a). We have prepared a reference table as a guide to supplement all the research models tested in Supplementary Table 4. We did not observe significant differential decline between the *APOE* ε4+ and ε4- group. Second, in the YO group, *APOE* ε4+ carriers performed worse on EF than their ε4- counterparts at age 63 (β = −0.210; SE = 0.100; *p* = .036) and had steeper decline over the 9-year period (β = −0.015; SE = 0.007; *p* = .020). Third, in the OO group, *APOE* ε4+ carriers had steeper decline on EF with age than their lower-risk (ε4-) counterparts (β = −0.029; SE = 0.011; *p* = .007) (Figure 1). Level of lifestyle activities did not significantly moderate *APOE* genotype on EF performance or change. We did not observe significant independent effects for *COMT* or *BDNF* allelic risk on EF performance or change, either overall (Supplementary Figure 1b and 1c) or as separated by age or lifestyle activities.

For RQ1b, we observed three significant associations. First, in the overall sample, there was a significant moderation effect for *BDNF* genotype by *APOE* status (ε4- versus ε4+). Specially, *BDNF* Met homozygotes in the *APOE* ε4+ group had the lowest EF performance at age 75 years compared to the *BDNF* Val/Met or Val/Val genotype (β = −0.373; SE = 0.179; *p* = .037). *BDNF* allelic higher risk carriers in the *APOE* ε4- group performed relatively well, as compared to the *APOE* ε4+ group (Figure 2). Second, in the YO group, *BDNF* Met homozygotes in the *APOE* ε4+ group had the lowest EF performance at age 63 (β = −0.330; SE = 0.145; *p* = .023) and a steeper slope than the *BDNF* Val homozygotes (β = −0.032; SE = 0.010; *p* = .023; Supplementary Figure 2). Third, in the higher lifestyle activities group, *BDNF* Met/Met homozygotes in the *APOE* ε4+ group had the lowest EF performance at 75 years (β = −0.525; SE = 0.252; *p* = .037) (Supplementary Figure 3), but did not differ from the other genotype groups in rate of change.

For RQ2a, we did not observe any significant effects for (a) *APOE* + *COMT*, (b) *APOE* + *BDNF*, and (c) *COMT* + *BDNF* risk overall or as separated by age or lifestyle activities.

For RQ2b, we observed two significant synergistic effects for the *COMT* + *BDNF* combination. First, *APOE* effect modification was observed for the *COMT* + *BDNF* additive effect on EF performance. *COMT* + *BDNF* allelic risk carriers showed an additive risk effect at age 75 and borderline decline in the *APOE* ε4+ group. Specifically, participants displayed poorer EF performance with increasing allelic risk in the *COMT* + *BDNF* risk panel at age 75 ($\beta = -0.307$; SE = 0.123; $p = .013$), and borderline 9-year decline ($\beta = -0.012$; SE = 0.006; $p = .054$) (Figure 3; Supplementary Table 4). Second, greater *COMT* + *BDNF* allelic risk was associated with less steep decline in EF performance for the *APOE* ε4- group with higher lifestyle activities ($\beta = 0.008$; SE = 0.004; $p = .046$) (Supplementary Figure 4). We did not observe any significant effects for *COMT* and *BDNF* cumulative risk as separated by *APOE* ε4 status and age group.

4. Discussion

In a previous cross-sectional study, we reported *COMT* + *BDNF* additive effects and *APOE* effect modification on EF performance (Sapkota et al., 2015). In the present and expanded longitudinal study, we first tested independent and additive associations of *APOE*, *COMT*, and *BDNF* allelic risk on EF performance and 9-year change in non-demented older adults. We then examined (a) *APOE* moderation effects separately for *COMT* and *BDNF* and (b) *APOE* effect modification for *COMT* + *BDNF*. Although this interactive and multimodal approach is growing (e.g., McFall et al., 2015b; Nagel et al., 2008; Papenberg et al., 2014; Sapkota et al., 2015), to our knowledge this is the first study to examine synergistic associations with EF performance and longitudinal change as separated by age group and lifestyle activities for these three aging-related genetic variants. Key results include the following. First, we observed a single-gene effect for *APOE*. The ε4+ carriers (and not *COMT* or *BDNF* risk carriers) were at higher risk for poor EF performance and steeper decline. Second, we observed that *APOE* ε4+ moderated the effects of the *BDNF* genotype such that the combined genetic risk was enough to negatively affect cognition even in the YO and higher lifestyle activity groups. Third, we observed *APOE* ε4 effect modification for *COMT* + *BDNF*: *APOE* ε4+ carriers had poorer EF performance with increasing allelic risk in the *COMT* + *BDNF* risk panel at age 75 and borderline 9-year decline. In contrast, adults in the *APOE* ε4- group with higher lifestyle activities were protected from the *COMT* + *BDNF* risk panel effect on EF. Specific comments for each research question follow.

