Integrating Characteristics of Executive Functions in Non-Demented Aging: Structure, Trajectories, Classification, and Biomarker Predictors

by

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Abstract

In aging, executive function (EF) performance (level) and change (trajectory) are linked to multiple interacting risk factors. Structurally, EFs have previously been represented as either a unitary (e.g., unidimensional) or diverse (e.g., multidimensional) set of abilities that change across the lifespan. With EF trajectory data from the Victoria Longitudinal Study (VLS), we investigated four key characteristics of EF change and variability in non-demented aging: trajectories, classification, structure, and biomarker predictors. The source sample characteristics included: $N = 914$; baseline M age = 71.91 ($SD = 9.18$, range = 53.24 – 100.16); % female = 66.2; M education (years) = 15.09. In two sequential studies, longitudinal analyses were conducted on three waves spanning over a 40-year band of aging (53-95). Study 1 investigated EF trajectory distributions, classification of subgroups based on level and slope, and biomarker risk predictors that discriminated these groups. Study 2 investigated subgroups associated with different structural characteristics (e.g., factor solutions) and biomarker risk predictors that discriminated EF subgroups of different dimensionality. For Study 1, we found the following results: (a) significant variability in EF trajectories over a 40-year band of aging; (b) relatively gradual overall EF decline; (c) two continuous quantitatively and distinct classes (higher/stable, lower/declining); (d) EF status classification was discriminated, in order of importance, by education, novel cognitive activity, *BDNF* polymorphism, and age. For Study 2, we found (a) individual differences within a two-factor EF solution characterized by two classes (compressed EF aging/unidimensional, complex EF aging/multidimensional); (b) EF dimensionality was discriminated, in order of importance, by age, novel cognitive activity, education, body mass index, pulse pressure, sex, balance, and physical activity. Clinical interventions that aim to promote functional maintenance and delay cognitive decline may benefit by identifying factors

that affect not only EF performance and structure, but also individualized trajectory patterns in late life.

Preface

This thesis is an original work by Hebert Sebastian Caballero. The research project, of which this thesis is a part, was funded primarily by the US National Institutes of Health (National Institute on Aging; PI: RA Dixon; R01 AG 008235). The project has received continuous (and current) research ethics approval from the University of Alberta Health Research Ethics Board. All participants contributed signed informed consent.

A portion of this thesis will be submitted for publication with co-authors G. Peggy McFall, Yao Zheng, Sandra A. Wiebe, and Roger A. Dixon. H. S. Caballero was responsible for concept formation, literature review, statistical analyses, and manuscript composition. G. P. McFall contributed with the statistical analyses and concept formation in Study 1. Y. Zheng assisted with the statistical analyses and concept formation in Study 2. R. A. Dixon was the supervisory author and was involved in all aspects of project development and execution.

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Introduction

Executive function (EF) refers to mental control processes, associated with neuroanatomical integrity of the brain, that monitor aspects of action and cognition in humans (Luszcz, 2011; Miyake & Friedman, 2012). Much empirical and theoretical work pertains to EF performance and change throughout the lifespan. One prominent theory has direct implications for research on brain and cognitive aging (Luszcz, 2011; McFall, Sapkota, Thibeau, & Dixon, 2017; West, 2017). The de/differentiation theory suggests that across the lifespan EFs are structurally differentiated (two or three dimensions) for older children, adolescents and mature young adults (Chevalier & Clark, 2017; Lee, Bull, & Ho, 2013; Miyake et al., 2000; Wiebe & Karbach, 2017), but as adulthood progresses there may be dedifferentiation that culminates in a unidimensional structure in both non-demented and impaired aging (de Frias, Dixon, & Strauss, 2006; Li, Vadaga, Bruce, & Lai, 2017; McFall et al., 2014). However, recent research has indicated that selected neurologically healthy and cognitively advantaged aging adults may retain EF differentiation (de Frias, Dixon, & Strauss, 2009). The three dimensions of EFs are: shifting (switching flexibly between tasks or mental sets), updating (monitoring and adding/deleting working memory representations), and inhibition (inhibit dominant, prepotent, or dominant responses; Miyake et al., 2000; Miyake & Friedman, 2012).

In adulthood, the three EF dimensions show a pattern described as "unity and diversity" due to their shared but distinct functions (Friedman & Miyake, 2017). In other words, the three dimensions are moderately correlated with one another, but are clearly separable and contribute differentially to EF performance. Evidence of the unity and diversity of EFs in older adults has been replicated in multiple studies (e.g., Fisk & Sharp, 2004; Hedden & Yoon, 2006; Hull, Martin, Beier, Lane, & Hamilton, 2008; Vaughan & Giovanello, 2010). The unity/diversity

model assumes that multiple brain regions support the same EF processes in all individuals (Friedman & Miyake, 2017). However, individuals may also have different levels or profiles of abilities, leading to differences in performance, structure, brain activation, volume, and connectivity.

The present research uses data from the Victoria Longitudinal Study (VLS), which includes multiple indicators of each of the three dimensions on participants followed over multiple years of aging. From the VLS archives, a series of two longitudinal studies were designed to examine four key characteristics of EF change and variability in non-demented aging. For Study 1, the aim was directed at examining trajectories, classification, and biomarker risk predictors that discriminated EF classification. For Study 2, the aim was directed at examining structural changes (unidimensional, multidimensional) of EF and biomarker risk predictors that discriminated these structural changes.

Background

Executive Function and the Aging Brain

Clinical studies have shown strong associations between EFs and the prefrontal cortex (PFC) when examining patients with executive dysfunction after PFC damage (Alvarez & Emory, 2006; Clark et al., 2008; Manes et al., 2002; Zelazo & Muller, 2002). Neuroimaging research has also shown support of the strong connection between EF and the PFC, with more specific activation in the lateral prefrontal cortex during EF tasks (Aron, Robbins, & Poldack, 2014; Konishi et al., 1998; Laird et al., 2005). However, there are also other areas of the brain associated with EF. For instance, areas of the fronto-parietal network, including posterior parietal cortex, ventrolateral prefrontal cortex, dorsolateral prefrontal cortex, and subcortical regions are

connected to EF (Buchsbaum, Greer, Chang, & Berman, 2005; Kim, Cilles, Johnson, & Gold, 2012; Moriguchi, 2017).

Developments in moderate to high density electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI) have been useful in enhancing our knowledge of the effects of aging on the neural basis of EF (West, 2017). EEG has been used to measure the spatial and temporal distribution of neural activity when performing EF tasks in young and aging adults (Finnigan & Robertson, 2011; Sauseng, Klimesch, Schabus, & Doppelmayr, 2005; West, 2016, 2017). Functional MRI studies on EF have found that older adults have less PFC activity on inhibition tasks (e.g., Chadick, Zanto, & Gazzaley, 2014; Jonides et al., 2000). However, older adults have greater increased activity in bilateral frontal and parietal regions when performing shifting tasks than younger adults (Jimura & Braver, 2009; Madden et al., 2007; Methqal et al., 2017; Townsend, Adamo, & Haist, 2006). These results suggest that there may be neuroplasticity occurring in some brain regions in healthy older adults to compensate for white matter degradation in other areas.

In the broader context of cognition, diffusion tensor imaging studies have found the following conclusions especially relevant to EF aging: (a) white matter integrity declines in healthy aging, (b) increased white matter is associated with better cognitive performance, (c) age mediates the effect of white matter integrity on cognitive performance, and (d) cortical disconnection contributes to cognitive decline in healthy older adults (Bennett & Madden, 2014). Specific to EF is the growing evidence showing how this cognitive ability is among the most age-sensitive due to age-related neurodegeneration in EF brain regions (Glisky, 2007; Peters & Morrison, 2012; Raz, Dahle, Rodrigue, Kennedy, & Land, 2011; Raz & Rodrigue, 2006). However, cognitively normal older adults are able to maintain stable EF performance and can

retain a multidimensional EF structure (de Frias et al., 2009). This suggests that there may be other factors such as genetic, health, and lifestyle that moderate EF decline. In contrast, EF decline may be exacerbated by genetic risk, functional health decline, and unhealthy lifestyle such as lack of physical activity (e.g., Erickson, Hillman, & Kramer, 2015; Ferencz et al., 2014; McFall et al., 2014; Small, Dixon, McArdle, & Grimm, 2011; Thibeau, McFall, Wiebe, Anstey, & Dixon, 2016).

EF and Genetic Factors

Two genetic variants that have received sustained attention for their role in age-related differences in EF performance are the *catechol-O-methyltransferase* (*COMT*) and the *brain-derived neurotrophic factor* (*BDNF*; e.g., Bilder, Volavka, Lachman, & Grace, 2004; Miyajima et al., 2008; Payton, 2009). COMT is essential in the clearing of dopamine in the PFC (Chen et al., 2004). The Val158Met *COMT* polymorphism at codon 158 on chromosome 22q11 increases COMT enzymatic activity, causing a decrease in dopamine levels mostly in the PFC; this results in *COMT* homozygotes for the Met allele to have greater dopamine levels than the homozygotes for the Val allele. Therefore, in non-demented older adults, there may be a greater risk for EF impairment for those with Val allele combinations (Val-Val, Val-Met) than Met-Met combinations (Nagel et al., 2008; Sapkota, Vergote, Westaway, Jhamandas, & Dixon, 2015; Wishart et al., 2011). BDNF is a molecule also present in the PFC and helps modulate brain plasticity (Komulainen et al., 2008). Furthermore, it supports the health and functioning of glutamatergic neurons, which are major projection neurons that connect cognitive brain regions. The *BDNF* Val66Met polymorphism is characterized by an amino acid substitution from valine to methionine at codon 66; substitution of Val to Met may result in disruption of neuronal trafficking and processing (Egan et al., 2003; Liu et al., 2014; Ventriglia et al., 2002). Research

has found that BDNF concentration declines in late adulthood. (Cotman & Engesser-Cesar, 2002; Erickson, Prakash et al., 2010). In addition, secretion of BDNF is higher in Val homozygotes than in Met carriers, which may place the Met homozygotes at greater risk of selective cognitive deficits (Nagel et al., 2008; Sapkota et al., 2015). Research exploring the synergistic effects of *COMT* and *BDNF* has shown that *COMT* Val carriers have lower EF performance when they are also *BDNF* Met carriers and the effects are magnified with older age (McFall et al., 2017; Nagel et al., 2008).

A polymorphism that has received attention in relation to cognitive decline and dementia is the *apolipoprotein E* (*APOE*; rs429358 and rs7412*)* genotype. ApoE plays an important role in repair and transport of cholesterol to tissues and cells. The *APOE* genotype consists of three alleles: ε2, ε3, and ε4. The ε4 allele (both homozygosity and heterozygosity) has been found to be a risk factor for age-related cognitive decline, mild cognitive impairment, and dementia (e.g., Brainerd, Reyna, Petersen, Smith, & Taub, 2011; Elias-Sonnenschein, Viechtbauer, Ramakers, Verhey, & Visser 2011; Wisdom, Callahan, & Hawkins, 2011). The ε2 allele has been found to confer a reduced risk of Alzheimer's disease (AD), increased longevity, and sustained cognitive health (e.g., de-Almada et al., 2012; Panza et al., 2000; Suri, Heise, Trachtenberg, & Mackay, 2013). The mechanisms underlying the risk effect of the ε4 allele and the protective effect of the ε2 allele may be found in the intrinsic difference of the apoE protein that result from these alleles. The apoE2 and apoE4 proteins differentiate by a single amino acid substitution (Suri et al., 2013). These substitutions may not only affect protein conformation and stability, but also activity (Hatters, Peters-Libeu, & Weisgraber, 2006; Mahley & Huang, 2012). For instance, in mouse models, research has shown that ε2 mice are more effective at clearing amyloid-β

(hallmark of AD pathology) from the bloodstream than ε4 mice, as well as promoting amyloid-β degradation more effectively than ε4 mice (Jiang et al., 2008; Sharman et al., 2010).

