Subjective memory decline and associations with non-demented memory aging:

The moderating role of genetic risk, vascular dysfunction and sex

by

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Abstract

INTRODUCTION: Subjective memory decline (SMD), defined as a self-perceived change in memory function without objective impairment, has been identified as a potential early marker of cognitive decline and other Alzheimer's disease (AD) related outcomes. A standard approach to SMD assessment includes two facets: memory complaints and memory concerns. We previously developed a four-facet model of SMD which encompassed the two standard facets, plus two additional facets: memory compensation and memory self-efficacy. In this study, we assembled a distribution of memory aging trajectories, classified into separate change-related classes, and tested SMD facets, sex and vascular health for class discrimination. We then examined the potential roles of SMD and additional AD risk factors (sex, *APOE*) in moderating pulse pressure and memory trajectory predictions.

METHODS: The accelerated longitudinal design featured individualized memory trajectories across a 40-year band (55-95 years) of non-demented aging (n = 580; M age at baseline = 70.2 years; 65% female) from the Victoria Longitudinal Study. We established two research goals, each with two parts, to examine prediction patterns for memory trajectories. For our first research goal, we used latent class growth analyses (LCGA) to identify distinct classes (based on an algorithm of level and slope) of episodic memory trajectories. Then, the four SMD facets, sex, and pulse pressure were tested as predictors of class membership. For our second research goal, we used a conditional latent growth model (CLGM) to test the independent effect of pulse pressure on memory change. In parallel, we utilized LCGA to identify latent classes for all four SMD facets. The SMD facet class membership results (for all four facets) were used as stratification variables in order to test SMD moderation of pulse pressure predictions on memory

trajectories. We then examined two-way interactions by further stratifying the analyses by: (1) SMD facet class and sex, and (2) SMD facet class and *APOE* genetic risk.

RESULTS: First, the LCGA produced four distinguishable and interpretable classes of memory trajectories. The classes were characterized as: (1) stable memory aging (SMA), (2) typical memory aging (TMA), (3) slowly declining memory aging (SDMA) and (4) rapidly declining memory aging (RDMA). Being male, having more memory concerns and higher pulse pressure was predictive of membership to at least one of the declining classes when using the SMA class as a benchmark. For the second research goal, after first determining that higher pulse pressure predicted lower memory level and steeper decline, our subsequent results revealed that memory complaints and memory concerns class membership significantly moderated these predictions. For females only, we observed significant sex and SMD class moderation for all four facets. For ε4- individuals only, we observed significant *APOE* and memory complaints class membership moderation as well as *APOE* and memory self-efficacy class membership moderation.

DISCUSSION: For the prediction of memory trajectory class membership, memory concerns was the only SMD facet predicting membership to the RDMA (lowest) as compared to the SMA (highest) class. Sex also differentiated the SMA class from more rapidly declining classes (e.g., RDMA). Pulse pressure predicted membership to the SDMA class as compared to the SMA class. For the moderated pulse pressure predictions of individualized memory trajectories, the two standard SMD facets demonstrated significant moderation. When stratified by sex groups, class membership for all four SMD facets demonstrated moderation selectively for females. When stratified by *APOE* genetic risk, membership to memory complaints and memory self-efficacy classes significantly moderated pulse pressure predictions of memory trajectories for ε4- individuals. These findings elucidate SMD prediction patterns in a number of at-risk groups, thus

identifying potential precision targets prior to the onset of pathological and clinical neurodegeneration associated with exacerbated memory decline.

Keywords: Subjective memory decline, pulse pressure, vascular health, sex, *APOE* genetic risk, Victoria Longitudinal Study

Preface

This thesis is an original work by Shannon Michelle Drouin. 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.

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Introduction

Subjective cognitive decline (SCD) is described as a self-perceived aging-related decline in cognitive function without accompanying objective impairment as observed with validated measures (Jessen et al., 2014a). As research in this area has continued to grow immensely in recent decades, more evidence has emerged in support of SCD presenting as an early indicator of non-normal changes in cognition. Indeed, research has shown that subjective complaints are associated with increased risk of progression to a clinical status of Mild Cognitive Impairment (MCI), Alzheimer's disease (AD) (Jessen et al., 2010), and incident decline in objective cognitive performance (Dufouil, Fuhrer & Alperovitch, 2005; Hohman, Beason-Held, Lamar & Resnick, 2011).

Nested within SCD exists a more precise perception of change in memory function. Coined as subjective memory decline (SMD), this perception has been shown to be specifically associated with an added risk of AD dementia (Jessen et al., 2014a). Although the SMD literature remains less developed than that of the neighbouring SCD area, the former concept may hold similar promise as an early signal of memory-related decline in performance, especially in everyday memory-demanding situations.

The main goal of this study was to investigate SMD in the context of a network of known and potential AD risk markers (vascular health, genetic risk, and sex) and their associations with actual memory change. Latent class growth analyses (LCGA) and conditional latent growth models (CLGM) in Mplus (8.2) were utilized to test independent and interactive effects of vascular health and SMD on actual memory trajectories over a 40-year band of aging. These analyses allowed us to estimate and test predictors of inter-individual variability and within-person memory trajectories. Two research goals, each with two parts, were stipulated. For the

first part of our first research goal, distinct classes in memory trajectories were identified using data-driven LCGA. The second part of our first research goal consisted of testing SMD facet, pulse pressure and sex predictions of episodic memory latent class membership. For the first part of our second research goal, we confirmed previously established pulse pressure-memory trajectory predictions. In parallel, we tested the moderating effect of SMD facet class membership on these predictions. For the second part of this research goal, these models were further stratified by sex and genetic risk to test differential effects with SMD facet classes on pulse pressure and memory trajectory predictions within these Alzheimer's disease (AD) risk groups (i.e., females and *APOE* ε4+ individuals).

Background

Subjective Memory Decline

With a greying global population, dementia prevalence has continued to grow. In Canada alone, it is estimated that the incidence rates of dementia will increase more than two-fold by 2038 while the cumulative direct health costs for dementia cases are expected to reach $500 billion by that same time (Alzheimer Society of Canada, 2008). Globally, total economic costs are estimated to reach $2 trillion by 2030 (Prince, Wimo, Guerchet, Ali, Wu & Prina, 2015). Spurred by a growing dementia burden, the development and implementation of preventative protocols in at-risk individuals prior to the onset of non-normative changes has occupied greater importance in recent brain and cognitive aging and dementia research (Anstey, Eramudugolia, Hosking, Lautenschlager & Dixon, 2015). Key to the development of prevention is the early detection of markers signaling transitions from healthier brain aging to a pre-prodromal phase of AD. Objectively, a detectable decline in episodic memory has been postulated to precede MCI and AD in what has been characterized as a lengthy preclinical phase (Bäckman, Small &

Fratiglioni, 2001). Early markers or predictors of future changes in objective cognition are accordingly imperative to the primary prevention of dementia and AD. Such markers may be objective, subjective, or a combination. There is mounting evidence that subjective perceptions of cognitive or memory health may present as a harbinger of future objective decline and clinical transitions into MCI and/or AD (Jessen et al., 2014a). These perceptions, in cognition or memory, may represent early stages of cognitive transitions into impairment which are not yet detectable using objective measures in research or clinical settings.

Interestingly, concerns or worries about one's perceived cognitive decline have been reported to better predict objective decline than the perception alone (Jessen et al., 2014b; Wolfsgruber et al., 2016), with the risk of AD comparable to those in early MCI (Jessen et al., 2014b). These concerns are also featured in the additional criteria for individuals to meet a classification of SCD *Plus,* which is associated with increased risk of dementia (Jessen et al., 2014a). This boosted risk classification includes perceived changes in the specific domain of memory within cognitive function as a whole, suggesting that subtle and noticeable changes in memory performance specifically (versus overall cognition), may be more indicative of AD-type pathological changes (e.g., rapid decline in memory).

Indeed, studies examining changes in memory beliefs specifically (i.e., SMD) have also shown strong predictions of future objective memory decline, associations with AD biomarkers, or increased risk of AD. SMD has been shown to be associated with both incident dementia (Buckley et al., 2016; Geerlings, Jonker, Bouter, Ader, & Schmand B, 1999; Mitchell, Beaumont, Ferguson, Yadegarfar, & Stubbs, 2014; Wang et al., 2004; Wolfsgruber et al, 2016) and cognitive decline (Glodzik-Sobanska, Reisberg, De Santi, Babb, Pirraglia, Rich & de Leon, 2007; Snitz et al., 2015b). Compared to cognitively normal adults with no memory complaints,

older adults with reported memory complaints experienced steeper decline and lower baseline levels of verbal recall (Koppara et al., 2015). This decline was especially marked in individuals with concerns accompanying their subjective complaints, as compared to those with complaints alone (Koppara et al., 2015). Memory complaints have also been reported to be associated with increased risk of dementia in cognitively normal individuals, but not in individuals with concurrent objective cognitive impairment (Tsutsumimoto et al., 2017).

There continues to be growing evidence that perceptions of memory decline are associated with non-normal changes in memory prior to the detectable onset of these changes. However, investigations of subjective memory measures specifically remain limited. Typically, SMD is represented by a single item (e.g., "Do you feel like your memory is becoming worse?") or multiple items encompassing this facet and that of concerns about perceived and reported change (Jessen et al., 2014b). A recent review of SCD self-report measures used in various international studies noted that more than half of the examined items were related to memory, emphasizing the significant overlap in the use of SCD and SMD (Rabin et al., 2015). These items were subdivided to capture SCD and SMD in two main categories: ability/disability-impairment (i.e., the perception of the presence/absence of memory problems) and change (i.e., the perception of change in memory abilities); both of which tap into the domains of memory complaints or concerns (Rabin et al., 2015). However, subjective perceptions of memory performance are not solely comprised of perceptions of impairment or change, and other incipient aspects of SMD and their associations with memory trajectories warrant thorough investigation.

With this in mind, we consulted neighbouring literatures in cognitive aging concerned with memory beliefs, affect, strategies, knowledge and compensation (de Frias, Dixon, &

Bäckman, 2003; Dixon, de Frias, & Bäckman, 2001; Dixon & de Frias, 2004; Dixon, Hopp, Cohen, de Frias & Bäckman, 2003; Hertzog, Dixon & Hultsch, 1990a; Hertzog, Dixon & Hultsch, 1990b; Hertzog, McFall, Small & Dixon, 2019; Ryan, 1992). From this review, we inferred that the two standard SMD facets could be supplemented by selected facets shown to be relevant in related memory and aging literature. We specifically developed a multi-facet concept of SMD which encompassed both memory complaints and memory concerns, as well as two novel facets: memory compensation and memory self-efficacy. Using items from the established Metamemory in Adulthood (MIA) (Hertzog et al., 1990a) and Memory Compensation Questionnaire (MCQ) (Dixon & de Frias, 2007), these four complementary but not previously differentiated facets of SMD were tested. This four-facet model of SMD was found to be selectively predictive of objective longitudinal change in memory performance (Drouin, Fu, McFall & Dixon, 2018). The four SMD facets can be described as follows:

Memory Complaints (Facet 1): This standard SMD facet is typically represented by a single item (e.g., "Do you feel like your memory is becoming worse?"; Jessen et al., 2014a). Specifically, the memory complaints facet reflects whether one believes that episodic memory has declined with time.

Memory Concerns (Facet 2): The second standard SMD facet reflects the extent to which one is concerned about one's decline in memory performance and the potential heightened or chronic level of worry about one's memory decline (Jessen et al., 2014b). This facet could include low-level (pre-clinical) memory anxiety. A typical item would follow-up reported memory complaints with the possibility to indicate that the feeling of memory change is worrying (or not).

Memory Compensation (Facet 3): This SMD facet refers to an alternative scenario of the above facets. Specifically, awareness of memory failures may lead to memory concerns and, differentially across older adults, to efforts to compensate for memory deficits and decline. The SMD memory compensation facet refers to the use of everyday compensation techniques to enhance memory performance that is perceived to be declining (de Frias & Dixon, 2005; Dixon & de Frias, 2007; Dixon et al., 2001).

Memory Self-Efficacy (Facet 4): This SMD facet refers to adults' beliefs about their overall mastery of everyday memory performance decline or about their specific ability to manage memory change and continue effectively using their memory in various situations (Hertzog et al., 1990b; Valentijn et al., 2006).