For RQ1a, the first main result was the observation that *APOE* ε4 carriers performed worse than their ε4- counterparts at age 75 in the overall group, at age 63 years in the YO group, and had steeper EF decline in the YO and OO groups. Although some previous research and meta-analyses on *APOE* and cognitive associations have reported similar findings in non-demented older adults, observers have also concluded that the genetic associations may be selective to specific cognitive domains (Marioni et al., 2015; Raz et al., 2009; Small et al., 2004). In contrast, we found that *COMT* and *BDNF* allelic risk did not predict differences in EF. Second, we observed an overall age and lifestyle activities effect on EF performance and change. We found an age effect whereby adults in the OO group were declining more in EF performance than their YO counterparts. Notably, for lower versus higher lifestyle activities, we observed a similar pattern of results. There were no independent effects of *APOE*, *COMT*, and *BDNF* in either of two lifestyle groups, but participants with higher lifestyle activities showed shallower decline in EF performance overall compared to those with lower lifestyle activities.

For RQ1b, we observed an *APOE* moderation effect for *BDNF* genotype on EF performance in the overall sample, in the YO group, and in the higher lifestyle activities group. *BDNF* Met homozygotes showed the worst EF performance in the presence of *APOE* ε4+ genetic risk, and this effect was present even among YO and those with higher lifestyle activities. A recent study reported an *APOE* and *BDNF* interactive effect for episodic memory performance (Ward et al., 2014). This study found that *BDNF* Met+ carriers with *APOE* ε4 allele had poorer performance compared to *BDNF* Met+ carriers with the *APOE* ε2 allele, but no further interactions were tested. Another recent study examined amyloid beta deposition in cognitively normal older adults (Adamczuk et al., 2013), suggesting a possible biological interaction between *APOE* ε4 status and *BDNF* Met status. Specifically, adults who were carriers of both *APOE* ε4+ *BDNF* Met+ genotypes had a higher amyloid load in multiple brain regions than did those with a *BDNF* Met- genotype. Although no further interactions were tested, the authors suggested that the lipid-metabolism pathway influenced by *APOE* genotype and the role of *BDNF* in neuronal survival may be linked in a way that modifies amyloid deposition. In the present study, we observed that this moderation effect was present in YO adults and those with higher lifestyle activities. As noted earlier, both younger age and greater physical engagement (a common combination according to Evenson et al., 2012) may be "protective" for cognitive performance and change, possibly related to amplified BDNF expression in these favorable conditions (Erickson et al., 2012). Further, the *APOE* moderation effect on *BDNF* in our study implies that the (a) *BDNF* Met/Met risk may only be detrimental for EF in the presence of *APOE* ε4+ risk, and (b) younger age and higher lifestyle activities may not be protective for those with the highest genetic risk combination (*BDNF* Met/Met and *APOE* ε4+).

We briefly note that for RQ2a, we did not observe additive effects for all three pairwise combinations (*APOE* + *COMT*, *APOE* + *BDNF*, *COMT* + *BDNF*) overall or as separated by age or lifestyle activities. Absence of additive effect supports our findings that (a) the *COMT* + *BDNF* risk panel is only detectable in the presence of *APOE* ε4+ risk and (b) *APOE* has a moderating or effect modification (and not additive) role with *COMT* and *BDNF* in non-demented older adults.