In relation to *APOE* non-ε4 carriers, *APOE* ε4 carriers perform significantly poorer on EF measures in healthy cognitive aging (Wisdom et al., 2011). Recent evidence suggests that the synergistic effects of *COMT* and *BDNF* risk alleles on EF may be modified by the presence or absence of *APOE* ε4 (Sapkota et al., 2015). Specifically, EF performance is significantly predicted when examining additive effects of *COMT* + *BDNF* + age as stratified by *APOE* risk and non-risk groups. Therefore, *APOE* may act directly or as a moderator of other gene-cognition associations in aging. However, what is not yet known is whether *APOE* has direct effects or acts as a moderator when examining differences in EF structure.

The *insulin degrading enzyme* (*IDE*; rs6583817) polymorphism has also been shown to affect EF performance and change in aging. In terms of function, IDE is responsible for the degradation of hormones and bioactive peptides (McFall et al., 2013). It is the most important proteolytic enzyme for insulin and it is involved in the processing of amylin, glucagon, and amyloid beta (Bennett, Duckworth, & Hamel, 2000; Kurochkin & Goto, 1994; Shen, Joachimiak, Rosner, & Tang, 2006). The *IDE* gene variants have been linked to increased risk of dementia and AD (Bartl et al., 2011; Belbin et al., 2011; Carrasquillo et al., 2010). Independent *IDE* effects in older adults show that those with the major *IDE* G allele perform better on EF and have better protection for normal cognitive functioning than homozygotes for the minor *IDE* A allele (McFall et al., 2013; McFall et al., 2014). Interestingly, *IDE* not only affects EF performance but is also able to moderate EF change in older adults. Longitudinal research has shown that those individuals who possess the G allele exhibit reduced EF decline compared to those who do not possess the G allele (McFall et al., 2013).

Effects of Functional Biomarkers on EF

In general, vascular health tends to decline with age and may contribute to cognitive decline and dementia (e.g., Gorelick et al., 2011; Qiu, Winblad, & Fratiglioni, 2005). A particular indicator of vascular health that has been commonly used is pulse pressure (PP; Dahle, Jacobs, & Raz, 2009; McFall et al., 2014; Waldstein et al., 2008). PP is a proxy for arterial stiffness and is calculated as systolic minus diastolic blood pressure. Research has found associations between PP and EF deficits in healthy young and older adults (Raz et al., 2011). More recent research has shown that worse PP (e.g., 72 mmHg) in older adults produces poorer EF performance and increased EF decline (McFall et al., 2014). Protective alleles from polymorphisms associated with EF may not protect against the detrimental effects of PP on EF. For instance, adults with the *IDE* G allele and less healthy levels of PP show decrements in EF performance and steep EF decline over 9-year trajectories (McFall et al., 2014).

Although there are biological reasons to believe that body fat predicts cognitive function, growing evidence shows that elevated body mass index (BMI) increases the risk of cognitive impairment, including poor EF performance and greater EF decline (e.g., Anstey, Cherbuin, Budge, & Young, 2011; Gunstad et al., 2007; Taki et al., 2008). MRI studies have shown that young, middle-aged, and older adults with elevated BMI have reduced gray matter volume in brain regions associated with EF (Taki et al., 2008). This may account for the association between lower EF performance and elevated BMI. Evidence from cross-sectional research showed that across a broad range of adulthood (20-82 years), overweight and obese adults (BMI > 25) exhibit poorer EF performance than adults with normal weight (BMI 18.5-24.9) and the relationship does not vary with age (Gunstad et al., 2007).

Another factor that may also be associated with EF is peak expiratory flow. Peak flow has been suggested to be a measure of lung function, overall vitality, and a sensitive index of general physical and cognitive functioning in older adults (e.g., Aleman, Muller, de Haan, & van der Schouw, 2005; Cook et al., 1995; Roberts, & Mapel, 2012; Simons, Simons, McCallum, & Friedlander, 2006). Peak flow has mostly been associated with general cognitive status (e.g., Allaire, Tamez, & Whitfield, 2007) and direct links with EF are still unclear. However, brain regions associated with EF may be affected due to a decreased amount of oxygen in the brain caused by poor lung function.

Aging has a detrimental effect on overall hand function, especially hand and finger strength (Ranganathan, Siemionow, Sahgal, & Yue, 2001). This negative effect may be attributed to deterioration of muscle coordination and degeneration of the central nervous system (Hunter, White, & Thompson, 1998; Ranganathan et al., 2001). A hand-held dynamometer is commonly used to measure grip strength. Grip strength is a useful indicator of frailty and general muscle strength (Mirelman et al., 2012). Research has found links between muscle strength and cognitive decline, including EF, in older adults (e.g., Boyle, Buchman, Wilson, Leurgans, & Bennett, 2009). A stable relationship has been found between decreased grip strength and decreased performance in aspects related to EF (e.g., processing speed) starting after 65 years of age (Sternäng et al., 2015). Greater decline and individual differences may also be observed as the aging process intensifies and accelerates.

Lifestyle Factors and EF

There is extensive evidence showing the positive effects that fitness training and exercise interventions have on healthy brain aging and overall health (e.g., Erickson, Raji et al., 2010; Kelly et al., 2014; Voss et al., 2013). However, everyday physical activity (EPA) has received

particular interest due to its impact on cognition, including EF. In general, EPA is a modifiable lifestyle factor that may increase gray matter volume in the brain; it encompasses a wide range of activities such as walking, jogging, exercising, and gardening (Erickson, Leckie, & Weinstein, 2014; Thibeau, McFall, Camicioli, & Dixon, 2017). Longitudinal studies examining middle-aged and older adult populations have shown that higher baseline EPA is associated with improvements and better EF performance and less EF decline (e.g., Blasko et al., 2014; Thibeau et al., 2016; Wang et al., 2012). In contrast, passive activity such as high frequency of TV viewing with little to no EPA predicts lower EF performance and may lead to further EF decline in young and older adults (Meijers, Harte, Jonker, & Meynen, 2015; Wang et al., 2006).

Engagement in cognitive activity such as reading books/newspapers, writing, solving crossword puzzles, and studying have shown to protect against cognitive impairment leading to dementia (e.g., Valenzuela & Sachdev, 2009; Wang, Karp, Winblad, & Fratiglioni, 2002; Wilson, Scherr, Schneider, Tang, & Bennett, 2007). An explanation for this may be attributed to the cognitive reserve theory which states that environments stimulating physical, cognitive, and social interactions may help compensate for neurodegeneration, thereby delaying the onset of dementia (Blasko et al., 2014). The exact mechanisms in which cognitive reserve may work on include improving cerebral blood flow, stimulating neurogenesis, and potentiating synaptic strength. Results demonstrate that cognitive activity (a) consistently correlates with parameters of EF, (b) is associated with better EF performance, and (c) reduces EF decline in older adults (Mueller, Raymond, & Yochim, 2013).

Mobility Markers and EF

Studies have hypothesized that cognitive decline affects mobility, especially when there is impairment in EF (e.g., Ble et al., 2005). Evidence suggests that this occurs because numerous

EF components are needed when particular mobility tasks are performed in everyday environments. For instance, response inhibition is needed to allow an individual to focus on gait when walking in an environment with numerous distractors. Research has found associations between gait speed and better EF performance in older adults (Holtzer, Verghese, Xue, & Lipton, 2006; Watson et al., 2010). EF decline has been found to be related to disturbances in gait stability and increases in fall risk (Mirelman et al., 2012; Springer et al., 2006). EF deficits also contribute to poor locomotion and difficulties performing a turn; these deficits may also be reflected in cognitive EF performance (e.g., Coppin et al., 2006; Giladi, Huber-Mahlin, Herman, & Hausdorff, 2007; Kearney, Harwood, Gladman, Lincoln & Masud, 2013).

Effects of Age, Sex, and Education on EF

The topic of age-related changes in EF has been extensively investigated in the past two decades (e.g., Luszcz, 2011; Rabbitt, 1997; Reuter-Lorenz, Festini, & Jantz, 2015). A recent compendium presents new research and perspectives on lifespan changes in EF performance and structure (Wiebe & Karbach, 2017). With the development of newer techniques in neuroscience, recent evidence has linked cortical thinning and volumetric loss in the PFC with chronological age, and poor EF performance (Li et al., 2017; Yuan & Raz, 2014). Evidence showing cognitive training affecting local brain structure (e.g., Engvig et al., 2010) may explain the relationship between age-related brain changes and EF performance. For instance, cortical thinning and volumetric loss may disrupt the response to increased cognitive activity (Yuan & Raz, 2014). Research examining age-related EF decline has found that the most common affected functions involve inhibition, abstraction, mental flexibility, and concept formation (e.g., Bielak, Mansueti, Strauss, & Dixon, 2006; Harada, Natelson Love, & Triebel, 2013; Hasher, Lustig, & Zacks, 2007; McFall et al., 2017). However, age-related deficits have also been found in the updating

and shifting domains of EF (Bopp & Verhaeghen, 2005; Kray & Lindenberger, 2000; Mayr, 2001; Wasylyshyn, Verhaeghen, & Sliwinski, 2011). In general, advancing age is associated with accelerated longitudinal decline in EF performance (e.g., McCarrey, An, Kitner-Triolo, Ferrucci, & Resnick, 2016).

Structurally, EFs undergo changes across the lifespan from EF differentiation in children and young adults (Chevalier & Clark, 2017; Lee et al., 2013; Miyake et al., 2000; Wiebe & Karbach, 2017; Wiebe et al., 2011) to EF dedifferentiation in older adults (Adrover-Roig, Sesé, Barceló, & Palmer, 2012; de Frias et al., 2006, 2009; Li et al., 2017; McFall et al., 2017; McFall et al., 2014). However, structural changes in EF may not affect the older adult population equally. In normal cognition, longitudinal invariance testing shows a multidimensional (three-factor) and unidimensional (one-factor) model of EF structure (de Frias et al., 2009; McFall et al., 2017), suggesting that EF structure in normal cognitive aging is variable and depends on other factors (e.g., genetic, lifestyle).