Using this four-faceted approach, we found that worse SMD (with all facets combined) was associated with lower level and steeper decline in episodic memory in females only (Drouin et al., 2018). When episodic memory level and slope were regressed on the intercept of each of the four facets in a CLGM, we observed facet-specific and sex-specific results. More memory complaints and memory concerns were both predictive of steeper objective decline in females, while worse memory self-efficacy was similarly predictive for males. As the SMD prediction patterns differed by sex, it is possible that other AD and memory aging risk factors could moderate these trajectory patterns. Specifically, both AD genetic risk (*Apolipoprotien E, APOE*) and vascular health (ie. pulse pressure, a robust proxy for aging arterial stiffness) have been linked independently and interactively with steeper memory decline and maintenance (McFall et al., 2015; McFall et al., 2019a; McFall, McDermott & Dixon, 2019b).

Genetic Risk

Apolipoprotein E (APOE) is a well-established risk factor for sporadic AD (Bertram, McQueen, Mullin, Blacker, & Tanzi, 2007), mild cognitive impairment (Brainerd, Reyna, Petersen, Smith, & Taub, 2011; Dixon et al., 2014), and longitudinal cognitive decline (Bretsky, Guralnik, Launer, Albert & Seeman, 2003). *APOE* consists of three isoforms, *ApoE2, ApoE3*, and *ApoE4*, and the corresponding ε2, ε3, and ε4 alleles (McFall et al., 2015). The ε3 allele is the most common, with the ε3/ε3 genotype being the most prevalent (McFall et al., 2015). Whereas the ε3 allele is considered neutral with respect to neurodegenerative disease, the ε2 allele is often noted as protective and has been previously found to be associated with lower risk of AD and dementia (Lim et al., 2017) and better cognitive functioning (Wisdom et al., 2011). *APOE* ε2+ carriers have also demonstrated protection from memory decline despite poor vascular health in a Victoria Longitudinal Study (VLS) sample (McFall et al., 2015; McFall et al., 2019a; McFall et al, 2019b). Conversely, the ε4 allele is the most salient genetic risk factor for sporadic AD, MCI and objective cognitive decline (Bertram et al., 2007; Bretsky et al., 2003; Laukka et al., 2013; McFall et al., 2019a). Associations with cognitive decline have been especially pronounced when ε4+ individuals have poorer vascular health (Ferencz et al., 2013; Yasuno et al., 2012). As the ε4 allele has been indicated as a criterion for a SCD *Plus* classification (Jessen et al., 2014a), it is additionally an important consideration within the SMD framework. The ε4 allele has been reported to be more prevalent in individuals with memory complaints compared to matched controls (Laws, 2002). In regard to SCD/SMD and objective decline, accelerated cognitive decline for ε4+ individuals with memory and cognitive complaints has been previously observed (Dik et al., 2001; Samieri et al., 2014). Memory complaints have also been reported to be associated with high amyloid burden in cognitively healthy ε4+ individuals (Zwan et al., 2016).

Vascular Health

Vascular health presents as an established modifiable factor which affects cognition and memory in aging (McFall et al, 2015; McFall, Sapkota, McDermott & Dixon, 2016). For example, maintenance of cognition has been observed for individuals without hypertension (Yaffe et al., 2009). Similarly, increased arterial stiffening, which is associated with increased risk of adverse cardiovascular events, also has recognized associations with poorer cognitive function in older adults (McFall et al., 2015; McFall et al., 2016). Pulse pressure, a proxy for arterial stiffness, is calculated by subtracting diastolic blood pressure from systolic blood pressure. Poorer vascular health is indicated by higher pulse pressure, which typically increases with age (McFall et al., 2015). Considered a better predictor of vascular health than systolic or diastolic pressure alone (Raz, Dahle, Rodrigue, Kennedy & Land, 2011), higher pulse pressure has been previously associated with memory deficits (Waldstein et al., 2008), AD-type neuropathology (Hughes et al., 2013; Nation et al., 2013; Rodrigue et al., 2013), plasma amyloid-B transport function (Jiang et al., 2018), cognitive decline and brain atrophy (Nation et al., 2016), functional decline (Werhane, Thomas, & Edmonds, 2018), and increased risk of AD or related dementias (Peters et al., 2013; Qiu, Winblad, Viitanen, & Fratiglioni, 2003). Notably, decline in some cognitive functions (e.g., visuospatial organization) have been found to be particularly pronounced among *APOE* ε4 carriers with vascular dysfunction (Nation et al., 2016). Specific to memory, sex-specific protective effects of *APOE* ε2 have been reported in episodic memory associations with pulse pressure (McFall et al., 2019a). Previous research on vascular dysfunction and SMD has been limited. While weak associations between vascular risk factors and subjective memory complaints were found cross-sectionally (Paradise, Glozier, Naismith, Davenport & Hickie, 2011), no longitudinal associations have been reported as of yet.

Sex Differences

Sex differences in AD incidence, prevalence and etiology have been widely reported (Carter, Resnick, Mallampalli & Kalbarczyk, 2012; Mielke, Vemuri, & Rocca, 2014; Schmidt et al., 2008; Tierney et al., 2017). Previous VLS research has shown female sex to be predictive of successful memory aging, but not of decline (McFall et al., 2019b). Other studies have reported more rapid decline in a number of cognitive functions for males (Gerstorf et al., 2011; McCarrey, An, Kitner-Triolo, Ferrucci & Resnick, 2016). Certainly, there has been a pattern of findings suggesting sex differences in a variety of normal and neurodegenerative functions (Tierney et al., 2017). It has been repeatedly established that, paradoxically, females are both 'better off' and 'worse off' as they age: although females live longer and are less likely to experience declines in memory (Lin et al., 2017; McFall et al., 2019b; Vassilaki et al., 2015), they also show greater rates of AD dementia longitudinally, suffer worse post-diagnosis outcomes (Dumas, 2017), and demonstrate greater rates of disability in older age (La Croix, Newton, Leveille & Wallace, 1997). These existing sex differences may be a result of a number of factors (e.g., lifestyle, hormonal), acting independently or interactively (Li, Cui & Shen, 2014; Mielke et al., 2014).

Sex-specific effects in relation to the associations between vascular health and cognition have also been reported. For example, deficits in episodic memory have been associated with hypertension in men (Elias, Elias, Sullivan, Wolf & D'Agostino, 2003; Saxby, Harrington, McKeith, Wesnes, & Ford, 2003). Specific to the SCD framework, baseline SCD has been recently reported to be more strongly associated with subsequent dementia diagnosis in females than in males (Heser et al., 2019). However, reported sex-specific vascular associations with SMD or SCD have been limited. Increased arterial stiffness (assessed by pulse wave velocity) has been reported to be associated with memory impairment in men with subjective memory

complaints (Kearney-Schwartz et al., 2009). To our knowledge, this is the only study examining the effect of vascular health on cognitive performance in individuals with subjective memory complaints. These findings highlight the importance of examining genetic and sex-specific associations within possible interactions between vascular health and subjective decline in memory. SMD may reflect sensitivity to multiple "doses" of AD risk, as evidenced by increasing memory failures and pulse pressure dysfunction, moderated by the precision factors of sex and genetic risk.

Research Goals

Building on the previously established findings of sex-specific SMD associations, this study aimed to integrate additional AD risk biomarkers (vascular dysfunction and AD genetic risk) in longitudinal analyses of dynamic networks of SMD and memory aging trajectories. Three-wave longitudinal data from the VLS covering a 40-year band of aging (53-95 years) were used to investigate two research goals. The first research goal was comprised of two parts. Research goal 1a involved the analysis of episodic memory trajectories for the identification of distinct latent classes of interindividual variability and change. Research goal 1b examined sex, SMD facets, and vascular health (i.e., pulse pressure) as predictors of episodic memory trajectory latent class. After testing pulse pressure predictions of memory trajectories, the second research goal also encompassed two sequential parts. Research goal 2a consisted of the identification of distinct classes of level and change in all four SMD facets in order to subsequently use class membership as a moderator in the prediction model. Research goal 2b examined whether this moderation occurs differentially by sex or *APOE* genetic risk.

Methods

Sample

Participants were community-dwelling older adults (initially aged 53-95 years) from the VLS, a large-scale longitudinal sequential study of biomedical and cognitive aging (Dixon & de Frias, 2004). Written consent was provided by all participants and data collection procedures were certified by prevailing ethics guidelines and boards. Longitudinal data were assembled from three VLS samples using standard procedures (e.g., Dixon, Small, MacDonald, & McArdle, 2012; McFall et al., 2015; McFall et al., 2019b), each with three available waves of data collected from 2002 onwards. In the present study, the first wave of each sample formed Wave 1 (W1), the second formed Wave 2 (W2) and the third Wave 3 (W3). Age coded as a continuous variable was used as the metric of longitudinal change. This allowed for the examination of level and change based on individual-varying age instead of wave. The resulting data set was an accelerated longitudinal design producing a distribution of trajectories spanning 40 years.

Due to the necessity of genetic data for this study's *APOE* moderation analysis, a source sample was defined by longitudinal genotyped participants with baseline data collected since 2002 (n = 652). The following exclusionary criteria were then applied: (1) a diagnosis or indication of Alzheimer's disease or any other dementia (n = 4), (2) a Mini-Mental Status Exam score of less than 24 (n = 1), (3) a self-report of "severe" for potential comorbid conditions (e.g., epilepsy, head injury, depression, alcohol dependence) (n = 60), (4) use of anti-psychotic medication (n = 2), and (5) a self-report of "severe" or "moderate" for potential comorbid diseases such as neurological conditions (e.g., stroke, Parkinson's disease) (n = 5). After exclusions, the final sample for this study consisted of 580 non-demented older adults. Participant demographic information for this study sample is presented in Table 1.

Measures

Episodic Memory. Three episodic memory tasks were used to extract four manifest variables for use in confirming the previously established memory latent variable (Drouin et al., 2018).

VLS word recall. This task consisted of immediate free recall of two structurally equivalent lists of 30 English words (Dixon et al., 2004). Each list consisted of 6 words from five taxonomic categories, typed on a single page in unblocked order. To eliminate content-related practice effects, a rotated design was used for test administration. All tasks were administered in all waves and no participant saw the same list twice. Participants were given 2 minutes to study each list and 5 minutes to write as many words as they could recall. The number of correctly recalled words averaged across the two lists was used for analysis.

Rey auditory verbal learning. This task assesses verbal learning and memory (Lezak, 1983; Vakil & Blachstein, 1993). Fifteen nouns were read aloud to the participant and immediate recall was required. This was repeated for 5 trials with the same list (A1–A5), followed by a second list of 15 unrelated nouns (REYB1 [free recall]). Finally, the participants were asked to recall the first list (REYA6). Two indicators were used for analysis: (1) the number of nouns recalled from List B1 was used to measure free recall and (2) the number of nouns recalled from list A6 was used to measure recall after interference (REYA6 [recall after interference]).

Benton facial recognition. This task is designed to assess facial recognition capabilities, an ability that is associated with nonverbal episodic memory (Benton, Sivan, Hamsher, Varney & Spreen, 1978). Participants were presented with a target picture and asked to choose the target individual from six test faces presented with the target picture. Both male and female faces are

used. There are no time constraints for this task. The computed overall score, in which a low score indicates severe impairment, was used for analysis.

Subjective Memory Decline. We assembled a SMD inventory using items from the MIA and MCQ. The MIA is a 108-item instrument measuring eight facets of metamemory in aging (Hertzog et al., 1990a). The MCQ is a 45-item instrument which measures awareness and use of everyday memory techniques used by older adults (e.g., Dixon & de Frias, 2007). Items from the MIA (17) and MCQ (2) were previously selected based on past research on SCD and SMD and each item's relevance to the facet (Table A1). Selection of candidate items to reflect each facet was performed by three independent researchers. Using confirmatory factor analysis, the items were assembled to create a four-factor latent variable, which included four related (but distinct) facets: (1) memory complaints, (2) memory concerns, (3) memory compensation, and (4) memory self-efficacy (Drouin et al., 2018). Items representing each facet were coded in a direction in which a lower score indicated less SMD (i.e., fewer memory complaints, less memory concerns, lower reported memory compensation efforts, and more memory self-efficacy). For the latter two facets, we hypothesize that high compensation, if successful, may reflect more SMD through the use of techniques in order to address perceived performance deficits in everyday life, thereby reflecting efforts to forestall perceived memory decline. More memory self-efficacy reflects less SMD as this facet refers to the concept that beliefs about one's own memory abilities and decline (and the extent to which memory aging may be controlled) play an important role in one's confidence and effort to perform well in everyday memory tasks.

Items representing each facet are presented in Table A1. Three items from the MIA formed the complaints construct. The memory concerns facet was formed using seven items

from the MIA. Three items from the MIA and two items from the MCQ formed the memory compensation facet. Four items from the MIA formed the memory-self efficacy facet.

