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

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Abstract

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

Keywords

Apolipoprotein E; *Clusterin*; Pulse pressure; Executive Function; Victoria Longitudinal Study

1. Introduction

Biomarkers associated with the risk of developing Alzheimer's disease (AD) may affect cognition long before clinical symptoms of AD occur (Anstey et al., 2015). AD-related risk or protection factors derive from genetic, biological, health, lifestyle, and other domains. Such factors may operate independently or interactively to predict level and slope of neurocognitive performance. Among key AD risk genes, *Apoliprotein E* (*APOE*) and *Clusterin* (*CLU*) have also been prominently implicated in differential cognitive decline in

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non-demented aging (Small et al., 2004; Thambisetty et al., 2013). Independently, these genes present relatively low penetrance and consequently low effect sizes, but together they may account for substantial cognitive risk (Barral et al., 2012; McFall et al., 2015a) especially within the context of other AD and vascular health risk factors (Josefsson et al., 2012; McFall et al., 2014; McFall et al., 2015b). One important vascular health factor is pulse pressure (PP), a proxy measure of arterial stiffness. Higher levels of PP are associated with decreased vascular health (Steppan et al., 2011), poorer cognitive outcomes (Al Hazzouri and Yaffe, 2014; McFall et al., 2014; Raz et al., 2011), and risk of dementia or AD (Peters et al., 2013; Qiu et al., 2003). This study examines the independent and additive effects of genetic variants within the *APOE* and *CLU* genes in interaction with a key vascular risk factor (i.e., PP) on executive function (EF) level and 9-year change in non-demented older adults.

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

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

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

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

2. Material and Methods

2.1. Participants

Participants were community-dwelling adults (initially aged 53-95 years) drawn from the Victoria Longitudinal Study (VLS). The VLS is a longitudinal sequential study designed to examine human aging in relation to biomedical, genetic, health, cognitive, and neuropsychological aspects (Dixon and de Frias, 2004). The VLS and all present data collection procedures were in full and certified compliance with prevailing human research ethics guidelines and boards. Informed written consent was provided by all participants. Using standard procedures (e.g., Dixon et al., 2012; Small et al., 2011), we assembled

longitudinal data consisting of three samples and all available waves (up to three) since the early 2000s. The EF tasks required for this study were installed in the VLS neuropsychological battery at this point. Therefore, the first included wave for each sample was the first exposure to the EF tasks. This study assembled (a) Sample 1 (S1) Waves 6, 7, and 8; (b) Sample 2 (S2) Waves 4 and 5; and (c) Sample 3 (S3) Waves 1, 2, and 3. For terminological efficiency, the respective earliest wave of each sample became Wave 1 (W1 or baseline) and the respective second and third wave became Wave 2 (W2) and Wave 3 (W3). The mean intervals between the waves of data collection were approximately 4.5 years (W1-W2; W2-W3). Although we used the three waves to organize the demographic information (Table 1) it is important to note that wave was not used as the metric of longitudinal change in the analyses. Specifically, age was used as the metric of change for this study. Statistically, using age in this manner permits us to account for variability associated with age as well as, or better than, if it were used as a covariate in the statistical models. Moreover, testing genetic-health interactions on EF across multiple linked longitudinal periods of up to 9 years ($M = 8.9$) allowed us to produce an accelerated longitudinal design covering a 40-year band of aging (i.e., 53-95 years).

Given the necessity for both genetic and longitudinal data in this study, these factors defined the initial opportunity in sample recruitment. VLS genotyping occurred in the 2009-2011 period and was limited by funding arrangement to about 700 continuing VLS participants. After initial evaluations, the eligible source sample consisted of 695 participants. Several exclusionary criteria were then applied to this source sample: (a) a diagnosis of Alzheimer's disease or any other dementia, (b) a Mini-Mental Status Exam (MMSE; Folstein et al., 1975) score of less than 24, (c) a self-report of “severe” for potential comorbid conditions (e.g., epilepsy, head injury, depression), (d) a self-report of “severe” or “moderate” for potential comorbid diseases such as neurological conditions (e.g., stroke, Parkinson's disease), and (e) insufficient EF data. The final study sample consisted of $n = 593$ adults. One participant (female) contributed data to W2 only. At W1 there were 592 adults, including 398 females and 194 males (M age = 70.3 years, $SD = 8.66$, range 53.2 – 95.2). At W2 there were 495 adults, including 332 females and 163 males (M age = 74.5 years, $SD = 8.53$, range 57.3 – 94.5). At W3 there were 319 adults, including 222 females and 97 males (M age = 76.2 years, $SD = 8.22$, range 62.4 – 95.6). The design stipulated that whereas S1 and S3 participants could contribute data to all three waves, S2 participants contributed data to W1 and W2 (the required data from the third wave are not yet available). The retention rates for each available and defined two-wave interval are as follows (a) S1 W1-W2 = 88%; (b) S1 W2-W3 = 80%; (c) S2 W1-W2 = 82%; (d) S3 W1-W2 = 84%; (e) S3 W2-W3 = 90%. Structural equation modeling estimates all missing data using maximum likelihood estimations. All missing data in conditional latent growth models were estimated by multiple imputations using Mplus 7 (Muthén and Muthén, 1998 - 2012). Specifically, the VLS practice is to generate 50 imputations of the data set and pool for all growth models (McFall et al., 2015b).