Sex and gender are conceptually distinct terms, with sex relating to biological and physiological (e.g., anatomy, hormones, chromosomes) differences between males and females, and gender relating to cultural or societal roles and aspects (e.g., socioeconomic status, occupation) that are used in a society to differentiate masculinity from femininity (Johnson, Sharman, Vissandjee, & Stewart, 2014; Ritz et al., 2014; Tierney, Curtis, Chertkow, & Rylett, 2017). The confusion between these terms may explain why past research encountered mixed results about differences in EF performance between males and females in brain and cognitive aging (e.g., Moering, Schinka, Mortimer, & Graves, 2003; van Boxtel, ten Tusscher, Metsemakers, Willems, & Jolles, 2001). Recent research examining cognitive function trajectories in both young (female mean age: 20.7 ± 0.3 years; male mean age: 21.2 ± 0.3 years)

and aging (50 years and over) groups has found the following results regarding sex or gender differences: (a) women have significantly less decline than men in memory, executive function, and global cognitive function; (b) at baseline, men outperform women in visuospatial ability; (c) cognitive change over time indicates steeper rates of decline for men on measures of perceptuomotor speed and integration, mental status, and visuospatial ability; (d) women improve more than men after practice on inhibitory tasks (Mansouri, Fehring, Gaillard, Jaberzadeh, & Parkington, 2016; McCarrey et al., 2016; Zaninotto, Batty, Allerhand, & Deary, 2018). An explanation for these findings is that women are less vulnerable to macrostructural and age-related changes in the brain, as supported by research showing males not only having less cortical thickness, but also experiencing cortical thinning at a greater rate than females (Luders et al., 2006; Pacheco, Goh, Kraut, Ferrucci, & Resnick, 2015; Sowell et al., 2007). Interestingly, genetic research has provided evidence of improved cognitive performance from physical activity in male *BDNF* Met non-carriers, but not in Met carriers, and no effect in females regardless of genotype (Watts, Andrews, & Anstey, 2018), suggesting gene-lifestyle interactions in determining sex differences in cognitive performance. Relating to cultural or societal aspects, recent research has found that childhood middle socioeconomic status is related to lower baseline levels of EF in women but not men (Zaninotto et al., 2018).

Having a high level of education appears to be a strong predictor of optimal cognitive functioning in older age and may also be a factor that protects against age-related cognitive decline in some cognitive domains (Alley, Suthers, & Crimmins, 2007; Bento-Torres et al., 2017; Bosma, van Boxtel, Ponds, Houx, & Jolles, 2003; Guerra-Carrillo, Katovich, & Bunge, 2017; Wilson et al., 2009). Those individuals with more education may have the advantage of possessing greater cognitive reserve capacity than those with less education (Stern, 2003; Tucker

& Stern, 2011; Tucker-Drob, Johnson, & Jones, 2009; Ward, Summers, Saunders, & Vickers, 2015). Cognitive impairment is delayed when there is a larger cognitive brain reserve capacity (Stern, 2003, 2012). Therefore, education helps in building reserve capacity to protect against the damaging effects that aging has on brain functions. In addition, early education may promote aspects of cognitive development during important stages of childhood that protect against cognitive decline in late-life (Zahodne, Stern, & Manly, 2015). These perspectives are supported by results that show EF decline with age is more pronounced in individuals with less education, specifically in shifting and inhibition tasks (Dorbath, Hasselhorn, & Titz, 2013; Tun & Lachman, 2008; van der Elst, van Boxtel, van Breukelen, & Jolles, 2006; van Hooren et al., 2007; Wecker, Kramer, Hallam, & Delis, 2005). In relation to sex or gender, recent research has suggested that lower baseline levels of EF are related to educational attainment in men, but not women (Zaninotto et al., 2018). As previously mentioned, in women, childhood middle socioeconomic status was related to lower baseline levels of EF.

Research Goals

The purpose of this research was to examine and predict longitudinal change in level of performance and structure of EF in a cognitively normal aging group. Two longitudinal studies were designed to integrate four key characteristics of EF change and variability in non-demented EF aging: trajectories, classification, structure, and biomarker predictors. A 3-wave VLS data set was assembled covering over a 40-year age span (53-95 years). Preliminary analyses were conducted to (a) confirm a one-factor EF latent variable for the whole sample and (b) test the measurement invariance of the EF latent variable model across the three waves. Three research goals were examined for Study 1 and two for Study 2. Study 1 goals were: (1a) use results obtained from preliminary analyses and determine an EF latent growth curve from trajectory

distributions, (1b) establish objective stable and declining groups of EF change, and (1c) test biomarker risk predictors (e.g., genetic, vascular, functional, lifestyle) that discriminate these groups. Study 2 goals were: (2a) identify subgroups associated with different structural characteristics (e.g., factor solutions or dimensions) and (2b) test biomarker risk predictors that discriminate EF subgroups of different dimensionality (unidimensional vs. multidimensional).

Method and Materials

Participants

Participants were community-dwelling adults of the Victoria Longitudinal Study (VLS). The VLS is an ongoing large-scale, multi-cohort, longitudinal sequential study of cognitive, neuropsychological, genetic, biomedical, and lifestyle aspects of human aging (Dixon & de Frias, 2004). Participants were originally recruited by using advertisement through the public media and requests from community groups. All participants provide written informed consent and are paid nominal fees for their participation. Data collection procedures are in full and certified compliance with human research ethics guidelines and boards. Using standard procedures (e.g., Dixon, Small, MacDonald, & McArdle, 2012; McFall et al., 2014; Small, Dixon, & McArdle, 2011), a longitudinal data set consisting of three sequential samples and all available waves since the early 2000s was assembled. The EF tasks used for this project were added to the VLS neuropsychological battery at this point. We assembled and merged (a) Sample 1 (S1) Waves 6, 7, and 8; (b) Sample 2 (S2) Waves 4, 5, and 6; and (c) Sample 3 (S3) Waves 1, 2, and 3. For terminological purposes, the earliest wave of each cohort is specified as Wave 1 (W1 or baseline) and the second and third wave as Wave 2 (W2) and Wave 3 (W3). The wave-to-wave retention rates were as follows: (a) S1 W1-W2 = 60%; (b) S1 W2-W3 = 80%; (c) S2 W1-W2 = 67%; (d) S2 W2-W3 = 66%; (e) S3 W1-W2 = 71%; (f) S3 W2-W3 = 77%. The initial

source sample included 914 persons (baseline *M* age = 71.91, *SD* = 9.18, range = 53.24 – 100.16, 66.2% female, *M* years of education = 15.09).

We applied multiple exclusionary criteria. Participants were excluded if they had (a) EF data missing from all three waves, (b) reported diagnosis of mild to very serious Alzheimer's disease or other forms of impairment and dementia, (c) self-reported history of very serious head injury (e.g., in a coma, hospitalized), epilepsy, and depression, (d) self-reported moderately serious to very serious stroke (either side of the brain), (e) self-reported history of moderate-to-severe Parkinson's disease, (f) Mini-Mental Status Examination (MMSE) score less than 24, and (g) use of anti-psychotic medication. After applying these exclusionary criteria, we established an EF trajectory sample comprised of 781 participants (baseline *M* age = 71.42, *SD* = 9.07, range = 53.24 – 95.25, 66.6% female). Table 1 shows descriptive statistics for the trajectory sample, including mean performance and standard deviation for each of the EF measures used. We used this sample for our preliminary analyses and to examine research goals 1a, 1b, and 2a.

Given the necessity of genetic data for the prediction analyses, a sub-sample of 570 (baseline *M* age = 70.10, *SD* = 8.50, range = 53.24 – 95.25, 66.5% female) participants who contributed genetic data during collection occurring from 2009 – 2011 was used. This cohort comprised our prediction sample and was used to examine research goals 1c and 2b. Table 2 shows baseline descriptive statistics for this sample, including the biomarker predictor variables.

Measures

Executive function (EF). Eight standard neuropsychological measures were used as indicators of three dimensions of EF: two each for inhibition and updating and four for shifting. The first six tests listed below have been used in previous studies (e.g., de Frias et al., 2006, 2009; McFall, Sapkota, McDermott, & Dixon, 2016; Thibeau et al., 2016) and represent

inhibition (Hayling, Stroop), shifting (Brixton, Color Trails), and updating (Computational Span, Reading Span). The last two non-verbal tests (Letter Series, Letter Sets) were tested in this research for their contribution to measuring the shifting domain. Overall, these tests have been included in multiple studies and their psychometric properties have been reported in both clinical and healthy populations (e.g., Bielak et al., 2006; de Frias & Dixon, 2014; McFall et al., 2014; McFall et al., 2013; Quereshi & Seitz, 1993; Sapkota et al., 2015).

Hayling sentence completion test. This test is associated with the inhibition domain and consists of two sections (Burgess & Shallice, 1997). Each section has a set of 15 sentences and each sentence has the last word missing. In Section 1, the participant listens as the examiner reads the sentence aloud and when the examiner finishes reading, the participant completes the sentence as fast as possible. For example, "the dispute was settled by a third . . . [participant says] party." The first section is used to measure response speed. In Section 2, the examiner reads the sentence aloud and the participant completes the sentence with a word that is completely unrelated or unconnected to the sentence in every way. For example, "none of the books made any . . . [participant says] computer." In this part, the participant has to restrain a strongly activated (automatic) response and, before answering, has to generate a new response. A response would be coded as an error if the participant fails to inhibit an automatic response (i.e., completing a sentence with a word that is connected to the sentence). The task yields two measures of response speed (from Section 1 and 2) and one error score (from Section 2). Scaled scores range from 1 to 10, with 1 being "impaired" and 10 being "very superior".

Stroop test. This test is associated with the inhibition domain. It requires the participant to inhibit the automatic response of reading a printed word and instead name the color in which the word is printed as fast as possible (Regard, 1981; Taylor, Kornblum, Lauber, Minoshima, &

Koeppe, 1997). The test consists of three parts. In Part A, the participant names, row by row, from left to right, and as fast as possible, the color of 24 dots printed in either red, blue, green, or yellow ink. The participant continues naming the color of each dot until the entire card is completed. The dots are arranged in a random order across the card. In Part B, the participant names the color in which the word is printed as fast as possible, ignoring the verbal content. In Part C, words are replaced by actual color words printed in red, blue, green, or yellow. For example, the word "blue" may be printed in red ink or the word "green" may be printed in blue ink. The participant names the color in which the word is printed as fast as possible. The performance score is based on the interference index (Part C – Part A / Part A).

Brixton test. The Brixton Spatial Anticipation Test (Burgess & Shallice, 1997) is a shifting task and consists of a booklet of 56 pages with numbers and circles that have the same basic design: There are 10 circles in two rows of 5, numbered 1-10 for the position, and one position is always colored blue. As the pages are turned, the blue dot moves around according to various patterns that come and go without warning. The participant is shown one page at a time and is asked to decide where the blue dot is going to be on the next page, based on the pattern shown on the previous page. Total errors are recorded based on the test manual: maximum of 54 errors and converted to a scaled score of 10. For the analysis, a standard scale score was used ranging from 1 (impaired) to 10 (very superior).

Color Trails Test (CTT). The CTT (D'Elia, Satz, Uchiyama, & White, 1996) was designed to measures shifting as an executive process and it consists of two parts. In Part 1, the participant makes pencil lines and connects encircled numbers in order from 1 to 25. The encircled numbers are scattered randomly throughout the page and the participant finds the numbers and connects them in order. The circles are arranged in pink and yellow background

with odd numbers having a pink background and even numbers a yellow background. In Part 2, there is a sequence of repeated encircled numbers from 1 to 25 and each sequence has alternating yellow and pink colors. For example, the encircled number 1 is shown twice, but one circle is pink and the other one is yellow. Similar to Part 1, the participant is still required to connect the circles from 1 to 25, but this time the participant has to alternate between pink and yellow circles and choose the circle with the number sequence that is the alternate version of the previous color circle (see D'Elia et al., 1996). The time to complete the task for both Part 1 and Part 2 is recorded in seconds. For the analysis, the latency score of Part 2 was used.