Genetic Risk. Saliva samples were collected to all recommended practices according to Oragene DNA Genotek technology protocol, including collection, preparation and stabilization (see McFall et al., 2013). Saliva was stored at room temperature until manual DNA extraction from 0.8 ml of saliva sample mix using the manufacturer's protocol with adjusted reagent volumes. A PCR-RFLP strategy was used to analyze the allelic status for *APOE* (determined by the combination of the SNPs rs429358 and rs7412). To examine the moderating effect of genetic risk, we used two groups in stratification analyses. First, a "lesser risk" group of *APOE* ε4- individuals characterized by the absence of a ε4 allele. Specifically, this group consisted of the following genotypes: ε2/ε2, ε2/ε3, and ε3/ε3. Second, an "at-risk" group of *APOE* ε4+ individuals characterized by the presence of at least one ε4 allele. Specifically, this group consisted of the following genotypes: ε3/ε4 and ε4/ε4. Individuals with *APOE* ε2/ε4 were removed from genetic analyses due to the relatively unknown effect of a protective and risk alleles in combination (McFall et al., 2015; McFall et al., 2019a). We considered parallel stratification by *APOE* ε2+/ε2- in order to investigate potential protective effects of *APOE* genetic risk. However, this was not possible due to small cell sizes involving ε2+ individuals in most of the stratified groups used in these analyses.

Vascular Health. Pulse pressure is a reliable proxy of arterial stiffness (McFall et al., 2015). We calculated this functional biomarker by subtracting average diastolic blood pressure from systolic blood pressure readings. Greater pulse pressure indicates worse vascular health. For all analyses, pulse pressure was used as a continuous variable and centered at the sample mean of 51.9 mm Hg.

Statistical Analyses

Structural equation modeling was conducted using Mplus 8.2 (Muthén & Muthén, 1998-2017). Confirmatory factor analyses were used to first confirm latent variable models of episodic memory and SMD. Model fit was determined using standard fit indices: (1) a non-significant χ^2 indicating a good fit, (2) comparative fit index (CFI) where ≥ .95 is a good fit and values between .90 and .94 demonstrate adequate fit, (3) root mean square error of approximation (RMSEA), where a value ≤ .05 would be considered good fit and between .06 and .08 would be considered adequate fit, and (4) standardized root-mean-square residual (SRMR) for which a value of ≤ .08 is considered good fit (Kline, 2011).

Longitudinal measurement invariance was tested using a chi-square based likelihood ratio test (measured as difference in χ^2). As this test is sensitive to reporting invariance in large sample sizes, recommended differences in CFI (<0.01) and the above-mentioned standard fit indices were also used to confirm measurement invariance (Little, 2013). Longitudinal measurement invariance is essential to establish construct equivalence across time prior to examining performance and change characteristics (Little, 2013). We confirmed longitudinal measurement invariance for episodic memory, the four-factor SMD variable, and each confirmed SMD facet. Configural invariance was first tested to establish whether the same indicators represented the latent variables at each wave of data collection. Second, factor loadings were constrained to be equal in order to test metric invariance. Third, indicator intercepts were constrained to be equal in order to test for scalar invariance. Fourth, indicator residuals were constrained to be equal accounting for error variability to test for residual invariance. Factor scores were computed from the best fitting model and used in all subsequent growth models. Due to the nature of CLGM,

only one wave of data for all participants is required. There was no use of listwise deletion in the CLGM analyses as all participants contributed to at least one wave of data.

For the episodic memory latent variable, four indicators (word recall, REYB1 [free recall], REYA6 [recall after interference], Benton) were used to confirm a one-factor model of episodic memory. Longitudinal invariance of this model was also confirmed as per the procedures outlined above.

To confirm the four-factor latent SMD variable, we first performed psychometric analyses to estimate reliability for each facet of the expected model. Internal consistency of the scales (or facets) were considered acceptable with a Cronbach's alpha of ≥ 0.7 (George & Mallery, 2003). Second, the nineteen indicators were used to confirm a four-factor model of SMD using confirmatory factor analysis. Factor loadings of >0.4 were considered to be ideal, especially in the case of lower internal reliability (Little, 2013). Third, we tested re-test reliability for each facet at the scale level. We then tested longitudinal invariance of the four-factor SMD model as per the standard fit indices described above.

Analyses for RG1. For the first part of the first research goal, data-driven latent class growth analyses (LCGA) were utilized to clarify the episodic memory trajectory data. The previously established baseline growth model for episodic memory (random intercept, random slope) represents the best single-group representation of change (Ram & Grimm, 2009). See Table 2 for growth model fit indices for the single-group solution. As three waves of data were used, only linear growth patterns were investigated. For these analyses, multiple models were run with random starting values in order to avoid local optima solutions. First, an unconditional latent class growth model with up to $k = 5$ classes was specified. Related past findings suggested up to four trajectory classes of memory aging (McFall et al., 2019b; Olaya, Bobak, Haro, &

Demakakos, 2017). Therefore, a maximum of a five-class solution model was run in accordance with the guideline that researchers test one more class than expected from theory or previous empirical findings (Jung & Wickrama, 2008). Beyond this, non-convergence, non-replication of the log-likelihood value or small class prevalence (<5%) were also used as determining factors of the highest *k*-class model run (Jung & Wickrama, 2008). LCGA involves the specification of a latent class growth model, which assumes no within-class variability (McFall et al., 2019b). Compared to the baseline growth model, these models assume that individual growth parameters are drawn from subpopulations instead of one homogeneous population (Jung & Wickrama, 2008). LCGA models specify that the covariances for the growth factors within each specified class are fixed at zero (Jung & Wickrama, 2008) and assume that all interindividual variability in growth factor estimates and covariances are explained by class membership (Petras & Masyn, 2010).

Following the specification of LCGAs, we applied growth mixture models (GMMs) to the trajectory data as this is a recommended follow-up in relevant mixture modeling literature (Jung & Wickrama, 2008; Petras & Masyn, 2010; Ram & Grimm, 2009). GMM modeling allows for the examination of the differences in variances and covariances across classes in addition to the mean change function for the different classes (Ram & Grimm, 2009). Specifically, as compared to LCGAs, GMMs account for the possibility that classes of episodic memory may not be completely homogeneous in regard to the spread of intercept and slope; some classes may show differing variability in these estimated parameters. We note that in cognitively normal (asymptomatic) older adults, there is considerable variability in episodic memory function and change (Figure 1). It is thus possible that within-class variability also exists. In order to specify the GMM models, classes were assumed to have freely estimated variances of intercept and/or

slope. Intercept and slope variances were first constrained to be equal across classes but not fixed to be zero. Next, variances were allowed to be freely estimated so that they differ across classes.

In order to select the optimal number of classes for both the GMM and LCGA specifications, we assessed model fit using standard criteria: (1) Akaike information criterion (AIC), (2) Bayesian information criterion (BIC), and (3) sample-size adjusted BIC (SABIC). Lower AIC, BIC and SABIC values indicate better model fit. Models with high values of entropy (>.80) were preferred in the case of similar relative fit indices between candidate models. Model selection for both the optimal number of classes and variability specifications (i.e., LCGA or GMM) were based on parsimony, relative fit indices, entropy, and the interpretability of the class means, variability, and proportions based on the literature (Ram & Grimm, 2009).

For the second part of the first research goal, baseline SMD facets, pulse pressure, and sex were assessed as predictors of episodic memory latent class membership using multinomial logistic regression. The three-step approach (R3STEP) in Mplus (8.2) was utilized for this purpose in order to include these predictors simultaneously as auxiliary variables (Asparouhov & Muthén, 2014). This three-step approach first estimates the latent class model to create a most likely class variable using the posterior distribution (obtained through EM iterations). The most likely class variable is then regressed on selected predictor variables (Jung & Wickrama, 2008). Including predictor variables in the model specification takes into account misclassification error that occurs in the creation of the most likely class variable (Jung & Wickrama, 2008). These analyses allowed us to determine the increased odds of membership to a class compared to a reference class as a selected predictor variable increases by one unit (with the other included predictor variables remaining constant). Due to the inclusion of multiple predictor variables, false discovery rate (10%) was controlled for using the Benjamini-Hochberg procedure

(Benjamini & Hochberg, 1995). This sequential procedure controls for the proportion of false positives (Benjamini & Hochberg, 1995; Thissen, Steinberg & Kuang, 2002). Less conservative than the widely used Bonferroni correction, the Benjamini-Hochberg procedure offers greater statistical power as the number of comparisons increase (Thissen et al., 2002). This approach consists of ranking *p*-values for all test results and comparing each value to a critical Benjamini-Hochberg value to determine significance (Thissen et al., 2002).

Analyses for RG2. For the first part of the second research goal, conditional latent growth models (CLGM) were used to investigate pulse pressure predictions of the full trajectory distribution of episodic memory level and change. Next, in parallel analyses, we used LCGA to conduct class analyses for the trajectory distributions for each SMD facet. Thus, four such analyses were conducted. The purpose was to transform the SMD facet latent variable from a continuous latent variable to a categorical latent variable. Subsequently, class membership was used as a stratification variable in CLGMs testing pulse pressure predictions of memory. We determined the optimal number of classes for each SMD facet as per the procedure outlined for the first research goal. Specifically, we used AIC, BIC, SABIC as well as class proportions and means to determine the selected final models. Next, each individual was assigned to their most likely class based on the selected optimal number of classes for each facet. For each SMD facet, we stratified CLGMs by class membership to test SMD facet moderation on the prediction of episodic memory by pulse pressure.

For the second part of the second research goal, these same models were tested in additional stratifications with SMD facet class: sex and an *APOE* genetic risk dichotomous classification (*APOE* ε4+/ε4-). These stratifications were tested in order to investigate potential two-way moderating effects of sex and genetic risk with SMD on the episodic memory

trajectories predictions by pulse pressure. For both parts of the second research goal, all moderation effects were tested using the *D* statistic between constrained and unconstrained models. For the former model, groups were constrained to be equal across intercept and slope.

Results

Confirmation of EM and SMD latent variable models

We confirmed that a one-factor model of episodic memory, consisting of four indicators, fit the data well (*RMSEA* = 0.04, *CFI* = 0.98, *SRMR* = 0.06) (see Table 3). We confirmed support of partial scalar invariance for Benton (Table 3). This indicates that the one-factor model measured the same construct longitudinally, but the word recall and the Rey auditory learning task manifest variables demonstrated mean differences across time. Establishing and confirming partial scalar invariance allowed us to use this latent variable model to subsequently make comparisons across time using factor scores.

For the four-factor SMD latent variable model, we found satisfactory internal reliability as measured by Cronbach's alpha for three of the four facets. Specifically, the memory complaints facet (α = .78), the memory anxiety/concerns facet (α =.83) and the memory self-efficacy facet (α = .71) demonstrated acceptable internal reliability. The memory compensation facet demonstrated somewhat lower reliability (α = .60). However, using confirmatory factor analysis, we confirmed that the four-factor model of SMD fit the data well (*RMSEA* = 0.03, *CFI* = 0.91, *SRMR* = 0.06). See Table 4 for factor correlations. The SMD latent variable also demonstrated satisfactory indicator variable loadings onto the four facets (ranging from 0.37-0.89), providing excellent evidence for psychometric validity of the latent variable model of SMD. Re-test reliability (W1-W2, W2-W3) for all four facets ranged from $r = 0.58$ to $r = 0.89$. We also confirmed support of residual (strict) invariance for the four-factor model of SMD

(Table 3), indicating that: (1) the same indicators represent SMD facets at each data collection wave, (2) the measurement model remained the same across time (i.e., factor loadings were invariant), (3) item intercepts were equivalent across time, and (4) residual error was invariant across time.

RG1a

The aim of research goal 1a was to use LCGA or GMM for the identification of distinct latent classes of interindividual variability and change of episodic memory trajectories. Fit statistics for all tested LCGA models are presented in Table 5. Fit statistics for all tested GMM models are presented in Table 6.

We computed LCGA models for two-, three-, four- and five-class solutions. These models showed improvements in AIC, BIC and SABIC from the baseline model (Table 5). The five-class LCGA model was removed from consideration due to a small latent class prevalence (<5%). Entropy values for the three-class (0.84) and four-class (0.85) LCGA models were consistent with Muthén and Muthén's (1998-2017) recommendation which indicates a relatively low misclassification rate. Following this, we tested GMMs with up to four classes. All GMMs were removed from consideration after thorough examination of entropy values, relative fit indices and class mean and variance interpretations, suggesting that accounting for within-class variability worsened model interpretation (Table 6). Following this, we considered the LCGAs exclusively as candidate models.

Thus, the four-class LCGA model was chosen as the optimal and final model, as this solution has the lowest AIC, BIC and SABIC values (see Table 5), satisfactory entropy (0.85), as well as interpretable class means consistent with previous literature (McFall et al., 2019b). Characteristics for each class, such as the intercept and slope means and class proportions are

reported in Table 7. Figure 2 displays the raw trajectory data for each individual and their estimated class membership (colour-coded).