2.2. Executive Function (EF) Measures

We assembled a robust latent EF variable using four manifest indicators of two key EF abilities: shifting (Brixton Spatial Anticipation, Color Trails Test Part 2) and inhibition

(Hayling Sentence Completion, Stroop test). For a more detailed description of these EF tasks see McFall and colleagues (2013). All EF tests have been used widely and frequently within the VLS and other projects, with established measurement and structural characteristics (e.g., Bielak et al., 2006; de Frias et al., 2006, 2009) and demonstrated sensitivity to health, genetic, and neurocognitive factors (e.g., McFall et al., 2014; Sapkota et al., 2015) in various older adult populations.

2.3. Pulse Pressure (PP)

PP is calculated as follows: PP = systolic – diastolic blood pressure. For all analyses PP centered at 51.9 mmHg, the population mean at baseline. Although the analyses are conducted with PP as a continuous variable, the results are displayed in terms of three clusters of PP (Figures 1-4). We planned to investigate typically aging older adults; thus, high blood pressure and participants taking antihypertension and lipid lowering medications were included in the study (Table 1).

2.4. Saliva Collection, DNA Extraction and Genotyping, and Gene Groupings

Saliva was collected according to standard procedures from Oragene-DNA Genotek and stored at room temperature in the Oragene® disks until DNA extraction. DNA was manually extracted from the saliva sample mix using the manufacturer's protocol. Genotyping was carried out by using a PCR-RFLP strategy as previously described (McFall et al., 2015a).

Genotypic distribution for *APOE* (clustered according to the presence of the ε4 risk allele; $\chi^2 = 0.58$ (1), $p > .05$) and *CLU* ($\chi^2 = 0.77$ (1), $p > .05$) are in Hardy-Weinberg equilibrium. As per typical VLS protocol, 27 ε2ε4 participants were excluded from all analyses. Genetic risk analyses were based on low, moderate, and high risk for *APOE* (ε2+ [ε2ε2, ε2ε3], ε3 [ε3ε3], ε4+ [ε3ε4, ε4ε4]) and *CLU* (TT, TC, CC). We then tested the additive risk of *APOE* and *CLU*. The genetic risk index was created by summing allelic risk for *APOE* (i.e., low risk (ε2ε2, ε2ε3) = 0, moderate risk (ε3ε3) = 1, high risk (ε3ε4, ε4ε4) = 2) plus *CLU* (i.e., low risk = 0 (TT), moderate risk = 1 (TC), and high risk = 2 (CC); see Ferencz et al., 2014). Given a maximum genetic risk score of 4, we determined three levels of additive genetic risk as follows: low risk = 0-1, moderate risk = 2, and high risk = 3-4. The low risk group ($n = 74$) is within the power protocols of multi-group structural equation model analyses (Little, 2013).

2.5. Statistical Analyses

Analyses pertaining to our RQs included confirmatory factor analysis and latent growth modeling. Statistical model fit for all analyses was determined using standard indexes: (a) χ^2 for which a good fit would produce a non-significant test ($p > .05$) indicating that the data are not significantly different from the estimates associated with the model, (b) the comparative fit index (CFI) for which fit is judged by a value of ≥ .95 as good and ≥ .90 as adequate, (c) root mean square error of approximation (RMSEA) for which fit is judged by a value of ≤ .05 as good and ≤ .08 as adequate, and (d) standardized root mean square residual (SRMR) for which fit is judged by a value of ≤ .08 as good (Kline, 2011).

Mplus 7 (Muthén and Muthén, 1998 - 2012) was used to confirm a one-factor EF latent variable reflecting contributions from the four manifest indicators. Using the best fitting EF model we calculated factor scores and these were used for all subsequent models. Invariance testing across the three waves of data resulted in metric and partial scalar invariance (Table 2). Achieving partial scalar invariance indicated that any potential EF practice effects were not significant and accounted for. As described earlier, age was used as the metric of change (i.e., the data were arrayed and analysed by age) a procedure that directly (not indirectly through covariation) includes actual chronological age in the analyses. We centered age at 75 years (the frequently used center point of the 40-year band of VLS W1 data; ranging from 53-95 years). We used multiple imputations to estimate missing values for PP, age, and EF factor scores for all growth models. Best fitting growth model resulted in random intercept, random slope (Table 2). We observed the expected patterns of EF performance and change. Specifically, individuals (a) varied in level of EF performance at age 75 ($b = .958$, $p < .001$), (b) exhibited significant 9-year EF decline ($M = -.010$, $p = .021$), and (c) showed variable patterns of decline ($b = .001$, $p < .001$). Power associated with our measurement model was 0.9. Chi-square difference tests (D)were calculated for all latent growth nested models. D statistics are equivalent to a Scheffe-like procedure accounting for multiple testing (McCoach et al., 2007).

For both RQs we tested conditional growth models for EF with PP as a predictor using independent *APOE* or *CLU* groupings and cumulative *APOE* plus *CLU* groupings as outlined in section 2.4. Moderation effects were calculated using the D statistic between the unconstrained and constrained model of the interaction. In addition, for all analyses we ran a model that included several covariates measured at W1: sex, education level, smoking status, body mass index, type 2 diabetes status, lipid lowering medication use, and antihypertension medication use. Two covariates exhibited a significant effect on EF level or change but these findings did not change the results of the PP and genetic risk models. Specifically, education significantly predicted EF level of performance at age 75 in all PP and gene models and 9-year EF change for all but the *APOE* × PP model. Antihypertension medication use showed significant covariant effects in the models; consequently, all analyses were repeated after removal of 152 participants using the medications. The analyses of this subgroup did not alter the original results.