Computational span. This working memory task is used to tap the updating domain (Salthouse & Babcock, 1991). Participants are asked to solve a series of arithmetic problems while remembering the last digit of each problem they solve in order to be recalled later. There is an increase in the number of problems in a series from one to seven, with three trials at each series length. The measure used was the highest span correctly recalled for two out of three trials.

Reading span. This task is associated with the updating domain and requires participants to answer questions about orally presented sentences while remembering the final word of each sentence for later recall. There is an increase in the number of sentences in the passage from one to seven, with three trials at each series length. The measure used was the highest span correctly recalled for two out of three trials.

Letter series test. This task was used for its contribution to the shifting domain. In the letter series test (Thurstone, 1962), participants are required to identify the pattern of a series of letters. Participants have to decipher the pattern in the target string and then match the letter in the string that is congruent with the pattern presented. The last letter of the series of letters has to

be placed in such a way that it would continue the established pattern. The outcome measure used was the total number correct out of 20 patterns.

Letter sets test. This task was used for its contribution to the shifting domain. Each problem in this test (see Ekstrom, French, Harman, & Dermen, 1976) has five sets of letters with four letters in each set. Four of the sets of letters are alike in some way. Participants are required to find the rule that makes the four sets alike. One of the sets of letters is different from the others and will not fit the rule. Participants circle the set of letters that is different. The outcome measure used was the total number correct out of 15 problems.

DNA extraction and genotyping. Saliva samples were collected according to Oragene DNA Genotek technology protocol, including preparation and stabilization (see McFall et al., 2013). Genotyping was carried out by using a Polymerase Chain Reaction Restriction Fragment Length Polymorphism strategy to analyze the allele status for *APOE* (determined by the combination of the SNPs rs429358 and rs7412), *BDNF* (rs6265), *IDE* (rs6583817), and *COMT* (rs4680). For the genetic analyses, a dichotomous genotype categorization was conducted based on the presence or the absence of the risk allele. For *APOE* genotype, we used ε4- (non-risk; composed of ε2ε2, ε2ε3, ε3ε3 allele combinations), and ε4+ (risk; composed of ε4ε4 and ε3ε4 allele combinations). For *BDNF* genotype, we used Met- (non-risk; composed of the Val/Val allele combination), and Met+ (risk; composed of the Met/Met and Val/Met allele combinations). For *IDE* genotype, we used G- (risk; composed of the AA allele combination), and G+ (non-risk; composed of the GG and GA allele combinations). For *COMT* genotype, we used Val- (non-risk; composed of the Met/Met allele combination), and Val+ (risk; composed of the Val/Val and Val/Met allele combinations).

Fifteen biomarker risk factor predictors. A total of 15 predictors were used to discriminate EF status classification (stable vs. declining) and structural dimensionality (unidimensional vs. multidimensional). *Demographic factors* were collected at baseline and included participants' (a) age (in years), (b) education (total years), and (c) sex (male or female). *Functional biomarkers* included baseline (a) pulse pressure [PP; equals systolic blood pressure (BP) - diastolic BP, in mmHG] based on an average of eight BP readings, (b) body mass index (BMI; equals weight/height ^{2}, in kilograms/meters^2), (c) peak expiratory flow (PEF; largest volume of air expired over three attempts, in litres/minute), and (d) grip strength (average hand strength, in kilograms/force). *Genetic factors* from DNA extraction and genotyping were (a) *APOE*, (b) *BDNF*, (c) *IDE*, and (d) *COMT*. *Mobility markers* included (a) balance or timed turn (360 degree turn, in seconds) and (b) gait or timed walk (20 feet, in seconds). *Lifestyle factors* were (a) everyday physical activity (based on n = 4 self-report questions), and (b) everyday novel cognitive activity (n = 27 self-report questions). These lifestyle variables are part of the VLS Activities Lifestyle Questionnaire (e.g., Hultsch, Hertzog, Small, & Dixon, 1999; Runge, Small, McFall, & Dixon, 2014) and are based on a 9-point scale (e.g., never = 0, daily = 8) that rates frequency of participation.

Statistical Analyses

Mplus 7 (Muthén & Muthén, 2010) was used to perform (a) confirmatory factory analysis and invariance testing for preliminary analyses, (b) latent growth modeling and growth mixture modeling for goals 1a and 1b from Study 1, and (c) factor mixture modeling for goal 2a from Study 2. R 3.3.2 (R Development Core Team, 2015) was used to perform random forest analysis (RFA) for biomarker predictions on goals 1c and 2b from Studies 1 and 2, respectively. Results from measurement invariance may be used to examine if data are missing completely at random

(MCAR) or at random (MAR). For instance, data may be MAR if the multi-group invariance constraints do not fit well, for example, by producing a significant χ^2 result (see McArdle, 2009). Missing data and attrition were estimated in growth models using maximum likelihood. For prediction analyses, the missForest package was used to estimate missing data. The missForest algorithm works as a nonparametric imputation method, fitting a random forest on the observed data and then predicting the missing data for each variable (Stekhoven, 2011). This process is repeated until reaching a maximum number of iterations. The algorithm assesses the performance between iterations by distinguishing between the previous and new iteration results. An imputation error is also estimated based on the out-of-bag (OOB) error estimate of random forest. A normalized root mean squared error (NRMSE; see Oba et al., 2003) and a proportion of falsely classified entries (PFC) are provided as part of the OOB error rate, indicating bad performance (values closer to 1) or good performance (values closer to 0). For our prediction sample, the following characteristics for missing data were observed: *M* percentage = 1.2% (range = 0.4% – 4%). For RFA using EF status classification groups, our OOB error was as follows: NRMSE = 0.233, PFC = 0.07. For RFA using structural dimensionality groups, our OOB error was as follows: NRMSE = 0.231, PFC = 0.08.

Preliminary analyses. Two sets of preliminary statistical analyses were performed. The first preliminary analysis involved testing and confirming a one-factor EF latent variable (previously observed: McFall et al., 2014; McFall et al., 2013; Sapkota et al., 2015; Thibeau et al., 2016) for the trajectory sample, based on eight indicators. For the second preliminary analysis, we tested the measurement invariance of the EF latent variable model across three waves. Measurement invariance for each model was tested, including (a) configural invariance (same indicator variables load onto the latent variable at each wave of data collection), (b) metric

invariance (factor loadings are constrained to be equal for each latent variable to indicate it measures the same construct), and (c) scalar invariance (indicator intercepts are constrained to be equal and allow mean differences to be evident at the latent mean level). Model fit for confirmatory factor analysis and invariance testing was determined using standard indices: (a) χ^2 for which a good fit would produce a non-significant test ($p > .05$), indicating the data are not significantly different from the model estimates, (b) comparative fit index (CFI) for which a value of $\geq .95$ is good and $\geq .90$ is an adequate fit, (c) root mean square error of approximation (RMSEA) for which a value of $\leq .05$ is good and $\leq .08$ is an adequate fit, (d) standardized root mean square residual (SRMR) for which a good fit is determined by a value of $\leq .08$, (e) Akaike Information Criterion (AIC) for which a lower value indicates better fit, and (f) Bayesian Information Criterion (BIC; sample-size adjusted value of AIC) for which a lower value indicates better fit (Kline, 2011; Little, 2013). EF factor scores for a one-factor EF latent variable were estimated in Mplus and used in all other latent growth models.

Study 1.

Analyses for RG 1a: Latent growth modeling of EF. Latent growth modeling was used to establish an EF latent growth curve. It is important to note that although wave was used to organize the demographic data, it was not used in the analyses as the metric of longitudinal change. Instead, age (in years) was used as the metric of change. Using age as the metric of longitudinal change in the statistical models can account for the variability of age as well as, or better than, if it were only used as a covariate (McFall et al., 2016). Age was centered at 75 years, which is the approximate mean over a 40-year span of data ranging from 53-95 years. Previous studies have found 75 years to be a common inflection point in cognitive aging (e.g., Dixon et al., 2012; Small et al., 2011). The best fitting model was established by testing (a) fixed

intercept model (assumes no inter- or intra-individual variability), (b) random intercept model (models interindividual variability, but no intraindividual change), (c) random intercept fixed slope model (allows interindividual variability in level, but assumes the rate of change is the same in all individuals), and (d) random intercept random slope model (allows interindividual variability in both level and change; see Singer & Willett, 2003).

Analyses for RG 1b: Growth mixture modeling on EF. Growth Mixture Modeling (GMM) on individualized EF trajectory data was used to determine EF status classification (stable or declining) on the basis of level and slope of the EF latent variable. GMM uses latent trajectory classes (e.g., categorical latent variables), which enables post hoc classification of individual EF trajectories based on EF performance level and change with the underlying assumption that each individual belongs to a latent class (Jung & Wickrama, 2008; Ram & Grimm, 2009; Wang & Bodner, 2007). Model fit was determined using conventional indices, including AIC, BIC, -2LL, and entropy.

Analyses for RG 1c: Biomarker risk predictors of EF status classification (stable vs. declining). Random Forest Analysis (RFA; Kuhn & Johnson, 2013) was used to determine the most important predictors of stable vs. declining EF status classification (from the pool of 15 demographic, functional, genetic, mobility, and lifestyle risk factors). RFA (in R 3.3.2; R Development Core Team, 2015) is a recursive multivariate data exploration method that combines the predictions of many classification and regression trees (*ntree*), each based on random sampling of participants and predictor variables (*mtry*). RFA was selected over logistic regression due to the interest in obtaining a ranking of the predictors in terms of importance. Additionally, RFA produces a conservative estimate of its predictive ability (out-of-bag error rate) and copes with a large number of predictor variables, restricting the number of variables

used in each *ntree*, which can show important predictors that could have been overshadowed by a stronger competitor (Strobl, Malley, & Tutz, 2009).

RFA was conducted using the "Party" package (Hothorn, Bühlmann, Dudoit, Molinaro, & van der Laan, 2006). Each forest was comprised of a number of *ntrees*, sufficient for good model stability, and an optimal *mtry* number of predictors at each potential split. Generally, *mtry* is set at $\sqrt{\#\ of\ predictors}$ (Genuer, Poggi, & Tuleau-Malot, 2010). Permutation accuracy importance was used to assess relative level of importance with the *cforest* function in the Party package. Model strength was assessed as the area under the receiver operation characteristic curve (c- statistic), with values closer to 1 indicating better model strength (see Hajian-Tilaki, 2013). Variables have an importance rank composed of their permutation accuracy importance, which is a measure of the relative strength of each variance in predicting outcomes. Those variables with values that are negative, zero, or are a small positive were not considered important predictors of EF status classification. Descriptive ranking of the predictor variables was used to define importance (McDermott, McFall, Andrews, Anstey, & Dixon, 2017; Strobl et al., 2009).

Study 2.