The first class was labeled as stable memory agers (SMA), characterized by the highest level and maintenance of memory performance over time (n = 79 [13.6%], intercept = 4.77, 95% *CI* 4.54, 5.0], slope = -0.02, 95% *CI* [-0.038, <0.001]). The second class was labeled as typical memory agers (TMA), characterized by mid-high level and slow decline (n = 222 [38.3%], intercept = 1.61, 95% *CI* [1.48, 1.74], slope = -0.05, 95% *CI* [-0.064, -0.038]). The third class was labeled as slowly declining memory agers (SDMA), characterized by mid-low level and moderately faster decline than typical agers (n = 198 [34.0%], intercept = -1.68, 95% *CI* [-1.80, -1.56], slope = -0.12, 95% *CI* [-0.135, -0.106]). The fourth class was labeled as rapidly declining memory agers (RDMA), characterized by the lowest level and the steepest decline (n = 81 [13.9%], intercept = -5.31, 95% *CI* [-5.45, -5.16], slope = -0.19, 95% *CI* [-0.212, -0.170]).

RG1b

Following the selection and interpretation of a four-class model of episodic memory change, research goal 1b tested the prediction of latent class membership using six baseline predictors as auxiliary variables: four subjective memory decline facets, sex, and pulse pressure. Tables 8 and 9 show the estimates and odds ratios for the included predictors for both the SMA and RDMA classes as reference classes.

An increase in reported memory concerns was associated with over a three-fold increase in the odds of being in RDMA (OR = 3.39, p = 0.005) and over a two-fold increase in the odds of being in SDMA (OR = 2.41, p = 0.021), as compared to the SMA class.

For sex, the odds of being in the three classes with faster decline, TMA (OR = 4.66, p = 0.006), SDMA (OR = 12.06, $p < 0.001$), and RDMA (OR =15.80, $p < 0.001$), as compared to the SMA class, were higher for males than for females when other predictors were held constant. The odds of being in the SMA (OR = 0.06, $p < 0.001$) or TMA (OR = 0.29, $p < 0.001$) classes, as compared to the RDMA class, were lower for males than for females when other predictors were held constant. However, males were not more likely to be in SDMA versus the RDMA class (OR = 0.76, p = 0.403).

The multinomial logistic regression results also indicated that pulse pressure predicted episodic memory class membership. The odds of being in the SDMA class relative to the SMA class increased by 1.6 times as pulse pressure increased (i.e., worsened) by 10 mm Hg (OR = 1.60, p = 0.012). Pulse pressure did not significantly predict membership to any other class.

RG2a

Prior to the moderation analyses for our second research goal, we confirmed that higher pulse pressure was associated with both lower level (b = -0.09, $p < 0.001$) and steeper decline in episodic memory (b = -0.004, $p < 0.001$). For research goal 2a, we tested the moderating role of SMD facet class on the prediction of episodic memory trajectories by pulse pressure. Specifically, we used SMD facet class membership to stratify CLGMs testing prediction of memory trajectories by pulse pressure. Relative fit indices and entropy values for all k-class models for each facet are reported in Tables 10 (memory complaints), 12 (memory concerns), 14 (memory compensation) and 16 (memory self-efficacy). Class means for the selected models are presented in Table 11 (memory complaints), 13 (memory concerns), 15 (memory compensation) and 17 (memory self-efficacy). Goodness of fit indices for the CLGM of pulse pressure predicting memory as stratified by the aforementioned classes are presented in Table 18.

Memory Complaints. For this facet, we tested models with up to five classes, as the inclusion of additional classes resulted in the non-replication of the log-likelihood value. The 4-class model was selected as the optimal model from all candidate models. Despite the 5-class model presenting a lower AIC and SABIC, the 4-class model had a lower BIC and higher entropy value. Additionally, the gains from the additional class can be considered negligible as supported by the 'elbow' dip in Figure 3, also known as a point of diminishing returns (Nylund, Asparouhov & Muthén, 2007). The four classes were labeled as follows: (1) a group with the lowest memory complaints, and a slight increase over time (lowest complaints); (2) a group with low complaints and a more noticeable increase over time (low complaints); (3) a group with moderate complaints, showing a slight increase over time (moderate complaints); and (4) a group with the highest level of complaints, and showing slight increase over time (highest complaints). Figure 4 displays the raw memory complaints trajectory data for each individual and their estimated class membership (colour-coded). LCGMs stratified by these four classes revealed that pulse pressure was not predictive of episodic memory level or decline for the two most extreme classes (i.e., the lowest complaints and highest complaints classes). On the other hand, higher pulse pressure predicted lower level and decline in memory for both the low complaints class (b_i = -0.16, b_s =-0.01) and the moderate complaints class (b_i =-0.09, b_s =-0.01). The model was constrained in order to test whether stratification by memory complaints class provided a better model, which was confirmed to be true ($\Delta\chi^2 = 33.2$, $\Delta df = 18$, $p = 0.02$). This finding indicates that memory complaints class is a significant moderator of predictions of episodic memory trajectories by pulse pressure.

In sum, we identified four statistically distinct classes of memory complaints trajectories. For individuals belonging to the two middle classes (i.e., low complaints and moderate

complaints), worse pulse pressure was associated with lower level and steeper decline in memory. On the other hand, increasing pulse pressure did not have a significant effect on memory trajectories (level or change) for individuals belonging to the lowest complaints (indicating potential protection conferred by low SMD) and highest complaints classes (indicating a potential threshold where, with progressing SMD, pulse pressure has a limited impact on memory trajectories).

Memory Concerns. For this facet, we computed LCGA models with up to five classes due to the non-replication of the log-likelihood value in higher-order models. These models showed improvements in AIC, BIC and SABIC from the baseline model (Table 12). The 5-class model exhibited one class with small class prevalence (3%) and was thus removed from consideration. The 4-class model was selected as the final model as it had the lowest relative fit indices as well as satisfactory entropy. The four classes were labeled similarly to the memory complaints classes: (1) a group with the lowest memory concerns, and little (non-significant) change over time (lowest concerns); (2) a group with low concerns and a slight increase over time (low concerns); (3) a group with moderate concerns, exhibiting little (non-significant) change over time (moderate concerns); and (4) a group with the highest level of concerns, exhibiting a decrease in concerns over time (highest concerns). Figure 5 displays the raw memory concerns trajectory data for each individual and their estimated class membership (colour-coded). Stratification by class analyses revealed that higher pulse pressure predicted lower memory level and steeper decline in all memory concerns classes except for the highest concerns class. For the lowest concerns class, higher pulse pressure predicted lower memory level (b = -0.11, p = 0.01) and steeper decline (b = -0.01, p = 0.006). For the low concerns class, higher pulse pressure similarly predicted lower memory level (b = -0.9, p = 0.04) and steeper

decline (b = -0.004, p = 0.03). Finally, for the moderate concerns class, higher pulse pressure also predicted lower memory level (b = -0.11, p = 0.03) and steeper decline (b = -0.006, p = 0.02). The stratified CLGM by memory concerns class was confirmed to be a better model ($\Delta\chi^2$ = 30.1, Δdf = 18, p = 0.04), indicating that memory concerns class moderated episodic memory trajectory predictions by pulse pressure.

In sum, we identified four statistically distinct trajectory classes for memory concerns. Poorer vascular health did not have a significant effect on memory trajectories for individuals belonging to the highest concerns class. However, increasing pulse pressure predicted lower level and steeper decline in memory for individuals belonging to the three classes reporting less memory concerns. Similar to memory complaints, this may be due to a potential pulse pressure effect threshold that accompanies increasing and progressing SMD.

Memory Compensation. We computed LCGA models with up to four classes due to the non-replication of the log-likelihood value in higher-order models. The 3-class model was chosen to proceed in subsequent analyses as it revealed the lowest AIC, BIC and SABIC values and had the highest value of entropy. The three classes were characterized as follows: (1) a group with the lowest use of memory compensation, and a slight decrease in compensation over time (lowest compensation); (2) a group with low use of memory compensation and little (non-significant) change in compensation over time (low compensation); and (3) a group with higher use of memory compensation, showing little (non-significant) change in compensation over time (high compensation). Figure 6 displays the raw memory compensation trajectory data and estimated class membership (colour-coded). Stratification by class analyses revealed that pulse pressure predicted level and change in episodic memory for the low compensation and high compensation classes. For the low compensation class, higher pulse pressure predicted lower

memory level (b = -0.08, p = 0.03) and steeper decline (b = -0.004, p = 0.02). For the high compensation class, higher pulse pressure predicted both lower memory level (b = -0.12, p = 0.002) and steeper decline (b = -0.005, $p < 0.001$). Pulse pressure did not predict memory level or change for the lowest compensation class. The constrained stratified model did not show worse fit than the unconstrained model ($\Delta\chi^2 = 9.42$, $\Delta df = 12$, $p = 0.67$), indicating that memory compensation class membership did not significantly moderate pulse pressure predictions of memory trajectories.

In sum, we identified three statistically distinct classes of memory compensation. Individuals belonging to the two classes reporting higher memory compensation exhibited lower level and steeper memory decline as pulse pressure increased; however, this trend was not statistically significant.

Memory Self-Efficacy. For this facet, we computed LCGA for 2-, 3- and 4-class models due to non-convergence occurring with additional classes. Due to low class prevalence in one class (3%) of the 4-class model, this model was excluded from the candidate models. The 3-class model showed the lowest AIC, BIC and SABIC values. Thus, the 3-class model was retained as the final model for subsequent analyses. The three classes were labelled as follows: (1) a group with the lowest self-efficacy and a slight decrease over time (lowest memory self-efficacy); (2) a group with low self-efficacy and a slight decrease over time (low memory self-efficacy); and (3) a group with the highest memory self-efficacy and a slight decrease over time (high memory self-efficacy). Figure 7 displays the raw memory self-efficacy trajectory data and estimated class membership (colour-coded). Stratification by class analyses revealed that pulse pressure predicted level and change in memory for the high memory self-efficacy and low memory self-efficacy classes. For the high memory self-efficacy class, higher pulse pressure also predicted

lower memory level (b = -0.08, p = 0.01) and steeper decline (b = -0.004, p = 0.002). For the low memory self-efficacy class, higher pulse pressure predicted lower memory level (b = -0.11, p = 0.01) and steeper decline (b = -0.005, p = 0.002). Pulse pressure did not predict memory level or change for the lowest memory self-efficacy class. Similar to the memory compensation facet, the constrained model did not show worse fit than the unconstrained model ($\Delta\chi^2 = 8.03$, $\Delta df = 12$, p = 0.78). Therefore, membership to memory self-efficacy class did not significantly moderate pulse pressure predictions of memory trajectories.

In sum, we identified three distinct classes of memory self-efficacy. Membership to the two classes reporting higher memory self-efficacy was associated with lower level and steeper memory decline as pulse pressure increases; however, this trend was not statistically significant.

RG2b

The main aim of research goal 2b was to test whether differential effects of SMD moderation occur by sex or *APOE* genetic risk groups. In order to test this aim, we further stratified the CLGMs for each facet by sex and *APOE* ε4+/-. The results are presented for each SMD facet, first by facet and sex stratifications, followed by facet and *APOE* ε4+/- stratifications.

Memory Complaints. Stratification by memory complaints class and sex revealed that pulse pressure predictions of memory level and change retained the previous pattern for memory complaints, but remained significant only for females. That is, higher pulse pressure predicted lower level and steeper decline in episodic memory selectively for females belonging to low complaints (b_i = -0.20, b_s =-0.01) and moderate complaints (b_i = -0.12, b_s =-0.01) classes. There were no significant pulse pressure predictions for males belonging to any class. The CLGM to predict memory was constrained in order to test whether stratification by memory complaints

class and sex provided a better model, which was confirmed to be true ($\Delta\chi^2 = 155.40$, $\Delta df = 40$, $p < 0.001$). Therefore, memory complaints and sex interactively moderated pulse pressure predictions of memory trajectories selectively for females.

In order to stratify by memory complaints class and *APOE* ε4+/-, the highest complaints class was removed as the prevalence of ε4+ individuals was too small for the model to converge. For *APOE* ε4- individuals in the low complaints class, higher pulse pressure was associated with lower memory level ($b = -0.15$, $p = 0.01$), but not decline. For individuals with no risk allele belonging to the moderate complaints class, higher pulse pressure was associated with steeper decline in memory ($b = -0.005$, $p = 0.01$), but not memory level. Pulse pressure did not significantly predict level or change in episodic memory for ε4+ individuals belonging to any memory complaints class, or ε4- individuals in the lowest and highest memory complaints classes. The constrained CLGM stratified by class and *APOE* ε4+/- was a worse fit ($\Delta\chi^2 = 55.93$, $\Delta df = 35$, $p < 0.01$) than the unconstrained model. This indicates that for there was a significant moderation effect of memory complaints and *APOE* genetic risk on pulse pressure-memory predictions which was selective to ε4- individuals.