3. Results

In preliminary analyses, we tested independent associations of PP, *APOE,* and *CLU* with EF level and change. First, as expected, better vascular health (lower levels of PP) was associated with higher EF performance at the centering age 75 ($p < .001$) and with less 9-year decline ($p < .001$; see Figure 1). As can be seen in the figure, the group with the lowest (healthiest) level of baseline PP (i.e., PP = 52 mm Hg) exhibited better EF performance (Mi = .216) and less 9-year decline (Ms = −.012) than did the groups with the medium (Mi = −.075; Ms = −.031) and highest levels of PP (Mi = −.366; Ms = −.050). Overall, this result established the benchmark for testing genetic moderation. Second, we observed no significant independent genotype associations with EF performance or decline (*APOE* bi = −.198, $SE = .136$, $p = .146$, bs = .012, $SE = .008$, $p = .186$; *CLU* bi = .008, $SE = .074$, $p =$.

919, *b*s = .001, *SE* = .005, *p* = .873). Moderation effects are still possible in the absence of direct effects.

For RQ1, separate analyses showed that both genotypes exhibited significant gene × PP interaction effects on EF performance and change. The contrasting PP-EF associations across levels of genetic risk are displayed in Figure 2 (*APOE*) and Figure 3 (*CLU*). For both *APOE* and *CLU* the low genetic risk groups exhibited no deleterious effects of PP on EF. This contrasts markedly with the patterns observed for the moderate and high risk groups. Regarding *APOE*, the ε2+ group (Figure 2a) exhibited non-significant diversity in EF performance (*b*i = −.014, *p* = .949) and change (*b*s = −.011, *p* = .353) across the levels of PP. In contrast, PP levels within the *APOE* ε4+ group (Figure 2c) predicted both EF level at age 75 years (*b*i = −.349, *p* = .002) and 9-year EF change (*b*s = −.018, *p* =.021). We observed a similar pattern in the *APOE* ε3ε3 group (Figure 2b) for EF performance (*b* = −.306, *p* <.001) and change (*b* = −.022, *p* <.001). Regarding *CLU*, the low risk group (TT; Figure 3a) exhibited non-significant diversity in EF performance (*b*i = −.152, *p* = .142) and change (*b*s = −.004, *p* = .572) due to level of PP. In contrast, PP levels within the *CLU* high risk group (CC; Figure 3c) predicted both EF level at age 75 years (*b*i = −.394, *p* <.001) and 9-year EF change (*b*s = −.029, *p* <.001). We observed a similar pattern in the *CLU* moderate risk group (TC; Figure 3b) for EF performance (*b*i = −.262, *p* = .002) and change (*b*s = −.017, *p* = .001).

For RQ2, we examined the combined genetic effects of these two polymorphisms. The analyses showed that the *APOE* plus *CLU* combination exhibited a significant interaction effect with PP on EF performance and change (Figure 4). Specifically, the low risk group (Figure 4a) exhibited non-significant diversity in EF performance (*b*i = −.079, *p* = .602) and change (*b*s = −.006, *p* = .486) across the three levels of PP. In contrast, in the highest genetic risk group (Figure 4c), PP predicted both EF level at age 75 years (*b*i = −.411, *p* <.001) and 9-year EF change (*b*s = −.028, *p* <.001). We observed a similar pattern in the moderate risk group (Figure 4b) for EF performance (*b*i = −.221, *p* = .007) and change (*b*s = −.016, *p* = .005). Examining the spreading of slope effect over the PP levels, we noted that *APOE* ε2+ (Figure 2a) exhibits the least diversity between levels of PP in EF performance at age 75 (intercept) whereas, *CLU* TT (Figure 3a) exhibits the least diversity in 9-year EF change (slope) compared to their genetic risk counterparts. This may indicate that *APOE* ε2 carriers influence more risk-reduction in level of EF performance and *CLU* TT homozygotes are associated with more risk-reduction in EF change. Thus, the combination of *APOE* and *CLU* low risk (Figure 4a) may add important information for both EF level and change to that available with *APOE* or *CLU* alone.

4. Discussion

The general aim of this research was to examine whether two established AD genetic risk factors moderated the effect of a known vascular health risk factor on cognitive changes in non-demented older adults. Using conditional growth modelling of longitudinal data we found significant interactive effects of PP with *APOE* or *CLU* (independently and in combination) on EF performance and nine-year change. In both cases, the effect of poor

vascular health was mitigated for carriers of risk-reducing (or protective) alleles of AD-related genotypes.

We began by confirming the expected “fan” (or spreading of slope) effect of PP on EF performance and change, with worsening vascular health predicting steeper cognitive decline (Figure 1; see also McFall et al., 2014). These results, corroborating the systematic stepwise effect of vascular health on cognitive performance and change in non-demented aging, constituted the necessary benchmark for the planned interaction analyses. We next tested the direct independent effects of the two genotypes on cognitive level or change, observing no significant association. Such null results are often observed in independent SNP-phenotype analyses (Harris and Deary, 2011) and positive associations are not required for examining gene × health interactions.