Analyses for RG 2a: Factor mixture modeling on EF. Factor Mixture Modeling (FMM) was used for subgroup classification of EF structure (unidimensional and multidimensional). FMM is a hybrid of latent class (or latent profile for continuous data) and factor analysis (Muthén, 2008). Within the FMM model, the latent class variable classifies individuals into groups and the latent continuous factor models the heterogeneity of the construct within latent class (Clark et al., 2013; Masyn, Henderson, & Greenbaum, 2010). The factor loadings, factor means, factor covariance matrix, and residual variances have the potential to be class-specific.

Therefore, the factor structure of the model can be different in each class. FMM models were tested with class-varying and class-invariant parameters (e.g., factor loadings) and model selection was based on fit indices, including: AIC, Sample-Size Adjusted BIC (SSABIC), Lo-Mendell-Rubin test (LMR), and Bootstrapped Likelihood Ratio Test (BLRT; see Bernstein, Stickle, & Schmidt, 2013; Clark et al., 2013; Muthén, 2008). A systemic approach to FMM involved testing and selecting the best models for classes (latent profile analysis), best factor structure models (factor analysis), and best FMM model.

A total of five FMM models were tested within classes and factors (FMM-1 to FMM-5). FMM-1 had class-invariant factor loadings, intercept means, and residual variance, class-varying factor means, and class covariance matrix fixed to zero. FMM-2 was different from the previous model in that it had a class-varying factor covariance matrix. FMM-3 was different from the previous model in that it had class-varying residual variance. FMM-4 was different from the previous model in that it had class-varying intercept means. FMM-5 was different from the previous model in that it had class-varying factor loadings.

Analyses for RG 2b: Biomarker risk predictors of EF structural dimensionality (unidimensional vs. multidimensional). Random Forest analysis was used to determine the most important predictors of unidimensional vs. multidimensional EF structural dimensionality (from the pool of 15 demographic, functional, genetic, mobility, and lifestyle risk factors). Procedures were used as previously described.

Results

Preliminary Analyses

Confirmatory factor analysis was used to test the structure of the eight indicators of EFs (Table 3). The one-factor EF model fit the longitudinal data well, χ^2 (219, N = 781) = 360.644, p

<.000, RMSEA = .029, CFI = .978, SRMR = .039. We then conducted measurement invariance testing (Table 3). Based on criteria to evaluate model fit and selection (see Chen, 2007; Rutkowski & Svetina, 2014), results supported metric invariance ($\Delta\chi2 = 61.414$, $\Delta df = 14$, p <.001, ΔRMSEA = .003, ΔCFI = .008, ΔSRMR = .017). Model fit criteria were not met for scalar invariance ($\Delta\chi2 = 371.205$, $\Delta df = 16$, p <.001, ΔRMSEA = .021, ΔCFI = .056, ΔSRMR = .035) and thus we proceeded to test a model with partial scalar invariance ($\Delta\chi2 = 42.485$, $\Delta df = 4$, p <.001, ΔRMSEA = .003, ΔCFI = .006, ΔSRMR = .01). This partial scalar model with intercepts constrained to be equal across time for Hayling and Stroop resulted in the optimal model and showed good fit indices, χ^2 (237, N = 781) = 464.543, p <.000, RMSEA = .035, CFI = .964, SRMR = .066). Because we did not observe full scalar invariance, residual invariance was not tested. Multi-group invariance constraints results indicated that the data were missing at random due to the loss of fit associated with scalar invariance. Measurement invariance results indicated that the EF model measured the same construct over time and the same indicator variables marked EF at each wave. Partial scalar results allowed comparison of latent variable means.

Study 1

RG1a: Latent growth modeling on EF. Using age (centered at 75) as the metric of change, latent growth modeling was performed using estimated EF factor scores. The best fitting model was a random intercept, random slope latent growth model (Table 4), and showed multiple results. First, the model indicated that older adults significantly vary in EF performance at age 75 (b = 1.084, p < .001) with a level of EF significantly different from 0 (M = .122, p = .003). Second, the model revealed a significant decline in EF performance across time (M = -

.003, p = .02). Third, older adults showed significantly variable patterns of decline (b = .001, p < .001). Figure 1 shows the individualized trajectories.

RG1b: Growth mixture modeling on EF. Growth Mixture Modeling (GMM) was performed to identify latent subpopulations with different latent trajectories (Table 5). Initial results showed a maximum of six classes to be tested for GMM. Empirical results revealed that the four-class model fit the data best (AIC = 2944.666, BIC = 3009.914, ENTROPY = .834). Although both the five- and six-class models fit the data better than the four-class model, both resulted in a class with proportion < 10%. Research has suggested disregarding models with class proportions < 1% (e.g., Jung & Wickrama, 2008). However, since our purpose was to use the classes obtained for further analyses, we did not consider models with class proportions < 10% (Uher et al., 2010). Therefore, the five- and six-class models were not considered further. GMM research suggests that model selection should be based on both statistical results and theory-based hypotheses from previous research in order to avoid the risk of capitalizing on chance (Muthén, 2004; Wang & Bodner, 2007). Previous VLS research on EF has suggested that there are two latent subpopulations: stable and declining (de Frias et al., 2009). Following statistical results and previous research, a two-class GMM model was obtained by a simple merging of neighboring and phenotypically similar classes. For the stable group, the top two classes from the four-class model were combined (higher level and slightly declining slope, moderate level and more moderately declining slope). For the declining group, the bottom two classes from the four-class model were combined (low level and more steeply declining slope, very low level and declining slope). Figure 2 shows this merged two-class model. The stable group is characterized by a higher level (intercept) and less declining slope, n = 397 (50.8%), intercept = .65 (SE = .022), slope = -.03 (SE = .002). The declining group is characterized by low

intercept (i.e., factor scores below 0) and steeper declining slope, *n* = 384 (49.2%), intercept = -.72 (SE = .019), slope = -.05 (SE = .002).

RG1c: Biomarker risk predictors of EF status classification (stable vs. declining). Using random forest analysis, the relative predictive importance of 15 risk and protective markers in discriminating stable from declining EF status classification was computed (Figure 3). EF decline was predicted by less education, less everyday novel cognitive activity, *BDNF* genotype Met+ (risk), and older age. Model classification performance (c-statistic) was 0.70, 95% CI [.66 - .75], *mtry* = 4, *ntree* = 5000. Overall, the important predictors represented demographic, lifestyle, and genetic domains.

Study 2

RG2a: Factor mixture modeling on EF. Using Factor Mixture Modeling (FMM), subgroup classification of EF structure (unidimensional and multidimensional) was established. Table 6 shows the systematic approach taken for FMM, the models tested, and the fit indices for each model (see Clark et al., 2013 for systematic example). First, latent profile analysis was conducted to determine the maximum number of classes/groups to use for FMM. Results revealed a maximum of three classes to be feasible for FMM due to small sample size proportion and non-significant LMR and BLRT *p* values (> .1) with the addition of more classes. Therefore, we used the two-class and three-class models for FMM analysis. Second, factor analysis was conducted to determine the maximum number of factors to use for FMM. Results revealed a maximum of two factors for FMM analysis. Therefore, we used the one- and two-factor models for FMM. Third, FMM models were tested based on the following characteristics obtained from previous steps: two classes, one factor; three classes, one factor; two classes, two factors; three classes, two factors. The FMM-4 model with two classes and two factors was the best fitting

model, AIC = 15681.1, SSABIC = 15743.3, ENTROPY = .803, LMR and BLRT < .001. Some information criteria (Log-likelihood, AIC, SSABIC) from model FMM-4 for three classes and one factor were smaller than model FMM-4 for two classes and two factors. However, model FMM-4 for two classes and two factors had fewer parameters (42) and thus resulted in a more parsimonious model. FMM-5 models were either unidentified or did not replicate and models FMM-2 to FMM-4 for three classes and two factors were either not positive definite or were not replicated.

Overall, for the FMM analysis, we selected the model characterized by two classes and two factors. These classes (subgroups of factor patterns) differed in the following characteristics: lower intercept means and no significant variability (unidimensional), and higher intercept means and significant variability (multidimensional).

RG2b: Biomarker risk predictors of EF structural dimensionality (unidimensional vs. multidimensional). Using random forest analysis, the relative predictive importance of 15 risk and protective markers in discriminating unidimensional from multidimensional EF structure was computed (Figure 4). Multidimensionality (differentiation) was predicted by younger age, more everyday novel cognitive activity, higher education, lower body mass index, lower pulse pressure, being female, better balance, and more everyday physical activity (marginally). Model classification performance (c-statistic) was 0.80, 95% CI [.75 - .85], *mtry* = 4, *ntree* = 5000. Overall, the important predictors represented demographic, lifestyle, functional, and mobility domains.

Discussion

We performed a set of two longitudinal studies designed to integrate four key characteristics of EF change and variability in non-demented aging: trajectories, classification,

structure, and biomarker predictors. We distributed this overall aim into three research goals for Study 1 and two research goals for Study 2.

The preliminary analyses involved confirmatory factor analysis and invariance testing. For the preliminary analyses, two main and expected findings were observed: (a) a one-factor model provided good fit to the data for this large group of normal aging adults, and (b) this one-factor model demonstrated both metric and partial scalar invariance over the three longitudinal waves. The unidimensional structure has been observed in previous work with normal aging and provides partial evidence for the de/differentiation theory (e.g., Li et al., 2017; McFall et al., 2014; McFall et al., 2013; Thibeau et al., 2016). The evidence is not conclusive because multidimensionality (two and three factors) has also been observed in healthy aging (Adrover-Roig et al., 2012; de Frias et al., 2009; Hull et al., 2008; Vaughan & Giovanello, 2010). These mixed results may be explained by individual differences in cognitive status and performance. Cognitive structure is not only associated with age, but also with performance ability and neuronal integrity (Anstey, Hofer, & Luszcz, 2003; McFall et al., 2017). Therefore, when different profiles of cognitive abilities are examined and EF de/differentiation is analysed based on these cognitive profiles, EF structures of varying dimensionality may be observed (de Frias et al., 2009). In addition, age-related structural changes in EF may be reduced or elevated by protection or risk biomarkers, including genetic, health, and functional factors (Anstey, Cherbuin, & Herath, 2013; Dodge et al., 2014; Harada et al., 2013; McFall et al., 2017). Our results supporting metric and partial scalar invariance indicated that the EF latent variable was unified and stable across the three waves. One contribution to the literature on de/differentiation in EF in aging is that it is essential to establish invariance in order to assess the psychometric equivalence of the EF construct across repeated measurement occasions. Measurement

noninvariance suggests that a construct cannot be tested meaningfully across different measurement occasions because it does not possess equivalency of structure or meaning for the same group when tested across time (Putnick & Bornstein, 2016).