In sum, the sex and memory complaints results extend on findings from the previous memory complaints class stratification. With increasing pulse pressure, individuals belonging to the two middle memory complaints classes (i.e., low complaints and moderate complaints) exhibited lower level and steeper decline in memory. Stratification by *APOE* and memory complaints class revealed that membership to these middle classes and poorer vascular health was predictive of lower level and steeper decline only for individuals without a risk allele.

Memory Concerns. Stratification by memory concerns class and sex revealed a selective effect for females. Specifically, females belonging to the lowest concerns class with higher pulse

pressure demonstrated lower level (b = -0.15, p = 0.02) and steeper decline (b = -0.005, p = 0.03). Females in the low concerns class also exhibited more memory decline as pulse pressure increased (b = -0.004, p =0.048), but did not show any significant differences in level. There were no significant pulse pressure predictions for males in any class, or for females in the moderate concerns and highest concerns classes. The constrained model was confirmed to be a better model ($\Delta\chi^2$ = 195.54, Δdf = 49, $p < 0.001$) than the unconstrained model, providing evidence for a significant moderation effect of memory concerns facet and sex on pulse pressure predictions of memory trajectories for females.

In order to stratify by memory concerns class and *APOE* ε4+/-, the highest concerns class was removed from stratification analyses due to the small number of individuals with an ε4 allele in this group. For ε4- individuals in the lowest concerns class only, higher pulse pressure was associated with lower level (b = -0.11, p = 0.03) and steeper decline (b = -0.005, p = 0.003). Pulse pressure did not significantly predict level or change in episodic memory for ε4+ individuals belonging to any memory concerns class. The CLGM was constrained in order to test whether stratification by class and *APOE* ε4+/- provided a better model. The constrained model did not show worse fit ($\Delta\chi^2$ = 33.85, Δdf = 35, p = 0.50) than the unconstrained model, suggesting the memory concerns and *APOE* interaction with pulse pressure was not a significant moderation.

In sum, higher pulse pressure predicted lower level and decline in females belonging to the lowest concerns class, and lower level in females belonging to the low concerns class. There were no significant pulse pressure predictions for males in any class. Unlike the class stratification analyses on their own, there were no significant pulse pressure effects for males or females in the moderate concerns class. *APOE* and memory concerns class stratification revealed

that vascular health for ε4- individuals in the lowest concerns class had a non-significant effect on memory.

Memory Compensation. Stratification by memory compensation class and sex revealed that pulse pressure predicted memory level and change selectively for females in the high compensation class. For females in this class, higher pulse pressure was associated with lower level (b = -0.13, p = 0.01) and steeper decline (b = -0.005, p = 0.001) in memory. For males in all classes, no memory compensation class moderation effects were observed. The stratified CLGM was confirmed to provide better fit ($\Delta\chi^2$ = 134.754, Δdf = 35, $p < 0.001$), indicating a significant sex and memory compensation class moderation in females.

In order to stratify by memory compensation class and *APOE* ε4+/-, the lowest compensation class was removed from stratification analyses due to the small number of ε4+ individuals in this class. For ε4- individuals in high compensation class only, higher pulse pressure was associated with lower level (b = -0.11, p = 0.03) and steeper decline (b = -0.005, p = 0.003) in memory. Pulse pressure did not significantly predict level or change in episodic memory for ε4+ individuals belonging to any memory compensation class. This CLGM was also constrained in order to test whether stratification by class and *APOE* ε4+/- provided a better model. The constrained model did not show worse fit ($\Delta\chi^2$ = 18.92, Δdf = 21, p = 0.59) than the unconstrained model, revealing a non-significant moderation effect of *APOE* and memory compensation class on pulse pressure predictions of memory trajectories.

In sum, we identified a significant moderation effect whereby higher pulse pressure predicted lower level and decline in females belonging to the high compensation class only. *APOE* and memory concerns class stratification revealed that vascular health in ε4- individuals in the high compensation class had a non-significant effect on memory.

Memory Self-Efficacy. Stratification by memory self-efficacy class and sex revealed pulse pressure predicted memory level and change selectively for females in the high memory self-efficacy class. For females in this class, higher pulse pressure was associated with both lower level (b = -0.01, p = 0.008) and steeper decline (b = -0.004, p = 0.004). For males in all classes, no memory self-efficacy class moderation effects were observed. The CLGM to predict memory trajectories was constrained in order to test whether stratification by class and sex provided a better model, which was confirmed to be true ($\Delta\chi^2 = 132.90$, $\Delta df = 35$, $p < 0.001$). This suggests that sex and memory self-efficacy class are significant interactive moderators of pulse pressure predictions of episodic memory trajectories (selective effects for females).

In order to stratify by memory compensation class and *APOE* ε4+/-, the lowest memory self-efficacy class was removed from stratification analyses due to the small number of ε4+ individuals in this class. In individuals with no ε4 allele, higher pulse pressure was associated with steeper decline and lower level in those in the low memory self-efficacy class (b_i = -0.11, b_s =-0.01) and the high memory self-efficacy class (b_i = -0.08, b_s =-0.004). Pulse pressure did not significantly predict level or change in episodic memory for ε4+ individuals belonging to any memory self-efficacy class. Membership to memory self-efficacy class and *APOE* demonstrated significant moderation of episodic memory predictions by pulse pressure in ε4- individuals, as the unconstrained CLGM provided better fit than the constrained model ($\Delta\chi^2 = 35.68$, $\Delta df = 21$, $p = 0.02$).

In sum, higher pulse pressure predicted lower level and decline in females belonging to the high memory self-efficacy class only. *APOE* and memory self-efficacy class stratification revealed that for individuals without an ε4 allele, poorer vascular health for individuals in both

the low memory self-efficacy and high memory self-efficacy classes were predictive of lower memory level and steeper decline.

Discussion

The overall goal of this study was to explore associations of SMD facets, pulse pressure, sex, and *APOE* genetic risk and their independent and interactive effects on episodic memory trajectories. We utilized two distinct quantitative modeling approaches: (1) data-driven discrimination of memory and SMD facet trajectory classes, and (2) conditional latent growth modeling to test prediction and moderation of the above-mentioned risk factors on episodic memory level and change.

Previous research identified SMD as a possible subjective harbinger of objective cognitive decline and increased dementia risk (Buckley et al., 2016; Jessen et al., 2014a; Snitz et al., 2015b; Wolfsgruber et al, 2016). Early markers (both objective and subjective) of rapidly declining memory function are of considerable interest for current research on (1) the origins of differential memory aging and (2) the identification of individuals with elevated risk for exacerbated memory decline. The latter could lead to new targets for dementia prevention efforts and promotion of healthier brain and cognitive aging. Accounting for precision moderators (e.g., sex) of objective decline and AD is of additional importance as these early markers have been shown to be differentially predictive of longitudinal memory trajectories (Drouin et al., 2018). For example, our previous findings revealed memory self-efficacy to be exclusively predictive of episodic memory change and level in males, whereas memory complaints and memory concerns demonstrated female-specific predictive value. Thus, we hypothesized that SMD interactions with other AD risk factors, such as sex and *APOE* genetic risk, may also differentially impact pulse pressure predictions of memory trajectories.

Discussion: RG1

For the first part of our first research goal, we used data-driven modelling technology as applied to a relatively large distribution of memory trajectories to identify distinct latent classes of change patterns, based on an algorithm of level and slope.

With a growing emphasis on heterogeneity in cognitive aging, an increasing number of studies have explored data-driven class trajectories of cognition in older adults, instead of grouping individuals based on outcome change cut-offs (e.g., score decrease in MMSE) (Melis, Haaksma, & Muniz-Terrera, 2019). Most commonly, trajectories of general functional markers and cognitive outcome variables (e.g., clinical rating scales score, MMSE), especially in clinical samples, have been explored (Baker et al., 2017; Haaksma, Calderon-Larranaga, Olde Rikkert, Melis, & Leoutsakos, 2018; Melis et al., 2019; Tampubolon & Pendleton, 2017). A limited number of studies have focused on memory trajectories specifically in cognitively normal older adults. Of non-VLS studies (McFall et al., 2019b), these studies either explored different types of memory (i.e., semantic) (Teipal et al., 2018) or utilized composite or manifest episodic memory variables (Ding et al., 2019; Olaya et al., 2017; Pietrzak et al., 2015).

Using a latent variable model of episodic memory, our results revealed that cognitively normal older adults can be objectively classified into four distinct and interpretable classes of memory aging trajectories. We observed variability in both initial level and change across a broad range of older adults, which was captured by four distinct groups: (1) a group performing above average at the age of 75, and showing maintenance of memory function (stable memory aging; SMA), (2) a group performing at an average level and exhibiting minimal decline (typical memory aging; TMA), (3) a group demonstrating mid-low level and moderate decline (slowly declining memory aging; SDMA) and (4) a group performing the worst at age 75 and declining

fairly rapidly over time (rapidly declining memory aging; RDMA). This finding was similar to a previous VLS study in which three classes with distinct longitudinal patterns of level and slope were observed. These previously observed classes were characterized as “stable memory aging”, “normal memory aging” and “declining memory aging” (McFall et al., 2019b). Our interpretation of the present four-class model class differences was concordant with the previous findings for non-demented adults and memory. The concordances included a similar pattern of memory trajectory subgroups (stable, typical, declining): a class with sustained memory trajectories, a class with limited decline, and two classes (SDMA, RDMA) exhibiting more accelerated decline. A few differences were as follows. For the previous 3-class model, the middle class was characterized by mid-range to low factor scores (under zero). For the present model, we observed two separable middle classes: (1) the TMA class representing an ‘upper-middle’ with level factor scores remaining above zero and decline being limited, and (2) the SDMA class representing a ‘lower-middle’ with factors scores well below zero and increasingly steeper decline. The present 4-class model also revealed smaller class sizes compared to the previously observed model. Notably, the SMA class is significantly smaller in the present model (13.6% versus 31%). We also observed near-identical sized RDMA and SMA classes, indicating that there are a similar number of individuals in the classes presenting with the most extreme level and change values. In addition, our four trajectory classes closely resembled findings in an older group of adults (aged 65-79 years) in which four trajectories groups of verbal episodic memory were identified (Olaya et al., 2017). Class proportions were also comparable in size and characterization (Olaya et al., 2017).

Specific to the declining classes, the RDMA class trajectory is also consistent with previous findings of a cognitively normal subgroup who exhibited decline at a non-normal rapid

rate within a larger sample of older adults with heterogeneous memory trajectories (Mungas et al., 2010). As rapid decline in episodic memory is often an early cognitive hallmark of preclinical AD (Bäckman et al., 2001; Hodges, 1998), it is possible that membership to these declining episodic memory classes (i.e., RDMA) is associated with a number of important risk factors of neurodegeneration. Likewise, membership to stable classes (i.e., SMA) may be associated with protective factors predicting sustained and higher levels of cognitive performance with aging. Although examining predictions of class membership beyond pulse pressure, sex and SMD was outside the scope of this study, the consideration of additional risk factors as possible predictors would be an important consideration in future research (e.g., Josefsson, de Luna, Pudas, Nilsson, & Nyberg, 2012; McFall et al., 2019a).

As a second part to our first research goal, we tested class discrimination by risk predictors, including sex, SMD facets and pulse pressure. Previous research has shown that older females often perform at higher levels and decline less in episodic memory than males of the same age (Herlitz, Nilsson & Bäckman, 1997; Herlitz & Rehnman, 2008; McFall et al., 2019b). Results of the current study further support these findings, as being female was associated with decreased odds of being in the TMA, RDMA and SDMA class as compared to the SMA class. As this study included two declining classes, the absence of a significant prediction by sex of membership to SDMA class when compared to the RDMA class is a novel finding in the context of a latent episodic memory variable. In these two declining groups, males and females were indistinguishable in their memory decline patterns. Previously, Olaya and colleagues (2017) found that sex was not associated with the low and declining verbal memory class as compared to the very low and declining class in an older age group of adults (65-79 years). As supported by these findings, sex conceivably plays a limited role in differentiating membership between

two declining classes. It is possible that female sex is initially protective of decline in memory, but that this protection is attenuated as memory decline begins to occur. In the context of cognitive aging and dementia prevention research, sex should be explored in a way that accounts for the possibility of diminishing importance as a risk/protective factor with progressing memory dysfunction in asymptomatic adults.