For RQ2b, we observed an *APOE* effect modification for the *COMT* + *BDNF* additive association on EF performance. *APOE* ε4+ carriers displayed poorer EF performance with increasing allelic risk in the *COMT* + *BDNF* risk panel at age 75 and accentuated 9-year decline. An additional allelic risk for either *COMT* or *BDNF* among *APOE* ε4+ carriers resulted in poorer EF performance, whereas *APOE* non-risk carriers (ε4-) were protected from the deleterious effect of *COMT* + *BDNF* allelic risk. Previous studies have reported that aging exacerbates the association between lower prefrontal DA levels (i.e., *COMT* Val homozygotes) and poorer cognitive performance in (Bäckman et al., 2010; Lindenberger et al., 2008; Papenberg et al., 2014). Although we did not observe differential patterns in our

YO versus OO age groups, we informally note a borderline aging magnification of *COMT* + *BDNF* genetic effects across the 40-year age range of this sample. This trend, which suggests magnification of genetic effects in older adults, deserves further research attention (Papenberg et al., 2015a). As for *BDNF* Val homozygotes, they have higher levels of neurotrophic factors (Marosi & Mattson, 2014), which has been associated with better cognitive performance (Nagel et al., 2008). In our additive association, we observed that an absence of *COMT* Val+ or *BDNF* Met + allelic risk did not eliminate the risk present with either *COMT* or *BDNF* genotype for *APOE* ε4+ carriers on EF performance.

We also observed that the groups carrying risk alleles for *COMT* and *BDNF* in the *APOE* ε4-group with the protective component of higher lifestyle activities showed least decline in EF performance over 9 years (Supplementary Figure 4). Some past studies show that higher levels of certain lifestyle activities may be protective against dementia (Scarmeas et al., 2001; Valenzuela et al., 2011) and support cognitive maintenance in non-demented older persons (Erickson et al., 2008). Among the proposed mechanisms are activity- or exercise-related increases in synaptic density and cognitive reserve, which may delay clinical symptoms (Scarmeas et al., 2001) and promote brain maintenance in old age (Wang et al., 2002). Higher lifestyle activities may counteract the negative effects and be most beneficial to persons with the highest combination of genetic risk (*COMT* + *BDNF*) for *APOE* ε4 non-carriers. Our results support this "differential susceptibility" model (Belsky et al., 2009; Ferencz et al., 2014), which suggests that adults with the highest allelic risk show the greatest amount of plasticity. Specifically, older adults with the highest genetic allelic risk combination in the *COMT* + *BDNF* risk panel and higher lifestyle activities had the least decline in EF performance compared to their lower genetic risk counterparts. This finding also extends our previous cross-sectional results by pointing to the moderating effect of lifestyle engagement on *APOE, COMT*, and *BDNF* genetic effects on EF.

We now note several strengths and limitations of the present study. A first strength is the sample of older adults ($n = 634$) tested at three waves and across a 40-year band of aging (age range = 53–95 years) from an ongoing longitudinal study. Although a larger sample size and additional waves would have been preferable, this design allowed us to compare age differences and changes across two older adult age groups and to examine and detect age magnification over a 40-year span. Second, we used an accelerated longitudinal design with age as the metric of change, thereby incorporating chronological age directly into our analyses (McFall et al., 2016). We note that although most longitudinal studies involving older adults are usually unstructured and do not address cohort effects, they do provide direct estimates of change (unlike cross-sectional designs) (Thompson et al., 2011). A latent growth modeling approach in Mplus by default accounts for missing data. The default method uses maximum likelihood estimation to generate factor scores for the dependent EF factor and maximizes the use of longitudinal data. Third, we used four standard cognitive tests contributing to a confirmed one-factor EF latent variable. The present latent variable approach represents the broader construct domain and it attenuates measurement error associated with single EF or other cognitive tests. Fourth, in extending an earlier cross-sectional study through 9 years with longitudinal data, we determined that the previous additive approach was effective and applied to change, but notably modified by the effects of *APOE* and lifestyle factors. Regarding limitations, first, we examined only one cognitive domain. Future studies should consider examining other domains, perhaps especially cognitive speed and episodic memory with *APOE*, *COMT*, and *BDNF* or other risk polymorphisms (Laukka et al., 2013). Second, the measurement of lifestyle activities was based on frequency and did not take into account the extent or intensity of participation. In addition, although we used multiple indicators and tapped four integrated aspects of lifestyle activities, the current approach was not designed to delineate separable contributions, if any, of these aspects. Third, because of ongoing data collection schedules, the longitudinal design did not include a third-wave opportunity for all participants. However, our results seem not to have been compromised because we used all data points available for each participant and confirmed that the latent EF variable was measurement invariant across all waves. By achieving partial scalar invariance, we accounted for any potential EF practice effects in our analyses (Kline, 2011). Fourth, we note that our participants were predominantly White, not of Hispanic origin, and that genotype allelic frequencies may differ in other racial populations. Our findings should be replicated in future studies with diverse or other racial backgrounds. Fifth, although we include sex and education as covariates, future studies should consider other relevant biomarkers including global cognition.