For Research Goal 1a (latent growth modeling of EF), we demonstrated significant individual variability in level and slope of EF performance (Figure 1). This means that although there was significant longitudinal decline, older adults showed variable patterns in EF level and change. In other words, the change-related variability and the general trajectory of decline demonstrate substantial variability in the aging of EF over a 40-year band. A general declining slope is evident; however, individual differences in onset age and rate of decline are substantial, indicating preserved EF ability in some individuals. These findings are consistent with previous studies that have examined EF performance and trajectories of change (e.g., Goh, An, & Resnick, 2012; Lin, Wang, Wu, Rebok, & Chapman, 2017). The individual differences in EF aging and stability suggest the possibility that differential, potentially and selective biological, environmental and lifestyle risk or protective factors may contribute to individualized trajectories of performance change. These factors could act independently or in combination to produce differential EF performance and long-term change patterns in normal aging (de Frias & Dixon, 2014; Dixon, 2011; Fotuhi, Hachinski, & Whitehouse, 2009; Lindenberger et al., 2008; McFall et al., 2016; Sapkota et al., 2015). The observed variability in performance and decline of EF allowed us to explore our next research goal: classifying stable and declining EF groups.

For Research Goal 1b (growth mixture modeling on EF), two classes were empirically distinguished from the observed individualized trajectories. The observed trajectories and the GMM-produced classes are shown in Figure 2. First, a stable class was identified with a higher-level intercept and less declining slope (see red color, Figure 2). Second, a declining class (blue

color, Figure 2) was identified with low intercept and steeper declining slope. The trajectory, including the intercept (baseline level) and slope (rate of change over time), was used to distinguish those participants who maintained relatively stable EF performance from those with more pronounced decline. These results indicate that at least two coexisting latent growth trajectory curves, representing a maintaining and declining pattern of EF performance, are present in normal aging. Corresponding to these classes of latent growth curves, individuals may be classified into stable and declining groups. Furthermore, the results obtained add to emerging literature showing similar subgroup classification of EF performance (de Frias et al., 2009; Lin et al., 2017) and contribute to theory-based hypotheses for studies searching for the longitudinal change trajectories of EF. Once we established objective stable and declining groups, our next question was: can we identify protective or risk biomarkers that distinguish these groups?

For Research Goal 1c (biomarker predictors of EF status classification), we observed (in order of importance) that EF decline was predicted by less education, less everyday novel cognitive activity, *BDNF* genotype Met+ (risk), and older age (Figure 3). The c-statistic showed an index of accuracy of 0.70, indicating good model performance in discriminating EF status. These predictors represented demographic, lifestyle, and genetic risk domains. Less education may be detrimental in retaining stability in EF performance in older adults because it diminishes cognitive reserve (Tucker-Drob et al., 2009; Ward et al., 2015). As previously mentioned, cognitive impairment is delayed when there is greater cognitive brain reserve capacity (Stern, 2003). Therefore, education may be a factor that helps maintain cognitive reserve capacity and protect against age-related changes in the brain. Recent research has also found that early childhood education may promote developmental changes that are essential to protect against cognitive decline in late-life (Zahodne et al., 2015). Engagement in cognitive activity has shown

to protect against cognitive impairment leading to dementia by enhancing cognitive reserve or plasticity (e.g., Blasko et al., 2014; Lachman, Agrigoroaei, Murphy, & Tun, 2010; Runge et al., 2014; Valenzuela & Sachdev, 2009; Wang et al., 2002; Wilson et al., 2007). Cognitive reserve may work to improve cerebral blood flow, stimulating neurogenesis, and potentiating synaptic strength (Barulli & Stern, 2013; Blasko et al., 2014; Esiri & Chance, 2012; Whalley, Deary, Appleton, & Starr, 2004). Research has suggested that the increase in brain volume in response to cognitive training may be due to increased neural activity and the ability of the brain to develop neural scaffolding (Park & Bischof, 2013). Individuals with the *BDNF* genotype Met+ (risk) have shown to secrete less BDNF compared to Met- (non-risk) individuals (Nagel et al., 2008; Sapkota et al., 2015). As previously mentioned, BDNF is a molecule that modulates brain plasticity in the PFC, is expressed also in the hippocampus (structure for learning and memory), and supports the functioning of cognitive brain regions (Bird & Burgess, 2008; Erickson, Prakash et al., 2010; Komulainen et al., 2008). Met+ carriers are at a greater risk of cognitive deficits than Met- carriers. Furthermore, *BDNF* Met+ may influence neurodegenerative disease progression through neuronal dysfunction and cognitive impairment associated with neurofibrillary tangles (Lim et al., 2016). The detrimental effects of older age on EF performance may be explained by age-related cortical thinning and volumetric loss, in regions such as the PFC, which disrupt the response of cognitive activity in the brain (Li et al., 2017; Yuan & Raz, 2014).

In sum, the results for Research Goal 1 were (a) significant variability in EF level and slope, (b) variability contributing to classification of stable and declining groups, and (c) EF decline is predicted, in order of importance, by less education, less everyday novel cognitive activity, *BDNF* genotype Met+ (risk), and older age. These results are significant because they

emphasize that not all individuals show the same decline in EF performance as they age; substantial individual differences suggest the action of other factors. The results contribute new information to the literature on EF aging in that they present important risk predictors that differentiate stable vs. declining EF performance. Some of these predictors (e.g., everyday novel cognitive activity) are modifiable and therefore may be integrated in clinical interventions.

For Research Goal 2a (factor mixture modeling on EF), we aimed to examine a gap in our understanding of differential EF change and variability, namely individual differences in factorial structure. Therefore, we investigated differences in factor patterns of EF performance by establishing a latent class variable that classified individuals into groups, and a continuous factor that modeled the heterogeneity of the construct within latent classes (See Table 6; Clark et al., 2013; Masyn et al., 2010). Within a two-factor EF solution, we tested for subgroups of factor patterns. We found two classes that were observed to differ in the following characteristics: (a) lower intercept means and non-significant variability and (b) higher intercept means and significant variability. The pattern of low means with no variability is suggestive of a compressed EF aging class, and this could be the result of overall EF dedifferentiation (from multidimensional to unidimensional EF structure with aging). This class could represent typical EF dedifferentiation that the literature has reported on normally aging older adults (e.g., Adrover-Roig et al., 2012; de Frias et al., 2006; Li et al., 2017). The pattern of high means and significant variability is suggestive of a complex EF aging pattern in which there is retention of EF differentiation (multidimensional EF structure) into late life. This new analytic approach adds to the literature in that it represents a novel and promising method of examining EF structural variability in aging. The results further confirm that researchers must be careful in asserting dedifferentiation without qualification. Given these promising results, we next aimed to

contribute further to the literature by identifying biomarker predictors of EF factorial dimensionality (unidimensional, multidimensional).

For Research Goal 2b (biomarker risk predictors of EF structural dimensionality), we observed (in order of importance) that multidimensionality (differentiation) was predicted by younger age, more everyday novel cognitive activity, higher education, lower body mass index, lower pulse pressure, being female, more balance, and more everyday physical activity (Figure 4). The c-statistic showed an index of accuracy of 0.80, which means good model strength in discriminating EF structural dimensionality. These predictors represented demographic, lifestyle, functional, and mobility domains. The effects of age, everyday novel cognitive activity, and education on EF structure may operate through mechanisms previously discussed in Study 1. Interestingly, more predictors that distinguished unidimensionality vs. multidimensionality of EF structure emerged compared to those that distinguished stability vs. decline of EF performance.

Within the functional domain, lower body mass index and lower pulse pressure (PP) predicted EF multidimensionality. Elevated BMI increases the risk of cognitive impairment through mechanisms causing pathophysiologic changes in vascular health, impaired insulin regulation, systemic inflammation, and poor cardiovascular fitness (Anstey et al., 2011; Colcombe & Kramer, 2003; Convit, Wolf, Tarshish, & de Leon, 2003; Gunstad et al., 2007; Rahmouni, Correia, Haynes, & Mark, 2005; Taki et al., 2008; Teunissen et al., 2003; Ylikoski et al., 2000). Therefore, maintaining lower BMI may be an indicator of underlying physiological contributions to EF differentiation. PP is commonly used as a proxy for arterial stiffness and is calculated as systolic minus diastolic blood pressure. Research has found associations between PP and EF deficits in healthy young and older adults (McFall et al., 2014; Raz et al., 2011). Specifically, lower values of PP (indicating better vascular health) may promote EF

differentiation by (a) preventing negative effects of hypertension, such as mini-infarcts and cerebral vascular damage (Cooper et al., 2016), and (b) reducing AD-related pathophysiology and other neurodegenerative processes (Nation et al., 2013; Warsch & Wright, 2010).

Within the demographic domain, we observed that being female predicted—less robustly when compared to predictors from the functional domain—EF differentiation. Recent research has reported women performing better and having significantly less decline in EF than men (Mansouri et al., 2016; Zaninotto et al., 2018). This difference may be partially explained by sex differences in regional brain structures during aging. For instance, a female advantage has been reported in relation to proportion of grey matter volume (Good et al., 2001; Leonard et al., 2008) and decreased rate of cortical thinning (Pacheco et al., 2015). Therefore, women may be less vulnerable to age-related brain changes that make them less susceptible to age-related EF decline (McCarrey et al., 2016).

We also noted that within the mobility domain, more balance was the only mobility marker that emerged as an important predictor (but less robust) of EF differentiation or multidimensionality. Research has suggested mobility impairment in gait and balance to be consequences of EF deficits, due to many EF components required during mobility tasks, and to be predictive of EF performance and change (Ble et al., 2005; Thibeau et al., 2017). This may explain the interaction between EF and balance as an important mobility marker. However, more recent evidence has suggested that performance on mobility tasks that assess gait and balance may reflect physical health (Laudani et al., 2013). In light of this evidence, it may be plausible that our balance performance measure reflects some of our functional and lifestyle (physical activity) markers that assess physical health. Neurogenesis and angiogenesis are some biological

mechanisms that may be engaged when actively maintaining physical health and enhancing cognition (Bherer, Erickson, & Liu-Ambrose, 2013; Nokia et al., 2016).

Within the lifestyle domain, differentiation of EF structure was predicted by more everyday physical activity. The effect was marginal, but it may be important to discuss it for future replication purposes. Studies have reported that everyday physical activity is associated with improvements and better EF performance and less EF decline (e.g. Thibeau et al., 2016; Wang et al., 2012). Engagement in more physical activity may promote EF differentiation by improving the molecular and cellular structure and function of the brain (Kramer & Erickson, 2007). Research has shown that engagement in more physical activity is positively associated with increases in gray matter volume and other neuroprotective effects in the prefrontal cortex, enhancing the planning/execution of responses and counteracting neural overactivity in older adults (Berchicci, Lucci, & Di Russo, 2013; Erickson et al., 2015; Phillips, Baktir, Srivatsan, & Salehi, 2014; Ruscheweyh et al., 2011).

In sum, the main results for Research Goal 2 were (a) within a two-factor EF solution, individual differences in factor patterns may indicate de/differentiation and suggest subgroups of compressed and complex EF aging, and (b) differentiation of EF was predicted by younger age, more everyday novel cognitive activity, higher education, lower body mass index, lower pulse pressure, and less robustly by being female, more balance, and more everyday physical activity. These results are significant in that they caution against asserting dedifferentiation without qualification because there may be individual variability in factor patterns of EF in healthy aging. They contribute to the literature in that they provide insight on biomarkers that predict the variability in EF structure, specifically de/differentiation. Clinical interventions may assess the extent to which some of these markers may be modifiable.