Predictions of memory trajectory class membership by SMD facets revealed that the memory concerns facet was a significant predictor of membership to the more steeply declining classes relative to the SMA class. Previously, using individualized trajectories instead of class membership, we found that more memory complaints, more memory concerns and less memory compensation were predictive of steeper decline in our entire sample (Drouin et al., 2018). As only baseline SMD facets were considered as predictors in the present study, it is likely that the consideration of baseline-only subjective memory diminishes the predictive value of this facet as compared to using the facets at all available waves. Additionally, while we previously found that other SMD facets (e.g., memory self-efficacy) predicted individual memory trajectories, these predictions were sex-specific (Drouin et al., 2018). As the current four memory trajectory classes were created using the entire sample (i.e., not stratified by sex), previously sex-specific facets would likely not be indicative of membership to declining classes for both males and females. The results of the current study suggest that the specific facet of memory concerns is particularly predictive of non-normal memory trajectories, as an increase in reported memory concerns was associated with increased odds of being in the SDMA or RDMA classes as compared to the SMA class. It is likely that increased memory concerns may be more revealing of everyday memory challenges and future declines in memory than the three other SMD facets. This may be due to the fact that concerns about memory change imply both an awareness of ongoing memory

decline, and the resulting negative impact (i.e., concerns and anxiety) resulting from this perceived change (Jessen et al., 2014a). As has been found in other SCD and SMD studies, these findings suggest that memory concerns present as a more severe form of memory complaints (Jessen et al., 2014b).

We also found pulse pressure to be predictive of memory trajectory latent class membership. Interestingly, when using the SMA as a reference category, an increase in pulse pressure increased the odds of being in the SDMA class, but not the RDMA class. As individuals in the RDMA class also demonstrate much lower levels of episodic memory than all other classes, it is possible that membership in this class is only partially captured by pulse pressure, perhaps due to the confounding effects of pre-existing memory decline. That is, higher pulse pressure may negatively impact memory performance to a certain threshold, but this impact may diminish once a particular amount of decline has occurred. Indeed, pulse pressure may be particularly predictive of cognitive decline in earlier, but not later (i.e., when the decline is more rapid), stages. Some studies have found that higher pulse pressure in the oldest-old (85 years and older) is associated with less cognitive decline (Molander, Gustafson, Loveheim, 2010; Sabayan et al., 2012). Sabayan and colleagues (2012) hypothesized that age may be confounded by already present cognitive decline. In addition, longitudinal findings suggest that blood pressure decreased three years prior to a dementia diagnosis, but this change was not present more than 3 years and up to 6 years prior to diagnosis (Qiu, von Strauss, Winblad & Fratiglioni, 2004). It is thus possible that higher pulse pressure (similarly linked to cardiovascular risk) is also predictive of some decline in memory, but not of a more rapid and exacerbated decline that often presents as a harbinger to MCI or dementia. It is likely, then, that membership to the RDMA class is associated with more robust biomarkers of cognitive decline and clinical neurodegeneration.

In sum, for our first research goal, we used LCGA to identify four distinct classes of memory aging trajectories. These classes were consistent with previous findings in this research area demonstrating the existence of distinguishable subgroups of memory performance change across a 40-year band of aging. The objectively determined subgroups represented a full range of memory aging trajectories from 55 to 95 years of age. The identified subgroups included a class of relatively high and sustained memory change and another of relatively low and rapidly declining memory change. Male sex, more memory concerns and higher pulse pressure were predictive of membership to more rapidly declining classes. These factors demonstrate a clear importance within the framework of dementia risk management and healthier cognitive aging as they are associated with undesirable and possible non-normal changes in memory function.

Discussion: RG2

The first part of our second research goal consisted of investigating pulse pressure associations with episodic memory trajectories as moderated by SMD facets. We first established a significant inverse association between initial pulse pressure and memory change, whereby higher (worse) PP was associated with lower and steeper memory decline. In the second part of the second research goal, we tested possible moderation of this association by SMD facets. For each of the SMD facets, we used LCGA to identify distinct latent trajectory classes based on an algorithm of level and slope. We found distinguishable classes for each of the SMD facets. We identified four classes for the memory complaints and memory concerns facets, and three classes for the memory compensation and memory self-efficacy facets. An individual's most likely class, as determined by posterior probabilities (see Asparouhov & Muthén, 2014), was used as a stratification variable to investigate moderation by SMD facet classes on pulse pressure predictions of memory level and change.

Overall, we found selectively significant moderation effects of SMD facets. Notably, moderation by SMD was specific to the memory complaints and memory concerns facets. For the memory complaints facet, higher pulse pressure was associated with lower level and steeper decline selectively for two of the classes, the low complaints and moderate complaints subgroups. For the memory concerns facet, higher pulse pressure was similarly associated with lower level and steeper decline only for the lowest concerns, low concerns and moderate concerns classes.

The memory complaints and memory concerns facets represent the typical items which are usually used to encompass SMD or SCD, and are criteria for an SCD *Plus* Classification (Jessen et al., 2014a). As such, these two facets may be considered at the core of SMD. It is possible that moderation by memory complaints and memory concerns was significant as these two facets represent more typical and common presentations of SMD. In addition, both the memory compensation and memory self-efficacy facets had fewer latent trajectory classes (i.e., 3 versus 4). Thus, differences between the extreme classes for these facets may be less pronounced than for memory complaints or concerns, and accordingly making effects more difficult to detect.

Our next step consisted of investigating whether this SMD moderation persisted or differed when accounting for sex or *APOE* genetic risk. We found that the sex and SMD facet interaction significantly moderated pulse pressure predictions of episodic memory trajectories for all four SMD facets. In the case of memory complaints, only females belonging to the low complaints and moderate complaints classes demonstrated lower level and steeper decline in memory with increasing pulse pressure. There were no pulse pressure effects on episodic memory trajectories for males in any class, or for females belonging to the lowest complaints and highest complaints classes. For females belonging to the highest complaints class, it is possible that the absence of a

pulse pressure effect is due to accurate perceptions of memory decline. Indeed, we previously established longitudinal associations between subjective memory complaints and objective decline in females (Drouin et al., 2018). Notably, females with higher memory complaints demonstrated lower memory level and declined faster over time than those reporting low complaints (Drouin et al., 2018). Previous studies on subjective complaints in healthy older adults also report that individuals with complaints are accurately perceiving objectively undetectable changes in cognitive function (Reisberg, Shulman, Torossian, Len & Zhu, 2010; St John & Montgomery, 2002), an effect that is especially strong for females (Heser et al., 2019). It is conceivable that females with increased memory complaints are accurately perceiving their memory decline. As such, females belonging to the highest complaints memory class would be experiencing declining memory function, which may no longer be affected by vascular dysfunction. As was the case with the RDMA class in our first research goal and with individuals in preclinical AD stages (Qiu et al., 2004), this further suggests that the effects of pulse pressure on memory are diminished when memory decline has already begun to occur.

Similarly, females with the lowest complaints may also be accurately perceiving memory changes (i.e., no change). Females belonging to this class, then, may not demonstrate the typical effects of poor vascular health, as they are likely not experiencing the same extent of 'normal' age-related decline as those perceiving low to moderate memory complaints. For the memory concerns facet, there were no pulse pressure effects on memory change for females in the highest concerns class. As memory concerns were also previously found to be indicative of memory decline (Jessen et al., 2014b; Wolfsgruber et al, 2016), specifically in females (Drouin et al., 2018), this finding similarly supports the possibility that pulse pressure no longer acts as an accurate marker of cognitive decline for females already exhibiting substantial decline.

For the memory compensation facet, stratification by SMD class alone did not significantly improve the model. This indicates that memory compensation class membership does not moderate pulse pressure and memory trajectory associations. However, the addition of sex in the two-way stratification analyses revealed significant effects for females belonging to one memory compensation class. Notably, in females with the highest use of memory compensation, higher pulse pressure predicted both lower level and steeper decline. Although we initially hypothesized greater use of compensatory techniques to be representative of worse SMD, it is also possible that low use of memory compensation may actually indicate a form of worse SMD. That is, the use of compensatory techniques, if successful, may cause less memory change to be perceived. With this directionality in mind, there would be no observed pulse pressure effects on memory for females with worse SMD for this facet (i.e., less reported memory compensation), similarly reflecting results found for the memory complaints and memory concerns facets.

For memory self-efficacy, class stratification on its own did not reveal significant moderation effects. Our results demonstrated that higher pulse pressure predicted both lower level and steeper decline in memory for females belonging to the class with high reported memory self-efficacy. This result is especially interesting as memory self-efficacy was previously found to be significantly predictive of objective decline in males only (Drouin et al., 2018). This suggests that predictions of objective decline by pulse pressure moderated by memory self-efficacy show different associations with sex than SMD associations alone.

The addition of vascular health and sex in the present study further supports and extends previous findings in two ways. First, the multi-faceted SMD findings demonstrate that vascular dysfunction interactions with early and accurate memory perception changes are facet-specific and occur in females only. SMD facets and pulse pressure may be early independent and

interactive predictors of cognitive decline in females, but have not been shown to be interactively involved in early prediction patterns for males. Second, it is likely that poor vascular health diminishes in importance as an AD risk factor once memory decline progresses. Indeed, as supported by our previous work demonstrating SMD-related memory trajectory predictions for females, the current results suggest that females belonging to classes which represent more SMD are likely already experiencing memory decline, and, in turn, their vascular health no longer has a significant effect on their memory decline. The results from the first research goal also support this finding, with those in the RDMA class not demonstrating pulse pressure effects.

Stratification of the memory trajectories prediction model by SMD facet classes and *APOE* ε4+/ε4- revealed significant moderation effects for both the memory complaints and memory self-efficacy facets. For these stratifications, pulse pressure associations with episodic memory were only found in *APOE* ε4- individuals. It is thus possible that these vascular effects are primarily driven by the larger number of ε3/ε3 individuals. While poor vascular health has been found to be particularly more predictive of decline in ε4 carriers (Ferencz et al., 2013; Yasuno et al., 2012), the results of this study suggest that this association does not occur interactively with SMD.

Limitations and Strengths

There are several limitations to this study. First, VLS participants are relatively healthy and free of neurodegenerative disease at intake and only asymptomatic participants were selected for this study. Therefore, this sample is not entirely representative of a broad population of older adults, as certain risk-reducing influences (e.g., higher education levels) are typical characteristics of these participants. However, present VLS sample characteristics may reflect a growing and independent subset of older adults in developed nations; therefore, the potential

range of generalizability may extend to older adults in these regions. Second, the analysis used (i.e., LCGA) for our second research goal to identify SMD facet classes and stratify our models by these classes may have introduced downward-estimate bias. The technique used is known as the "classify-analyze" approach, which assumes that classification is true class membership without entirely accounting for measurement error (Bray, Lanza & Tan, 2015). However, there are a number of reasons why this was the best available analytic approach. Using SMD as a stratification variable allowed for a thorough examination of potential SMD moderation effects, as latent variable interactions are often difficult to detect and interpret (Maslowsky, Jager & Hemken, 2015). In addition, for the memory complaints and memory concerns facets, we can be relatively confident that classification accuracy is satisfactory due to the high value of entropy. Moreover, any potential bias introduced by the classify-analyze approach leads to an attenuation of estimates (Bray et al., 2015), suggesting that stronger SMD moderation effects than those found in this study may actually be present. Of course, it is important to note that for both the memory compensation and memory self-efficacy facets, more caution is required in the interpretation of these predictions as sub-standard values of entropy may indicate inadequate delineation of classes (Celeux & Soromenho, 1996). Third, the study of the *APOE* moderation (in RG2b) was limited due to restricted number of *APOE* ε4+ individuals belonging to those classes. However, we were still able to proceed with the moderation analyses for all four SMD facets.

There were also several notable strengths to this study. First, our sample was reasonably large (W1 $n = 580$). Second, we used age (as a continuous variable) instead of wave as the metric of change with participants contributing up to 9 years of data spanning a 40-year band of aging. This accelerated longitudinal design allowed longitudinal analyses to be conducted across a wide

range of ages and avoid the common pitfalls that accompany simple cohort longitudinal or, especially, cross-sectional designs. Third, LCGA account for heterogeneity present in the data. As older adults are known to be a widely heterogeneous group (Lowsky, Olshanky, Bhattacharya & Holdman, 2013), especially in asymptomatic or early preclinical dementia stages, this methodology allows for more accurate capturing of the population of interest (Masyn, 2013). Fourth, the inclusion of auxiliary variables directly in the model (R3STEP approach) for our first research goal is the current standard in mixture modeling techniques as it takes into account possible misclassification (Asparouhov & Muthén, 2014).