In conclusion, the *APOE* genotype presents a systematic array of potential associations with cognitive performance and change. When appropriate data are available, researchers may observe *APOE* associations that take the following forms: (a) overall independent effects on level and change, (b) moderation effects on *BDNF* genotype, and (c) effect modification of *COMT* + *BDNF* combined panel effects. In addition, as has been implicated in other contexts and with other cognitive phenotypes, both chronological age and lifestyle activities may moderate some or all of these forms of *APOE* associations. It is important to note that even in the absence of initial single-gene (independent) effects on EF, both *COMT* and *BDNF* allelic risk may play a role in predicting cognitive change but primarily in the context of interactive or magnified risk. At present, these synergistic neurobiological partners include Alzheimer's genetic risk (*APOE* ε4+ carriers) and lifestyle engagement (lower lifestyle activities). Future research should be directed at detecting the roles played by the protective aspects of these risk factors: These include potential sources of protection ranging from the genetic (*APOE* ε2 carriers) to profiles of lifestyle and health activities that (independently or interactively) may protect against the neurobiological mechanisms underlying the various combinations of magnified risk examined in this study. Finally, we emphasize (a) the integrative role that *APOE* may play in all such complex and dynamic interactions, (b) the fact that the often-noted inconsistencies in single-gene *COMT* and *BDNF* association studies can be clarified in interactive and longitudinal contexts, and (c) the importance of multifactorial and dynamic approaches to understanding neurobiological aging and its influences on cognitive functioning.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- *APOE* genotype affects cognitive aging both directly and synergistically
- Both *BDNF* and *COMT* may affect EF aging through interactive risk combinations
- *APOE* ε4+ carriers had poorer EF performance with increasing *COMT* +*BDNF* risk
- *COMT*+*BDNF* risk in the *APOE* ε4- and high lifestyle group showed protected EF change