Accordingly, as shown in Figures 2 and 3, we observed two significant interaction effects. In both cases, the results showed that the simple fan effects of PP on EF change in non-demented aging are moderated independently by each of the AD-related genetic polymorphisms. Notably, we observed that the deleterious effects of poor vascular health on EF performance and change were evident in both moderate- and high- risk *APOE* and *CLU* genotypes. Essentially, the overall fan effect of PP on cognition was replicated in these genetic risk sub-groups. In contrast, for both polymorphisms, not only was the fan effect not observed in the low-risk genotypes but the level (intercept) differences were not significant and the decline slopes were somewhat reduced, relative to those seen in carriers of the risk-elevating genotypes. These results are consistent with an inference of protection against the powerful negative effects associated with increasingly poorer vascular health.

Putting these concordant interaction results in context, we note first that the *APOE* ε4 and *CLU* C carriers showed poorer EF performance at age 75 and 9-year decline with higher PP levels. Although similar results (on other cognitive domains) have been reported for *APOE* ε4 carriers (McFall et al., 2015b), we are not aware of closely corresponding results for *CLU*. Both *APOE* and *CLU* are commonly studied and replicated SNPs for dementia and occasionally (but not always) show associations with cognitive deficits in non-demented aging. For example, *APOE* ε4+ allelic risk has been associated with poorer cognitive performance (Bender and Raz, 2012; Fotuhi et al., 2009) and *APOE* ε2+ with preserved cognitive functioning in non-demented adults (Deary et al., 2004a; Deary et al., 2004b; Lindahl-Jacobsen et al., 2013). Similarly, in a smaller literature, cognitive decline has been observed among *CLU* C+ risk carriers who eventually reached MCI status (Thambisetty et al., 2013). However, that they both moderate the negative effects of worsening pulse pressure —in homologous patterns—has not been previously reported. The apolipoprotein E (ApoE) protein is involved in brain lipid metabolism and recent studies suggest that this role may be acquired by other lipoproteins in the brain such as clusterin (CLU), which is also known as Apolipoprotein J. CLU is a multifunctional protein that interacts with a variety of molecules including lipids and amyloid proteins. Both ApoE and CLU play a role in amyloid beta clearance in the brain by binding to lipoprotein receptors (Jones et al., 2010). As hypothesized, the two genetic variants, with some similar structure and function, independently moderated the effects of poor vascular health on older adult EF performance and change—and they did so with similar patterns of selective protection for low-risk

genotype carriers in the context of substantial vascular health risk for the moderate and high-risk genotype carriers.

Given these favorable results we then moved to our second research question. We tested the cumulative effects of *APOE* and *CLU* in interaction with PP on EF performance and change. We again observed results consistent with our risk-reduction hypothesis (Figure 4). Low combined allelic risk from both *APOE* and *CLU* showed patterns that were consistent with an interpretation of risk suppression or protection for even those adults with poor vascular health. Poor vascular health leads to microvascular disease that can result in reduced brain tissue volume and widespread changes in brain function, especially in the prefrontal cortex (Chuang et al., 2014; Raz et al., 2003; Raz et al., 2007). Notably, ε2+ carriers exhibit increased levels of ApoE protein when compared to ε3/ε3 or ε4+ carriers. This increase may lead to a preserved ability to repair neuronal damage in ε2 carriers (McFall et al., 2015b). In addition, CLU has been linked with nerve cell survival and post-injury neuroplasticity, and both CLU and ApoE have similar neuronal function. Cumulatively, *CLU* and *APOE* may influence the impact of vascular health damage specifically in the frontal lobe (Wu et al., 2012). As expected, we also observed that moderate and high genetic risk of *APOE* and *CLU* combined to magnify the negative effects of poor vascular health, as shown by lower EF performance and steeper EF decline. Prior reports indicate that *APOE* allelic risk may change the amount of CLU present in the frontal lobe in AD (Harr et al., 1996; Nuutinen et al., 2009; Wu et al., 2012), thereby reducing neuronal repair. Our results support this observation and further link *APOE* and *CLU* to EF performance and the frontal cortex. However, we observed no evidence to suggest that the combined effect of the two AD-risk genes produced more than marginally different patterns than those observed separately for each polymorphism. Future work may examine other genetic risk scores as constituted with additional complementary biological mechanisms in order to perhaps separate the patterns observed with the moderate and high risk carriers.

There are five main limitations of our study. First, VLS participants may represent a segment of the older adult population with some relevant advantages, including access to universal health care and relatively high levels of education. Although our sample is not representative of all older adults, it does provide a good estimation of genetic and health factors affecting cognitive performance in a growing segment of the population of older adults in western countries. Second, we considered one important aspect of vascular health (PP), but future research could benefit from a broader representation of vascular health or reactivity. However, PP as a proxy for pulse wave velocity has previously demonstrated sensitivity to cognitive change in non-demented older adults (McFall et al., 2014) and was observed to be sensitive, as expected, in this study. Third, although this sample is relatively large and includes three waves (over 9 years) it should be noted, again, that not all participants had an opportunity to contribute to a third wave. However, this design characteristic did not affect the results at least as evidenced by the invariance testing (as reported in Table 2) and change-related analyses. Fourth, we investigated two selected AD-related genes even though many others exist with the potential to influence EF through synergistic association with vascular health. We chose *APOE* and *CLU* (*APOJ*) specifically given their robust association with cognitive change and mechanistic similarities. Future studies could examine other cognition- and AD-related genetic polymorphisms. Fifth, our results are robust and theoretically

coherent, but they are not tested beyond the interactive nexus of connections among these AD-related genetic and bio-health risk factors and the EF phenotype. We underscore the extent to which dynamically interactive factors in non-demented aging require careful *a priori* biological coherence in order to produce viable mechanistic interpretations.