Conclusion

Previous findings suggest a network of mechanisms connecting SMD with differential cognitive and memory trajectories and clinical outcomes (Buckley et al., 2016; Geerlings et al., 1999; Mitchell et al., 2014; Tsutsumimoto et al., 2017; Wang et al., 2004; Wolfsgruber et al, 2016). Among these potential differentiating predictors are vascular health, sex, and *APOE* genetic risk. To date, vascular associations with SMD and these potential moderators of memory change trajectories remain vastly understudied. The identification of significant predictors (including pulse pressure) of episodic memory latent class membership provides further understanding of early markers and their interactions in predicting distinct memory-related trajectories. In addition, the present study detected SMD facet-specific interactions with sex and *APOE* genetic risk that moderate the effect of aging vascular dysfunction on memory trajectories differentially. The investigation of independent and interactive effects of vascular and other key AD risk factors (e.g., *APOE,* sex) and SMD in the prediction of differential changes in memory aging also provides insight into the precision nature of some of the associations (e.g., females only) and potential directions for personalized intervention. Accordingly, this could lead to the detection of

precision targets in at-risk groups prior to the onset of clinical neurodegeneration associated with accelerated memory decline.

Tables

Table 1. Participant characteristics by wave (W1-W3).

Characteristics	W1	W2	W3
n	580	474	392
Age, years (SD)	70.2 (8.60)	74.3 (8.50)	77.8 (8.10)
Gender (% females)	65	64.6	64.8
Education, years (SD)	15.3 (3.0)	15.4 (3.0)	15.4 (3.2)
Pulse Pressure, mmHG	51.92 (10.11)		
APOE, *n* (%)			
ε2/ε2	33 (5.7)		
ε2/ε3	37 (6.4)		
ε2/ε4	29 (5.0)		
ε3/ε3	345 (59.5)		
ε3/ε4	125 (21.6)		
ε4/ε4	11 (1.9)		
MMSE	28.7 (1.21)	28.4 (1.75)	28.14 (2.6)
CES-D	7.0 (5.4)		
NEO-Anxiety	21.5 (4.5)		

Table 2. Single-group latent growth model of EM.

Model	-2LL	AIC	BIC	*D*	Δdf
Fixed intercept	7712.92	7720.92	7738.37	–	–
Random intercept	5593.61	5603.61	5635.43	2119.31	1
Random intercept Fixed slope	5580.65	5592.65	5618.83	12.96	1
Random intercept Random slope	4728.71	4744.71	4779.61	856.94	2

Table 3. Confirmatory factor analyses and invariance testing for SMD and EM.

Model	*AIC*	*BIC*	χ^2	*df*	*p*	*RMSEA*	*CFI*	*SRMR*	$\Delta\chi^2$	*Δdf*
SMD-Configural	59619.06	60901.79	2374.15	1416	0.000	0.03	0.91	0.06	–	–
SMD-Metric	59611.58	60763.42	2426.66	1446	0.000	0.03	0.91	0.06	52.51	30
SMD-Scalar	59626.26	60612.31	2517.34	1484	0.000	0.04	0.91	0.06	90.68	38
SMD-Residual	59600.65	60421.10	2567.73	1522	0.000	0.03	0.91	0.06	50.39	38
EM-Configural	21420.06	21642.58	43.38	39	0.000	0.01	0.99	0.03	–	–
EM-Metric	21435.39	21631.73	70.71	45	0.000	0.03	0.99	0.05	27.33	6
EM-Scalar[a]	21442.61	21630.22	81.92	47	0.000	0.04	0.98	0.06	11.21	2

Table 4. Correlations between SMD facets (four-factor model) at wave 1.

	Memory Complaints	Memory Concerns	Memory Compensation	Memory Self-Efficacy
Memory Complaints	-	0.50	0.56	0.15
Memory Concerns	0.50	-	0.37	-0.05
Memory Compensation	0.56	0.37	-	-0.07
Memory Self-Efficacy	0.15	-0.05	-0.07	-

Table 5. Fit statistics and class proportions for tested unconditional LCGA models of EM.

k	**Class Proportions**	**AIC**	**BIC**	**SABIC**	**Entropy**
1	-	7446.50	7468.32	7452.45	-
2	0.46 / 0.53	6781.07	6815.98	6790.58	0.79
3	0.44 / 0.38 / 0.17	6442.91	6490.90	6455.98	0.84
4*	0.13 / 0.13 / 0.34 / 0.38	6167.70	6228.77	6184.33	0.85
5	0.16 / 0.04 / 0.11 / 0.34 / 0.32	5973.90	6048.07	5994.11	0.88

**Selected final model*

Table 6. Fit statistics and class proportions for tested unconditional GMM models of EM.

k	**Class Proportions**	**AIC**	**BIC**	**SABIC**	**Entropy**
1	-	7446.50	7468.32	7452.45	-
2	0.86/0.14	4635.16	4683.16	4648.24	0.78
3	0.06/0.15/0.78	4561.57	4622.65	4578.21	0.83
4	0.06/0.19/0.04/0.69	4536.95	4611.12	4557.15	0.79

Table 7. Parameter estimates (means) for the selected 4-class EM model.

Class 1: SMA (13.6%)	***Class 2: TMA (38.3%)***	***Class 3: SDMA (34.0%)***	***Class 4: RDMA (13.9%)***
i: 4.77 *s:* -0.02	*i:* 1.61 *s:* -0.05	*i:* -1.68 *s:* -0.12	*i:* -5.31 *s:* -0.19

**LCGA: variances were fixed at 0 and are not reported*

Table 8. Estimates, odds ratios for predictors using SMA as reference class.

	Sex[1]		**Memory Complaints**		**Memory Concerns**		**Memory Compensation**		**Memory Self-Efficacy**		**Vascular Health**	
k	Estimate	Odds Ratio	Estimate	Odds Ratio	Estimate	Odds Ratio	Estimate	Odds Ratio	Estimate	Odds Ratio	Estimate	Odds Ratio
TMA	1.54*	4.66	0.01	1.01	0.34	1.41	1.49	4.44	0.34	1.40	0.25	1.28
SDMA	2.49*	12.06	0.09	1.09	0.88*	2.41	2.19	8.94	0.47	1.60	0.47*	1.60
RDMA	2.76*	15.80	0.45	1.57	1.22*	3.39	0.28	1.32	1.01	2.75	0.41	1.51

[1]Reference category for sex is female.
**significant after Benjamini-Hochberg FDR (10%) correction*

Table 9. Estimates, odds ratios for predictors using RDMA as reference class.

	Sex[1]		**Memory Complaints**		**Memory Concerns**		**Memory Compensation**		**Memory Self-Efficacy**		**Vascular Health**	
k	Estimate	Odds Ratio	Estimate	Odds Ratio	Estimate	Odds Ratio	Estimate	Odds Ratio	Estimate	Odds Ratio	Estimate	Odds Ratio
SMA	-2.76*	0.06	-0.45	0.64	-1.22*	0.30	-0.28	0.76	-1.01	0.36	-0.41	0.66
TMA	-1.22*	0.29	-0.44	0.64	-0.87*	0.42	1.21	3.35	-0.67	0.51	-0.16	0.85
SDMA	-0.27	0.76	-0.36	0.70	-0.33	0.72	1.92	.15	-.54	0.58	0.05	1.05

[1]Reference category for sex is female.
**significant after Benjamini-Hochberg FDR (10%) correction*

Table 10. Fit statistics and class proportions for tested unconditional LCGA models of memory complaints.

k	**Class Proportions**	**AIC**	**BIC**	**SABIC**	**Entropy**
2	0.64/0.36	1564.28	1599.19	1573.79	0.86
3	0.23/.45/0.32	1387.57	1435.65	1400.64	0.77
4*	0.20/0.45/0.09/0.26	1255.43	1216.52	1272.07	0.80
5	0.08/0.20/0.13/0.20/0.39	1208.81	1282.98	1229.01	0.74

**Selected final model*

Table 11. Parameter estimates (means) for the 4-class memory complaints model.

Class 1: Lowest Complaints (20.3%)	***Class 2: Low Complaints (25.9%)***	***Class 3: Moderate Complaints (44.8%)***	***Class 4: Highest Complains (8.9%)***
i: -0.75 *s:* 0.007	*i:* -0.21 *s:* 0.013	*i:* 0.32 *s:* 0.006	*i:* 0.83 *s:* 0.007

Table 12. Fit statistics and class proportions for tested unconditional LCGA models of memory concerns.

k	Class Proportions	AIC	BIC	SABIC	Entropy
2	0.65/0.35	1392.22	1427.13	1401.73	0.87
3	0.17/0.32/0.51	1028.92	1076.91	1041.99	0.86
4*	0.301/0.32/0.23/0.14	857.99	919.08	874.63	0.81
5	0.03/0.40/0.12/0.19/0.26	735.53	809.69	755.73	0.85

**Selected final model*

Table 13. Parameter estimates (means) for the 4-class memory concerns model.

Class 1: Lowest Concerns (30.7%)	***Class 2: Low Concerns (32.3%)***	***Class 3: Moderate Concerns (23.4%)***	***Class 4: Highest Concerns (13.6%)***
i: -0.55 *s:* 0.003	*i:* -0.15 *s:* 0.004	*i:* 0.36 *s:* -0.001	*i:* 0.95 *s:* -0.008

Table 14. Fit statistics and class proportions for tested unconditional LCGA models of memory compensation.

k	Class Proportions	AIC	BIC	SABIC	Entropy
2	0.40/0.60	-2082.69	-2047.78	-2073.18	0.71
3*	0.49/0.12/0.39	-2403.68	-2355.69	-2390.61	0.73
4	0.20/0.29/0.40/0.10	-2590.41	-2529.33	-2573.77	0.71

**Selected final model*

Table 15. Parameter estimates (means) for the 4-class memory compensation model.

Class 1: Lowest Compensation (12.7%)	***Class 2: Low Compensation (48.8%)***	***Class 3: Moderate Compensation (38.5%)***
i: -0.27 *s:* -0.003	*i:* -0.047 *s:* -0.001	*i:* 0.15 *s* < 0.001

Table 16. Fit statistics and class proportions for tested unconditional LCGA models of memory self-efficacy.

k	Class Proportions	AIC	BIC	SABIC	Entropy
2	0.72/0.28	463.76	498.66	473.27	0.78
3*	0.31/0.09/0.60	402.88	450.88	415.95	0.73
4	0.06/0.27/0.03/0.63	351.14	412.23	267.78	0.85

**Selected final model*

Table 17. Parameter estimates (means) for the 4-class memory self-efficacy model.

Class 1: Lowest Memory Self-Efficacy (8.9%)	***Class 2: Low Memory Self-Efficacy (30.5%)***	***Class 3: High Memory Self-Efficacy (60.6%)***
i: 0.620 *s:* 0.009	*i:* 0.205 *s:* 0.009	*i:* -0.180 *s:* 0.005

Table 18. Goodness of fit indices for conditional latent growth models of pulse pressure predicting EM.

Model	AIC	BIC	-2LL	*D*	*p*
Stratified by memory complaints	15001.04	15261.56	14881.03	-	-
Stratified by memory complaints (constrained)	14998.19	15180.56	14914.19	33.14	0.02
Stratified by memory complaints and sex	14947.42	15468.48	14707.42	-	-
Stratified by memory complaints and sex (constrained)	15004.82	15313.11	14862.82	155.39	<0.001
Stratified by memory complaints and *APOE*	12958.73	1336.78	12778.73	-	-
Stratified by memory complaints and *APOE* (constrained)	12944.66	13175.69	12834.66	55.93	0.01
Stratified by memory concerns	15013.04	15273.57	14893.05	-	-
Stratified by memory concerns (constrained)	15007.09	15189.47	14923.10	30.05	0.04
Stratified by memory concerns and sex	14902.44	15423.49	14662.44	-	-
Stratified by memory concerns and sex (constrained)	14999.98	15308.27	14857.98	195.54	<0.001
Stratified by memory concerns and *APOE*	12432.92	12805.51	12252.92	-	-
Stratified by memory concerns and *APOE* (constrained)	12396.77	12624.46	12286.77	33.85	0.5
Stratified by memory compensation	15006.31	15201.71	14916.31	-	-
Stratified by memory compensation (constrained)	14991.73	15135.02	14925.72	9.42	0.67
Stratified by memory compensation and sex	14966.71	15357.50	14786.71	-	-
Stratified by memory compensation and sex (constrained)	15011.46	15250.28	14901.46	134.75	<0.001
Stratified by memory compensation and *APOE*	12576.21	12826.76	12456.21	-	-
Stratified by memory compensation and *APOE* (constrained)	12553.13	12715.99	12475.13	18.92	0.59
Stratified by memory self-efficacy	15018.82	15214.21	14928.82	-	-
Stratified by memory self-efficacy (constrained)	15002.85	15146.14	14936.85	8.04	0.78
Stratified by memory self-efficacy and sex	14931.21	15322.01	14751.21	-	-
Stratified by memory self-efficacy and sex (constrained)	14994.09	15232.91	14884.10	132.88	<0.001
Stratified by memory self-efficacy and *APOE*	13040.43	13293.07	12920.43	-	-
Stratified by memory self-efficacy and *APOE* (constrained)	13014.11	13178.32	12936.11	35.68	0.02

Figures

Figure 1. Individualized raw trajectories of EM.