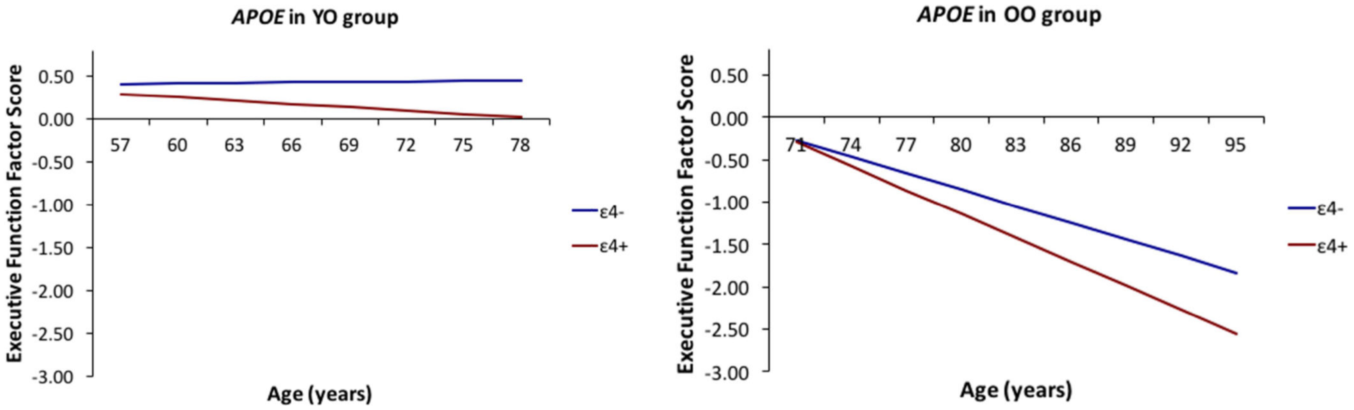

Figure 1.

In the young-old (YO) group, *APOE* ε4+ carriers performed worse at age 63 and had steeper 9-year decline in EF than their non-risk (ε4-) counterparts. In the old-old (OO) group *APOE* ε4+ carriers showed steeper 9-year decline on EF than their non-risk counterparts.

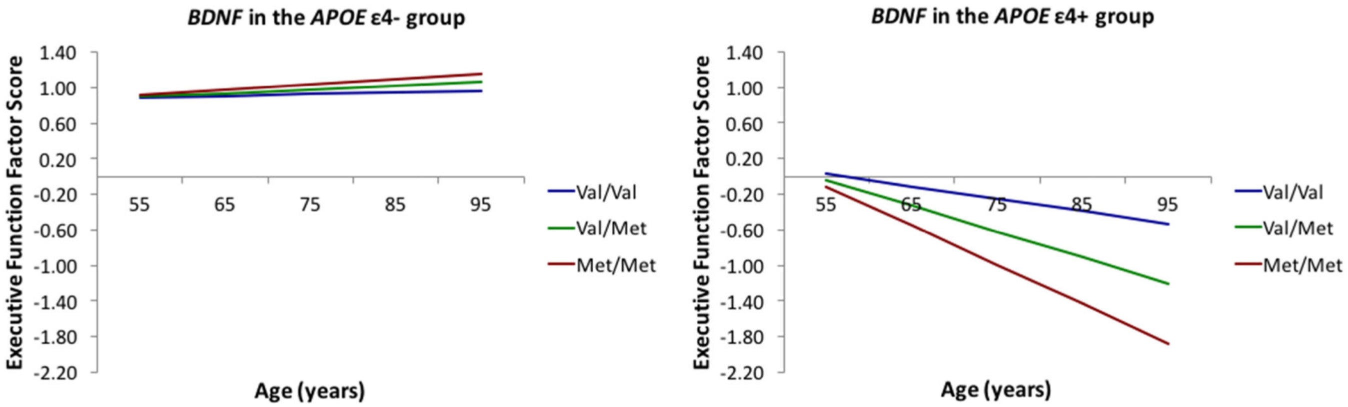

Figure 2.

In the *APOE* ε4+ group, *BDNF* Met/Met homozygotes had the worst EF performance compared to their non-risk counterparts (Val homozygotes) at 75 years. In contrast, in the *APOE* ε4- group, *BDNF* genotype did not affect EF performance.