There are also several strengths of this study. First, we used multiple standard and well-established manifest variables which contributed to a validated, longitudinal EF latent variable. Second, we used an accelerated longitudinal design such that the combination of multiple age cohorts allowed for the inclusion of adults spanning a wide range of age (a band of about 40 years). Third, we employed contemporary statistical methods designed specifically to most accurately investigate our research goals. Fourth, our approach and results emphasize neurobiological and neurocognitive coherence in the context of dynamic changes and interactions predicting an important phenotype in non-demented aging.

In sum, we observed that the risk of poor vascular health on EF performance and change in non-demented older adults is evident in the presence of *APOE* and *CLU* genetic risk polymorphisms, both independently and cumulatively. Moreover, most interestingly, we found that risk-reducing *APOE* and *CLU* genotypes protected against the deleterious effects of moderate to high PP on EF. Notably, our results suggested that the combination of neurodegenerative-related genetic polymorphisms may provide important EF level and slope information beyond that of either individual SNP. Further investigation of the cumulative risk of these (and other) genetic polymorphisms related to neurodegeneration holds promise for understanding the complex genetic and health interactions that produce differential trajectories (from shallow to steep) of cognitive decline with biological aging.

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Highlights

- Poor vascular health is associated with poorer older adult executive function (EF)
- *APOE* low risk carriers are protected from negative effects of poor vascular health
- *CLU* low risk carriers are protected from negative effects of poor vascular health
- *APOE* plus *CLU* risk may contribute different but complementary EF predictions

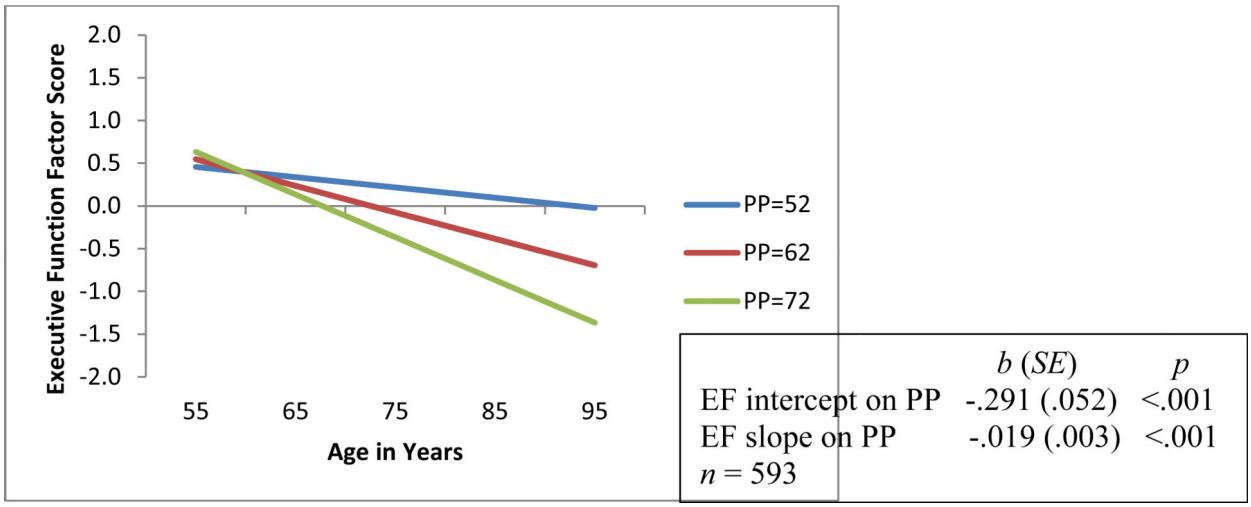

Figure 1.

Predicted growth curve model of executive function (EF) with continuous pulse pressure (PP, mm Hg) as predictor. Three categories of PP are depicted for convenience of display. Age in actual years was the metric of change. The age variable was centered at 75 years.