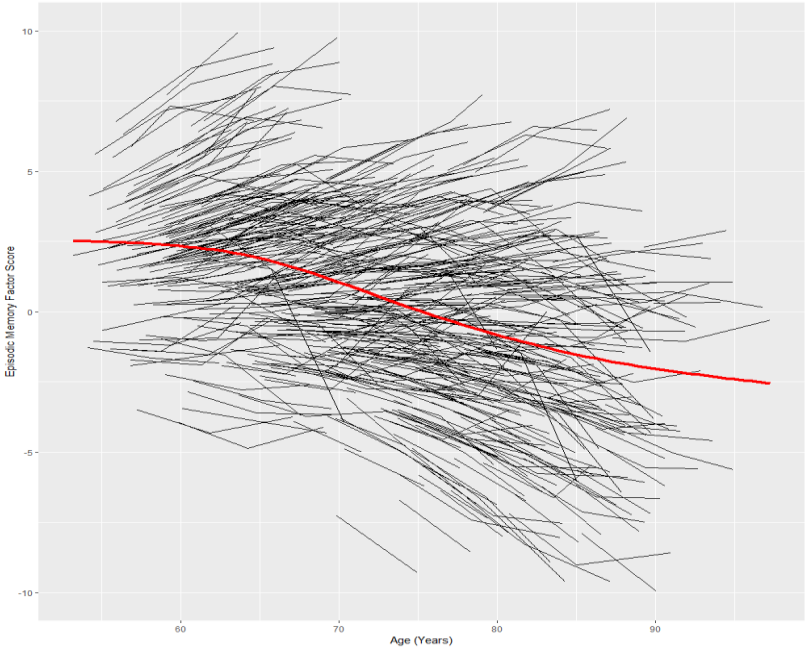


Figure 2. Individualized raw trajectories of EM (colour-coded class membership).

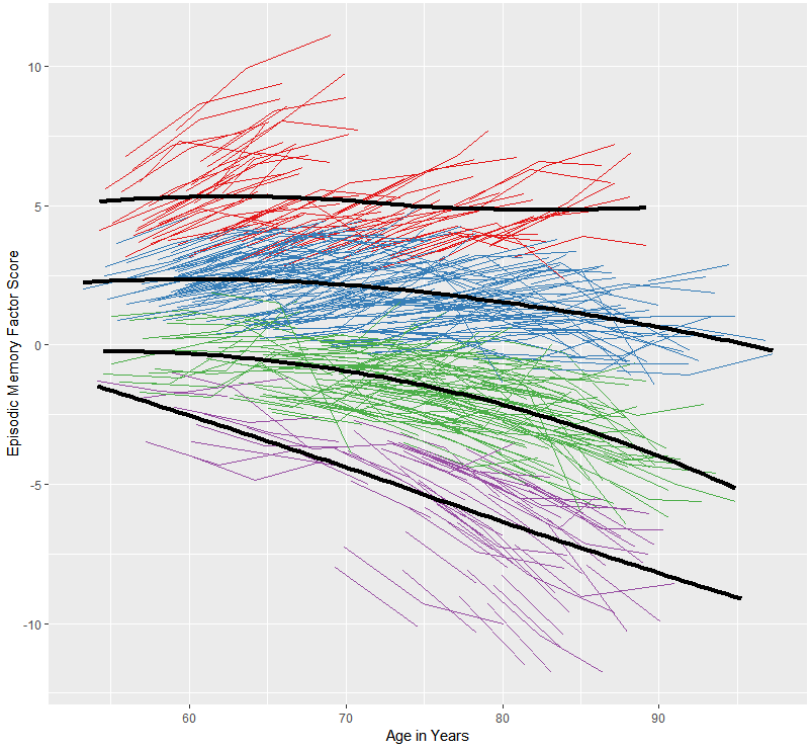


Figure 3. Elbow Plot for Memory Complaints LCGA.

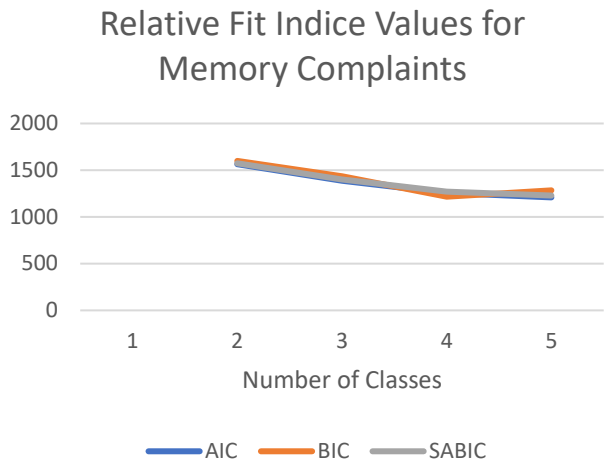


Figure 4. Individualized raw trajectories of memory complaints (colour-coded class membership).

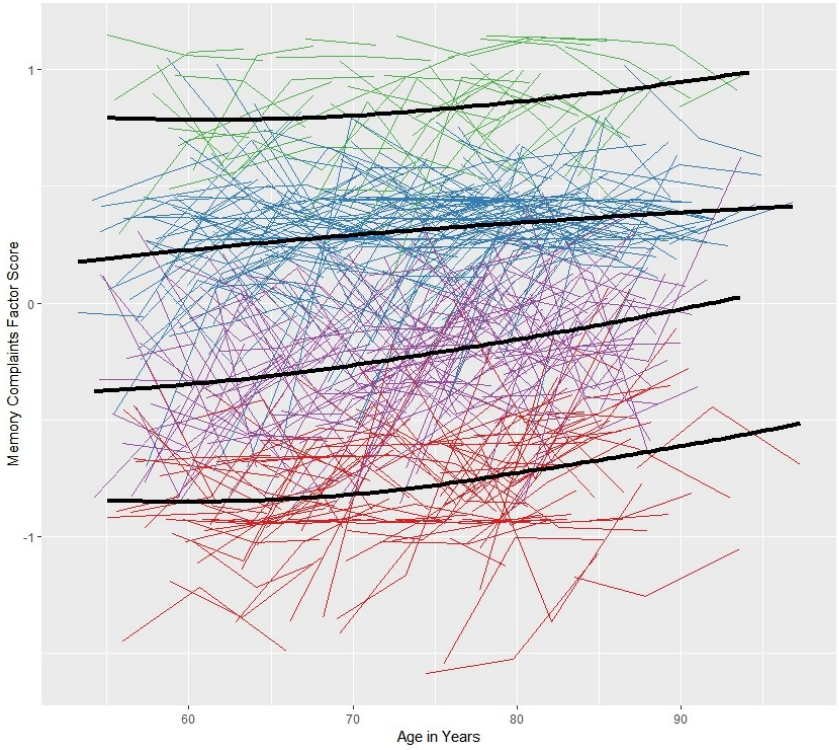


Figure 5. Individualized raw trajectories of memory concerns (colour-coded class membership).

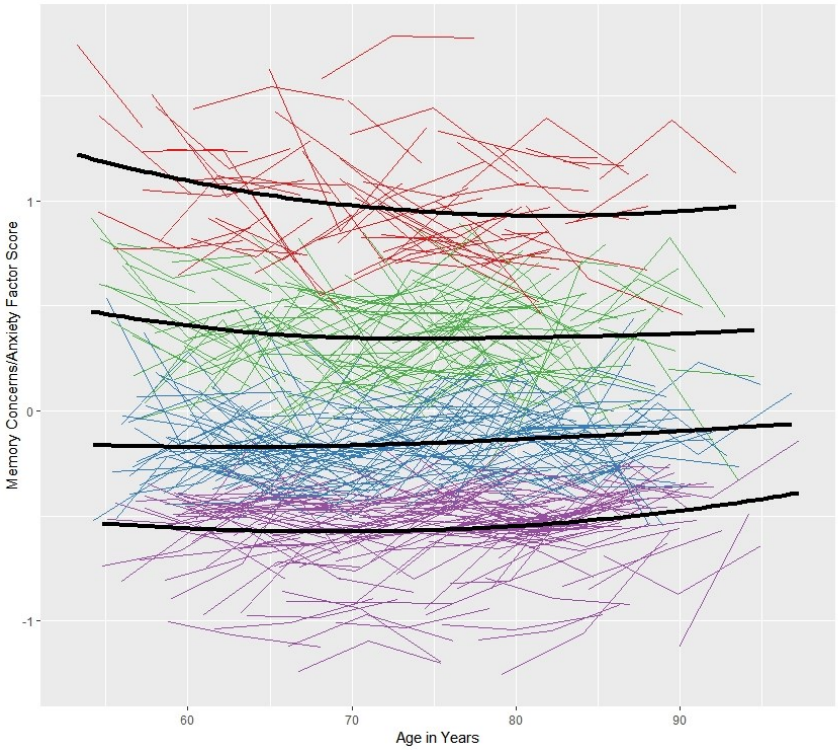
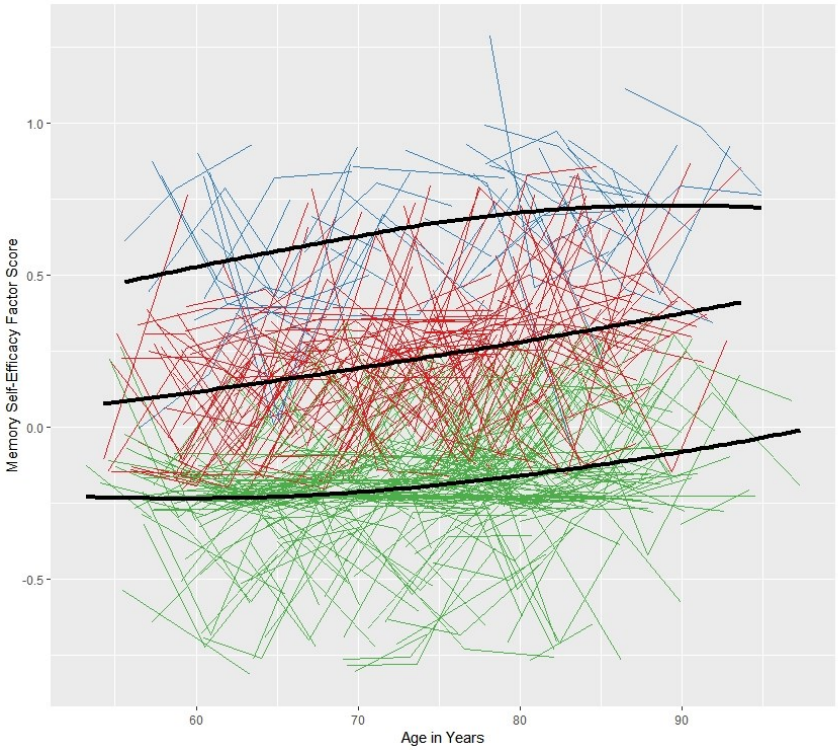


Figure 6. Individualized raw trajectories of memory compensation (colour-coded class membership).

Figure 7. Individualized raw trajectories of memory self-efficacy (colour-coded class membership).



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Appendix A

Table A1. Selected Items in the Metamemory in Adulthood and Memory Compensation Questionnaire.

Memory Complaints	Memory Concerns	Memory Anxiety	Memory Compensation	Memory Self-Efficacy
My memory has declined greatly in the last 10 years	It bothers me when others notice my memory failures	I get anxious when I am asked to remember something	Do you use such aids for memory as notebooks or putting things in certain places more or less often today compared to 5-10 years ago?	I think a good memory comes mostly from working at it
I'm less efficient at remembering things now than I used to be	I get tense and anxious when I feel my memory is not as good as other peoples'	I am usually uneasy when I attempt a problem that requires me to use my memory	Do you post reminders of things you need to do in a prominent place, such as bulletin boards or note boards?	It's up to me to keep my remembering abilities from deteriorating
The older I get the harder it is to remember clearly	I get upset when I cannot remember something	I would feel on edge right now if I had to take a memory test or something similar	Do you use memory tricks such as repeating things to yourself or grouping things in categories more or less often today compared to 5-10 years ago?	If I were to work on my memory I could improve it
		I do not get flustered when I am put on the spot to remember new things	Do you ask other people to remind you of something?	No matter how hard a person works on his memory, it cannot be improved very much
			Do you write yourself reminder notes?	