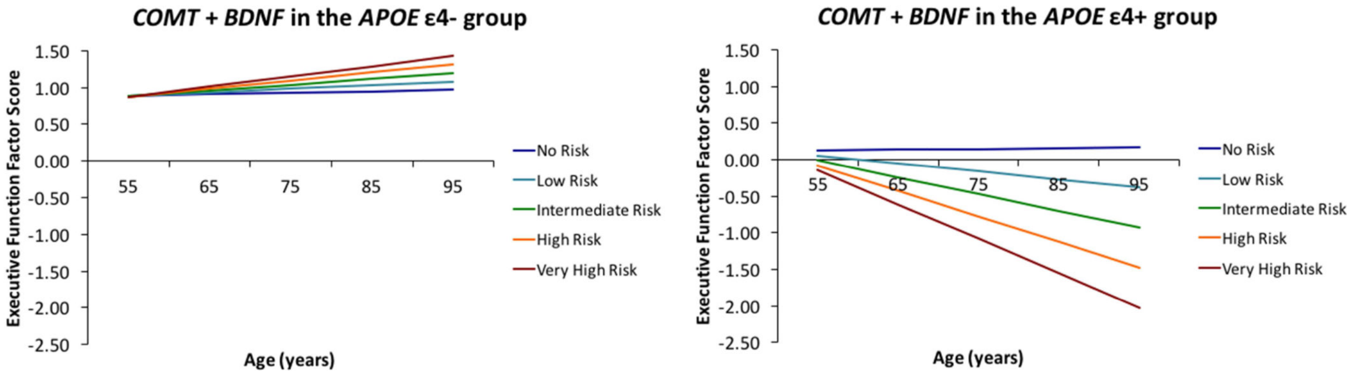

Figure 3.

APOE effect modification was observed for *COMT + BDNF* additive effect on EF performance. *APOE* ε4+ carriers had poorer EF performance with increasing allelic risk in the *COMT + BDNF* risk panel at age 75 years and borderline 9-year decline. In contrast, the *APOE* ε4- group was protected from the deleterious effect on EF performance and decline with increasing allelic risk in the *COMT + BDNF* risk panel.

Table 1

Participant characteristics by age group and genotype.

Characteristics												
Young-Old	***COMT***				***BDNF***				***APOE***			**Total**
	Met/Met	**Met/Val**	**Val/Val**	***p*-value**	**Met/Met**	**Met/Val**	**Val/Val**	***p*-value**	**ε4-**	**ε4+**	***p*-value**	
n	70	152	74	--	15	79	202	--	201	79	--	296
Age (years)	62.32 (4.47)	62.70 (4.58)	63.37 (4.39)	0.356	64.09 (4.63)	63.10 (4.24)	62.55 (4.60)	0.333	62.50 (4.52)	63.28 (4.44)	0.191	62.77 (4.51)
Education (years)	15.21 (3.01)	15.73 (2.75)	15.38 (3.25)	0.418	15.77 (2.97)	15.15 (3.09)	15.65 (2.88)	0.425	15.44 (2.97)	15.81 (3.02)	0.345	15.52 (2.95)
Sex (F/M)	54/16	105/47	52/22	0.458	12/3	58/21	141/61	0.625	149/52	49/30	0.045	
MMSE	29.04 (0.92)	28.99 (1.05)	28.76 (1.29)	0.215	29.07 (0.80)	29.05 (0.95)	28.90 (1.16)	0.513	28.87 (1.16)	29.09 (0.95)	0.129	28.95 (1.09)
Old-Old	***COMT***				***BDNF***				***APOE***			
	Met/Met	Met/Val	Val/Val	*p*-value	Met/Met	Met/Val	Val/Val	*p*-value	ε4-	ε4+	*p*-value	
n	76	186	76	--	12	110	214	--	252	70	--	338
Age (years)	77.37 (4.82)	77.51 (4.55)	77.23 (5.01)	0.904	74.09 (2.59)	77.44 (5.05)	77.59 (4.56)	0.043	77.55 (4.81)	77.28 (4.35)	0.665	77.42 (4.71)
Education (years)	14.66 (3.20)	15.03 (2.81)	15.34 (3.06)	0.361	15.67 (2.46)	15.12 (2.93)	14.94 (3.00)	0.658	14.99 (2.96)	15.25 (3.13)	0.518	15.02 (2.96)
Sex (F/M)	47/29	120/64	44/32	0.547	6/6	70/40	135/79	0.648	155/97	44/26	0.827	
MMSE	28.42 (1.35)	28.48 (1.27)	28.36 (1.32)	0.799	29.25 (0.75)	28.51 (1.23)	28.36 (1.34)	0.053	28.50 (1.27)	28.19 (1.39)	0.082	28.44 (1.30)

Note. *n* = total number; *COMT* = *Catechol-O-methyl transferase*; *BDNF* = *Brain-derived neurotrophic factor*; *APOE* = *Apolipoprotein E*; $p < .05$. MMSE = Mini-Mental State Exam. Standard deviations are in parentheses. For the analyses involving the *APOE* genotypes, ε2/ε4 carriers (*n* = 30) were deleted from the sample.