There are several limitations associated with this two-part study. First, by design the participants were selected to be relatively healthy and cognitively normal. As a group, they may not represent the broader population of aging adults. Additional contributors to prediction patterns could be revealed if participants were taken from a broader sample of aging adults, including impaired and diverse groups. Nonetheless, our sample reflects a portion of older adults in western or developed countries where there is rapid older population growth. Second, predictors were taken from baseline performance. The predictive importance of a predictor may change if tested at different time points. Therefore, testing time-varying predictors may yield interesting results. However, this reflects a different research question and a different approach to the analyses; specifically, the goal of the alternative approach would be interesting, but would be aimed at predicting actual performance changes and whether they are coupled with predictor changes. In these studies, our aim was to examine prediction of EF change classes as rendered across multiple waves of data. Third, the effectiveness of the proposed factor mixture model method in evaluating structural dimensionality of EF in class membership could be limited by (a) convergence problems (Gagné, 2006) and (b) recovery of spurious latent classes in nonnormal data and/or nonlinear variable relationships (Bauer & Curran, 2004). More clear guidelines (e.g., sample size requirements) are still being researched (Leite & Cooper, 2010; Lubke & Muthén, 2005, 2007). Nevertheless, the present analytic method is the latest one available and is useful in that it allows researchers to examine differences in factor patterns or parameters within classes, providing more information about the differences in factor structure in subgroups than other methods.

There are also several strengths associated with this research. First, we used a relatively large, well-characterized sample spanning over 40 years of aging. This was important in order to

capture the substantial variability we found in the EF level and change data. Second, using age as the metric of change through an accelerated design allowed us to examine EF trajectories over a 40-year band of aging. This accelerated longitudinal approach was essential because it enabled us to cover a wide age range of interest in a shorter period of time, which would not be possible with a single cohort longitudinal design (Galbraith, Bowden, & Mander, 2017). Third, we used standard, reliable neuropsychological manifest variables to create our EF latent variable. This is valuable because with a latent variable approach (e.g., latent growth modeling), we can examine individual change trajectories and patterns of variability among individuals, which is not possible with other conventional methods (see Duncan & Duncan, 2009). With this, we were able to classify individuals by their trajectories over time. Fourth, we introduced a new approach to examine individualized patterns of EF structure among classes. Specifically, we used factor mixture model, which allowed us to examine individual differences in factor patterns within a two-factor solution. In turn, this allowed us to evaluate differences in factor structure within classes. Fifth, we used contemporary statistical methods, including machine learning, to systematically analyse our research goals. Specifically, random forest analysis was used to capture the relative level of importance of each variable, which in turn allowed us to establish a rank order of variable importance.

In conclusion, results from Study 1 indicate that (a) there is significant variability in level and slope of EF performance in healthy aging, (b) two continuous and quantitatively distinct classes (higher/stable, lower/declining) of EF aging trajectories may be established, and (c) decline in EF performance is predicted most importantly by less education, less everyday novel cognitive activity, *BDNF* genotype Met+ (risk), and older age. Results from Study 2 indicate that individual differences within a two-factor EF solution could be classified in two latent subgroups

of EF structure: (a) compressed EF aging with overall de-differentiation (unidimensional) with lower EF profiles and no significant variability and (b) complex EF aging with retention of EF differentiation (multidimensional) with higher EF profiles and significant variability. This is a new portrait of EF aging de/differentiation that helps characterize cognitive status groups. Furthermore, these compressed and complex EF aging subgroups are discriminated by a combination of 8 risk/protective factors from demographic (age, education, sex), lifestyle (everyday novel cognitive activity, everyday physical activity), functional (body mass index, pulse pressure), and mobility (balance) domains. Complex EF aging was predicted by younger age, more everyday novel cognitive activity, higher education, lower body mass index, lower pulse pressure, being female, more balance, and more everyday physical activity. Overall, these results may provide useful insight for future clinical interventions. For instance, more specific clinical interventions for EF deficits may be developed with this new understanding about the risk and protective factors that produce differential effects in the individual growth trajectories of EF performance and structure in aging, leading to better and faster recovery.

Table 1

Descriptive Statistics for Trajectory Sample by Longitudinal Wave

	W1	W2	W3
n	778	541	407
Age	71.42 (9.07)	74.94 (8.70)	78.12 (8.19)
Range	53.24-95.25	57.27-94.53	62.44-97.26
Gender (% Female)	66.6	66.0	67.6
HAY	5.43 (1.50)	5.43 (1.48)	5.50 (1.40)
STRP [b]	1.28 (.75)	1.39 (1.10)	1.36 (.90)
Color trails [b]	98.01 (33.87)	101.56 (38.62)	110.24 (46.10)
Brixton	4.72 (2.18)	5.32 (2.01)	5.35 (2.04)
LSER	11.33 (4.44)	11.19 (4.38)	10.97 (4.29)
LSET	8.36 (2.89)	8.34 (2.95)	8.26 (3.00)
CSPAN	3.05 (1.27)	2.97 (1.27)	2.88 (1.15)
RSPAN	2.88 (1.02)	2.74 (.99)	2.63 (1.03)

Note. Results presented as Mean (Standard Deviation) unless otherwise stated. HAY = Hayling; STRP = Stroop; LSER = Letter Series; LSET = Letter Sets; CSPAN = Computational Span; RSPAN = Reading Span; W1 = Wave 1; W2 = Wave 2; W3 = Wave 3; [b] Lower scores indicate better performance.

Table 2

Baseline Descriptive Statistics for Prediction Sample

	W1
n	570
Age	70.10 (8.50)
Range	53.24 – 95.25
Gender (% Female)	66.5
Education (Years)	15.32 (2.96)
BDNF (% Met+)	34.9
IDE (% G-)	13.3
APOE (% ε4+)	23.0
COMT (% Val+)	77.4
Pulse Pressure	52.06 (10.30)
Body Mass Index	26.91 (4.17)
Gait	6.33 (1.64)
Balance	2.78 (1.01)
Peak Expiratory Flow	426.02 (119.06)
Grip Strength	29.63 (9.44)
Everyday Physical Activity	15.95 (5.15)
Everyday Novel Cognitive Activity	75.81 (16.78)

Note. Results presented as Mean (Standard Deviation) unless otherwise stated; W1 = Wave 1; *BDNF* = Brain Derived Neurotrophic Factor; *IDE* = Insulin Degrading Enzyme; *APOE* = Apolipoprotein E; *COMT*= Catechol-O-Methyl Transferase; Met+ = risk allele combinations; G- = risk allele combination; ε4+ = risk allele combinations. Val+ = risk allele combinations.

Table 3

Goodness of Fit Indices for Executive Function Confirmatory Factor Analysis One-Factor Model and Measurement Invariance Testing

Model	$\chi 2$	df	*p*	RMSEA	CFI	SRMR
One-factor EF (W1)	23.708	18	.165	.020 (.000-.040)	.995	.020
One-factor EF (W2)	30.044	18	.037	.035 (.009-.057)	.987	.025
One-factor EF (W3)	23.532	18	.171	.027 (.000-.055)	.992	.030
One-factor EF (W1, W2, W3)	360.644	219	<.000	.029 (.023-.034)	.978	.039
Metric	422.058	233	<.000	.032 (.027-.037)	.970	.056
Scalar	793.263	249	<.000	.053 (.049-.057)	.914	.091
Partial Scalar [a]	464.543	237	<.000	.035 (.030-.040)	.964	.066

Note. RMSEA = Root Mean Square Error of Approximation; CFI = Comparative Fit Index; SRMR = Standardized Root Mean Square Residual; EF = Executive Function; W1 = Wave 1; W2 = Wave 2; W3 = Wave 3; [a] Preferred model.

Table 4

Absolute Fit Indices for Executive Function Latent Growth Models

Model	-2LL	AIC	BIC	D	*Δdf*
Fixed intercept	2472.391	4952.782	4971.424	-	-
Random intercept	933.360	1876.719	1900.022	1539.0	1*
Random intercept fixed slope	918.817	1849.634	1877.597	14.5	1*
Random intercept random slope [a]	364.757	745.514	782.798	554.0	2*

Note. -2LL = -2 log likelihood; AIC = Akaike information criterion; BIC = Bayesian information criterion; D = deviance statistic; *df* = degrees of freedom; [a] Preferred model. * $p<.001$

Table 5

Fit Indices and Entropy for Estimated Growth Mixture Models

Model	Log Likelihood	AIC	BIC	Entropy
One-class	-2213.383	4436.767	4460.070	-
Two-class	-1859.812	3735.624	3772.908	.733
Three-class	-1614.991	3251.981	3303.248	.821
Four-class [a]	-1458.333	2944.666	3009.914	.834
Five-class	-1297.685	2629.369	2708.599	.863
Six-class	-1297.685	2635.369	2728.581	.877

Note. AIC = Akaike information criterion; BIC = Bayesian information criterion; [a] Preferred model.

Table 6

Model Comparison Results

Model	-2LL	Par.	AIC	BIC	SSABIC	ENTROPY	LMR (*p*-value)	BLRT (*p*-value)	RMSEA	CFI	SRMR
Latent Profile Analysis											
One-Class	-8739.2	16	17510.4	17584.9	17534.1	-					
Two-Class	-8180.5	25	16411.0	16527.4	16448.1	.774	0	0			
Three-Class	-8039.2	34	16146.4	16304.8	16196.8	.740	.001	0			
Factor Analysis											
One-Factor	-7969.3	26	15990.6	16111.7	16029.1	-	-	-	.017	.997	.018
Two-factor	-7968.5	27	15991.1	16116.8	16031.1	-	-	-	.016	.998	.017
Factor Mixture Analysis											
2-Class, 1-Factor											
FMM-1	-8180.5	25	16411.0	16527.4	16448.1	.832	.239	0			
FMM-2	-8006.4	27	16066.9	16192.6	16106.9	.317	.002	0			
FMM3[*]	-7878.5	34	15825.1	15983.4	15875.5	.777	.011	0			
FMM4[*]	-7841.6	41	15765.3	15956.2	15826.0	.796	0	0			
3-Class, 1-Factor											
FMM-1	-8058.4	27	16170.9	16296.6	16210.9	.750	.000	0			
FMM-2[*]	-8004.3	29	16066.6	16201.6	16109.5	.586	.038	.030			
FMM-3[**]	-7802.9	44	15693.8	15898.7	15758.9	.788	.001	0			
FMM-4[**]	-7768.6	58	15653.2	15923.3	15739.1	.794	.165	0			
2-Class, 2-Factor											
FMM-1	-8180.5	25	16411.0	16527.4	16448.1	.832	0	0			
FMM-2	-7954.2	31	15970.4	16114.8	16016.3	.483	.008	0			
FMM-3[*]	-7849.6	36	15771.8	15938.9	15824.6	.790	.006	0			
FMM-4[*] [a]	-7798.5	42	15681.1	15876.7	15743.3	.803	0	0			
3-Class, 2-Factor											
FMM-1	-8056.0	28	16168.1	16298.1	16209.6	.750	.000	0			

Note. -2LL = -2 log likelihood; Par. = number of estimated parameters; AIC = Akaike information criterion; BIC = Bayesian information criterion; SSABIC = sample-size adjusted BIC; LMR = Lo-Mendell-Rubin test; BLRT = Bootstrapped Likelihood Ratio Test; RMSEA = Root Mean Square Error of Approximation; CFI = Comparative Fit Index; SRMR = Standardized Root Mean Square Residual; [*] Variance fixed in 1 class; [**] Variance fixed in 2 classes; [a] Preferred model