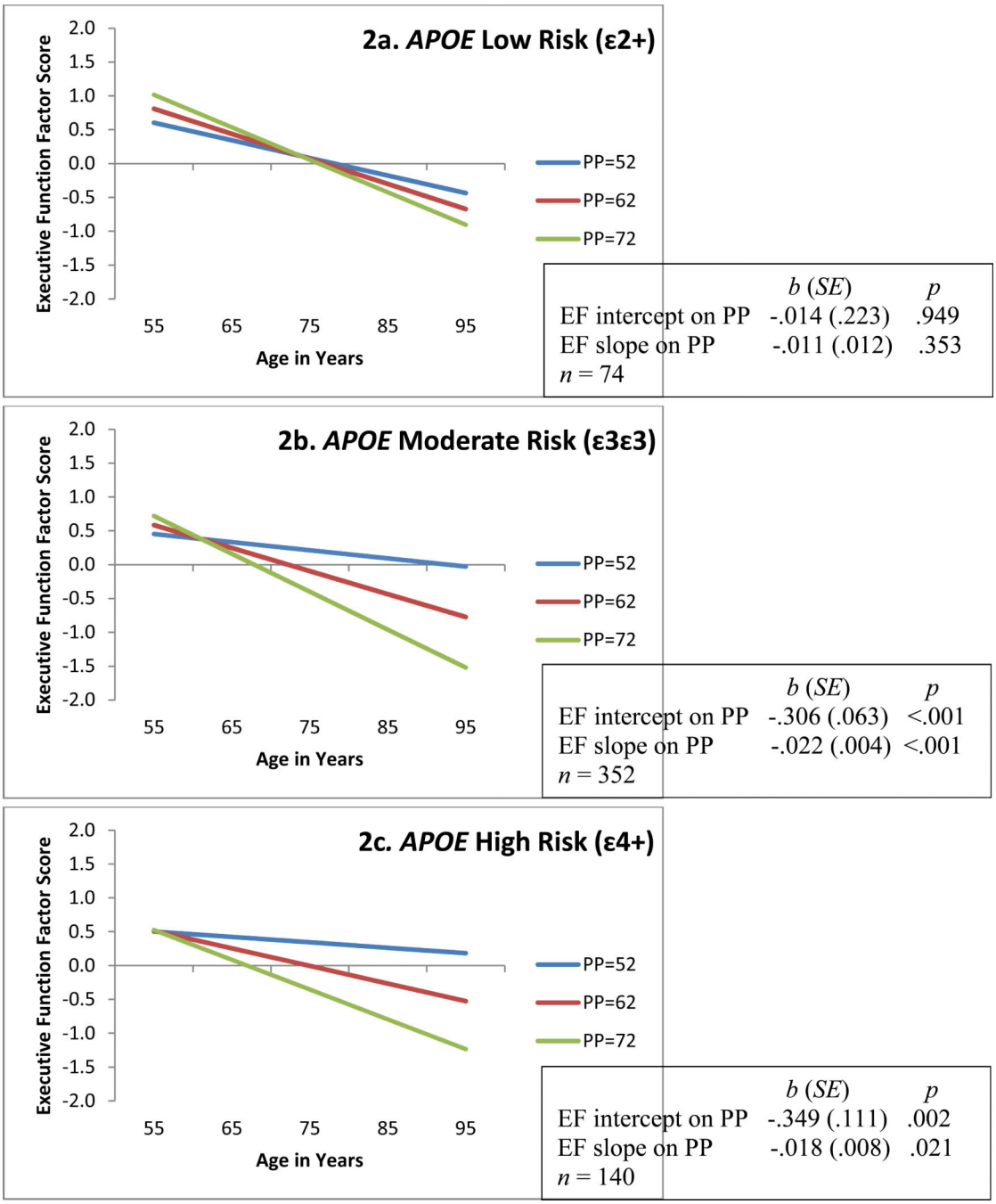

Figure 2.

Predicted growth curve model of executive function (EF) with continuous pulse pressure (PP; mm Hg) as predictor and moderated by *APOE* (ε2+, ε3ε3, ε4+) groupings. Three categories of PP are depicted for convenience of display. Age in actual years was the metric of change. The age variable was centered at 75 years. Moderation analyses $D = 45.4$, $\Delta df = 14$, $p < .001$.