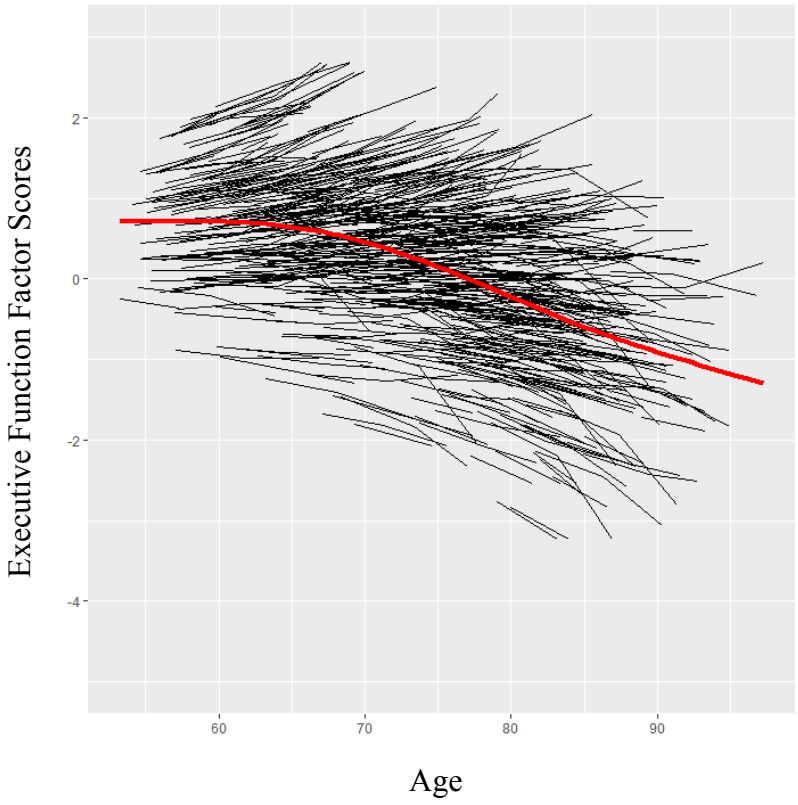

Figure 1. Executive function trajectory distribution. The black lines show the individualized trajectories and the red line show the group-level mean of individualized trajectories based on factor scores from latent growth model.

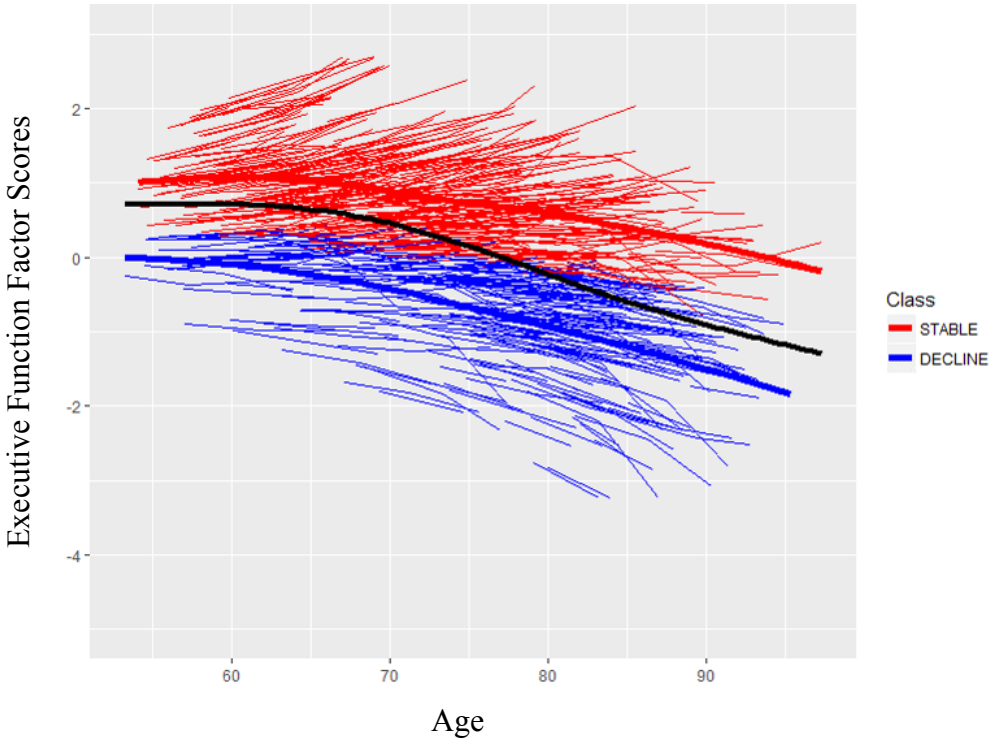

Figure 2. Executive function classification status. Two statuses were identified based on executive function level and slope. Red lines represent stable executive function performance and blue lines represent declining executive function performance. The thick lines represent mean group change. Black line represents overall change.

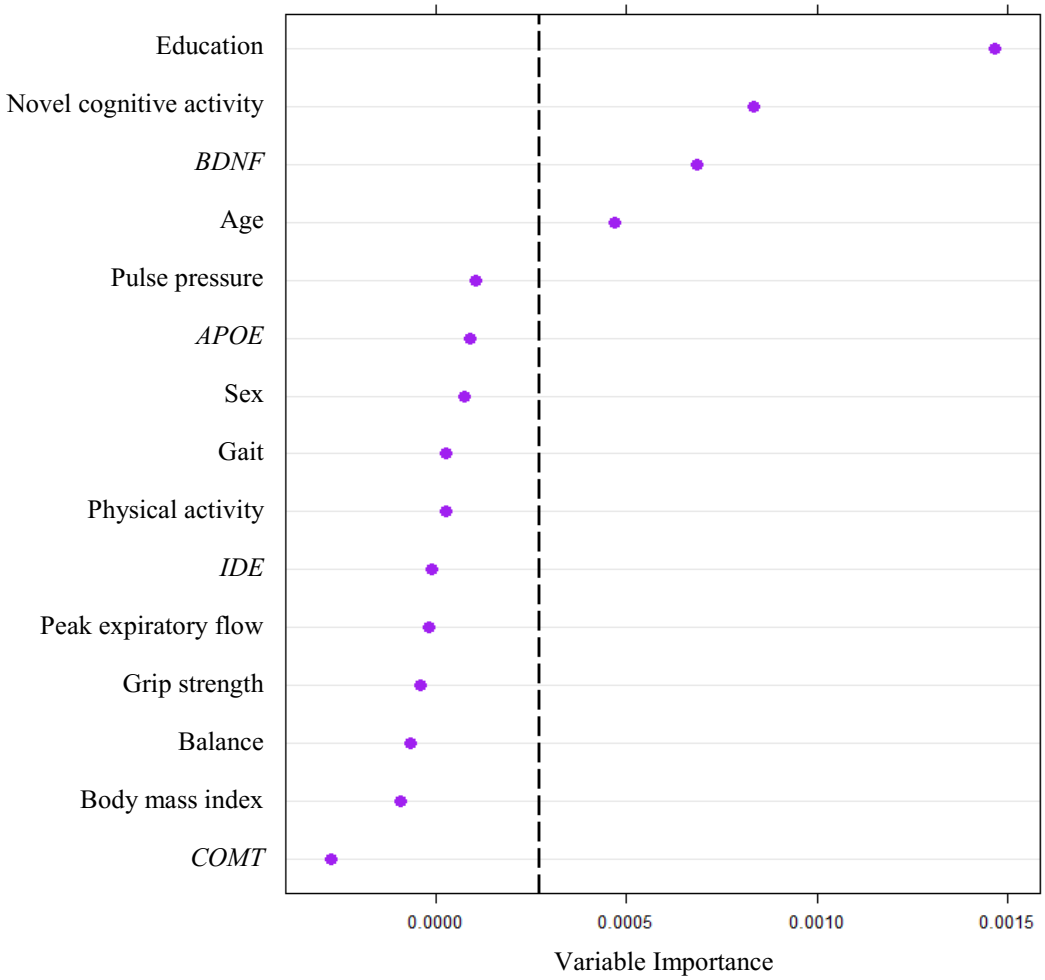

Figure 3. Relative importance of predictors of stable versus declining executive function status classification.

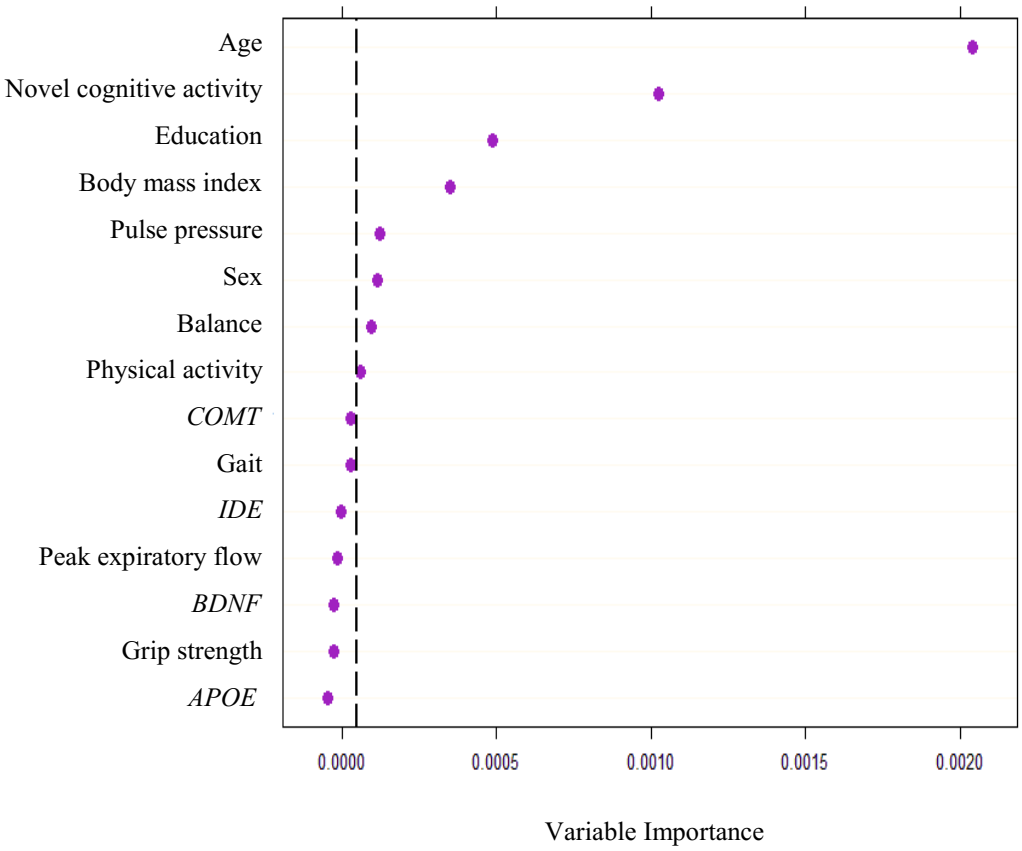

Figure 4. Relative importance of predictors of unidimensional versus multidimensional executive function structure.

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