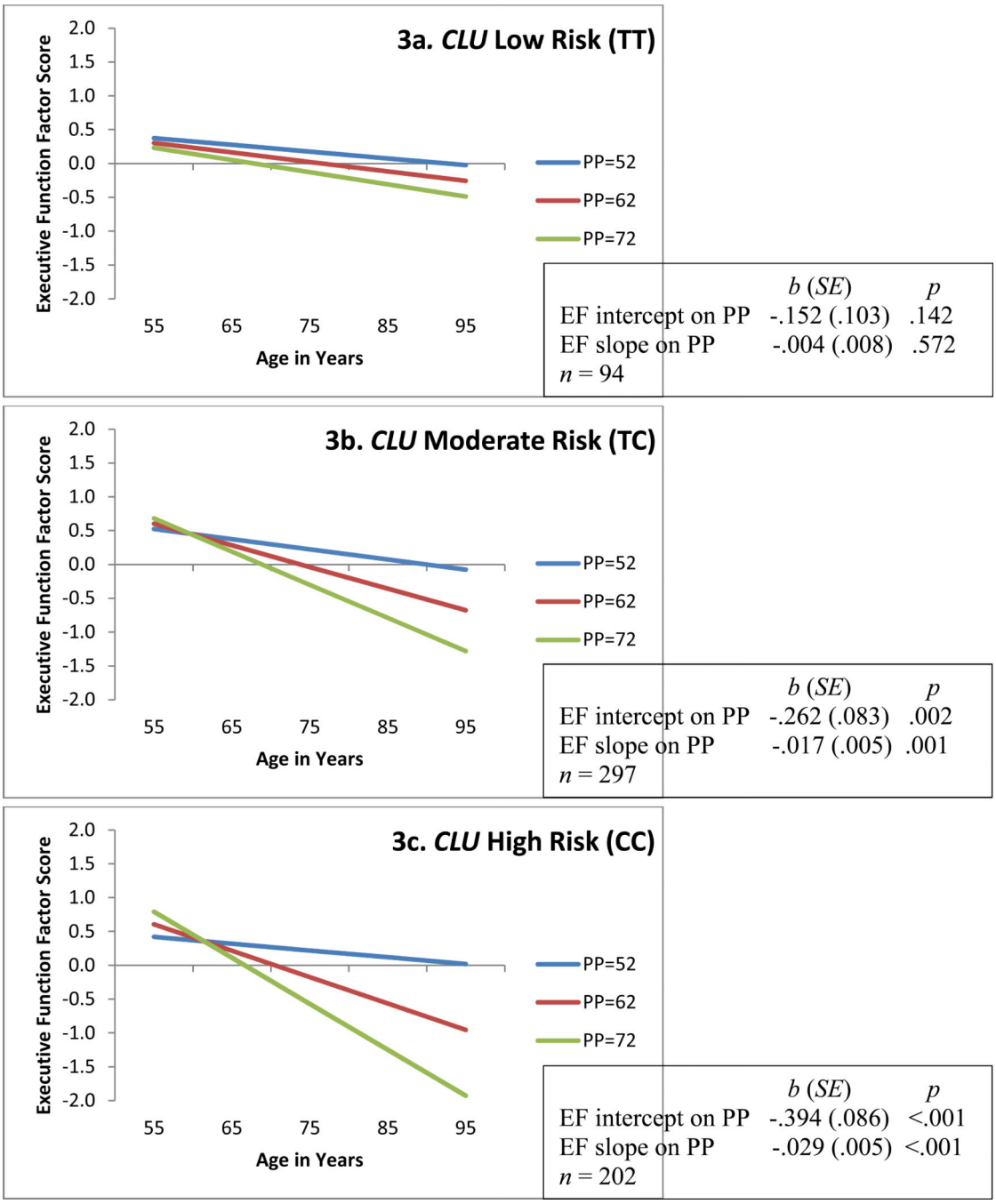

Figure 3.

Predicted growth curve model of executive function (EF) with continuous pulse pressure (PP; mm Hg) as predictor and moderated by *CLU* (TT, TC, CC) groupings. Three categories of PP are depicted for convenience of display. Age in actual years was the metric of change. The age variable was centered at 75 years. Moderation analyses $D = 25.2$, $\Delta df = 14$, $p = .033$.

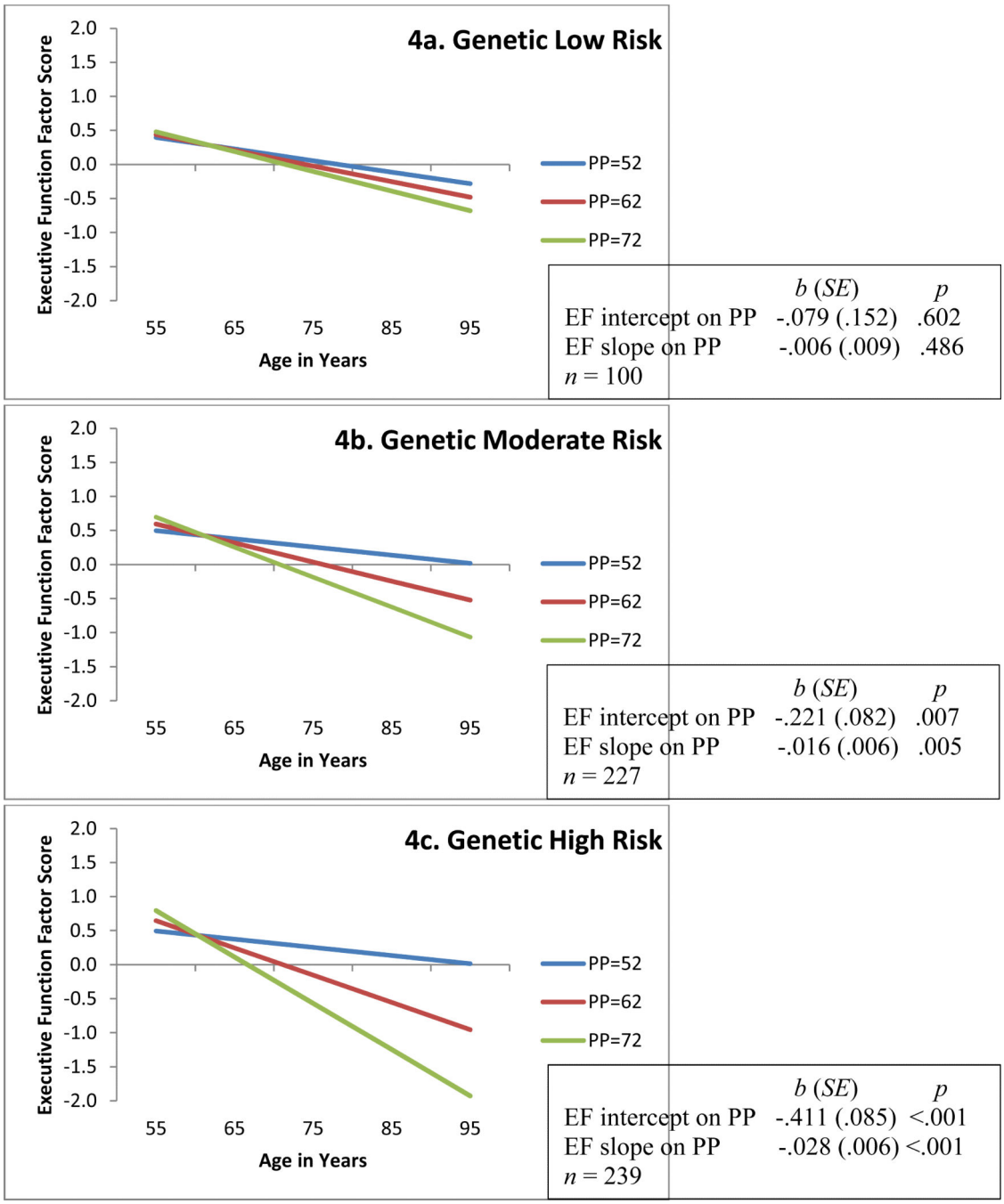

Figure 4.

Predicted growth curve model of executive function (EF) with continuous pulse pressure (PP; mm Hg) as predictor and moderated by *APOE* plus *CLU* (Low, Moderate, High) risk groupings. Three categories of PP are depicted for convenience of display. Age in actual years was the metric of change. The age variable was centered at 75 years. Moderation analyses $D = 27.7$, $\Delta df = 14$, $p = .016$.

Table 1

Participant Characteristics Categorized by Time Point

	Wave 1	Wave 2	Wave 3
N	592[a]	495	319
Years between waves	-	4.45 (.56)	4.42 (.70)
Age	70.3 (8.66)	74.5 (8.53)	76.2 (8.22)
Range	53-95	57-95	62-96
Sex (% Female)	67.3	67.1	69.6
Education	15.3 (2.95)	15.4 (3.01)	15.3 (3.20)
Health to perfect[b]	1.78 (.719)	1.85 (.714)	1.84 (.789)
Health to peers[c]	1.56 (.683)	1.63 (.652)	1.65 (.730)
Pulse Pressure	51.9 (10.2)	55.0 (12.3)	55.2 (12.2)
Range	32.1-99.2	26.0-102.6	29.0-95.5
Systolic Blood Pressure	126.2 (14.3)	126.8 (15.3)	126.8 (14.9)
Range	86.2-171.8	89.1-164.1	94.5-172.8
Hypertension ≥160 *n* (%)	7 (1.2)	7 (1.4)	8 (2.6)
Diastolic Blood Pressure	74.3 (9.31)	71.8 (8.87)	71.7 (8.61)
Range	45.9-105.9	50.9-106.4	52.1-100.6
Hypotension ≤60 *n* (%)	34 (5.7)	39 (6.6)	30 (5.1)
Hypertension Med (%)	26	38	36
Body Mass Index (kg/m^2)	26.8 (4.14)	26.5 (4.28)	26.6 (4.38)
Range	15.0-43.3	16.2-41.0	17.6-40.5
Type 2 diabetes (%)	7.8	7.3	6.9
Smoking Status (%)			
Present	4.1	3.3	1.3
Previous	52.7	55.0	52.5
Never	43.2	41.8	45.6
Mini Mental State Exam	28.7 (1.23)	28.5 (1.39)	28.6 (1.50)
APOE	ε2+	ε3ε3	ε4+
n	74	352	140
Lipid Lowering Med.	4.3	14.2	16.3
Hypertension Med.	31	28	19
CLU	TT	TC	CC
n	88	286	188
Lipid Lowering Med.	11.4	14.0	14.4
Hypertension Med.	26	24	30

Note. Results presented as *Mean* (*Standard Deviation*) unless otherwise stated. Age and education presented in years. Smoking and drinking status are reported in percentages of total sample.

[a] One participant contributed data at Wave 2 but not at Wave 1.

[b] Self-reported health relative to perfect.

[c] Self-reported health relative to peers. Self-report measures are based on 1 “very good” to 5 “very poor”. All vascular health measures are reported in mmHg. Medication use is reported as percentage of self-reported use. These characteristics are represented by wave for convenience only: all longitudinal analyses were conducted with chronological age as the metric of change.

Table 2

Confirmatory Factor Analyses and Latent Growth Goodness of Fit Indexes for Executive Function Models

Model	AIC	BIC	χ^2	df	*p*	RMSEA	CFI	SRMR
CFA for One Factor Model								
Configural Invariance	21288.77	21538.73	41.33	33	.151	.021 (.000-.038)	.995	.029
Metric Invariance	21285.59	21500.46	54.14	41	.082	.023 (.000-.039)	.992	.051
Scalar Invariance	21431.61	21620.17	212.16	47	<.001	.077 (.067-.088)	.895	.101
Partial Scalar Invariance[a,b]	21316.01	21522.11	88.56	43	<.001	.042 (.030-.055)	.971	.076
Model	AIC	BIC	−2LL	*D*	Δdf	*p*		
Latent Growth Model								
Fixed intercept	4349.89	4358.66	4345.89	-	-			
Random intercept	2897.46	2910.46	2891.31	1454.58	1	<.001		
Random intercept Fixed slope	2848.24	2865.78	2840.24	51.07	1	<.001		
Random intercept Random slope[b]	2055.61	2081.92	2043.61	796.63	2	<.001		

AIC = Akaike Information Criteria. BIC = Bayesian Information Criteria. χ^2 = chi-square test of model fit. df = degrees of freedom for model fit. RMSEA = root mean square error of approximation. CFI = comparative fix index. SRMR = standardized root mean square residual. CFA = confirmatory factor analysis. −2LL = −2 log likelihood. *D* = difference statistic (using −2LL). Δdf = change in degrees of freedom.

[a] Brixton and Color Trials free to vary.

[b] Best fitting model.