FUNCTIONAL ACTIVITY FEATURES IN SUCCESSFUL COGNITIVE AGING

by

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DISSERTATION

Presented to the Faculty of

The University of Texas at Dallas

in Partial Fulfillment

of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY IN

COGNITION AND NEUROSCIENCE

THE UNIVERSITY OF TEXAS AT DALLAS

December 2019

ACKNOWLEDGMENTS

I would like to thank my advisor, Denise Park, for her mentoring me as a doctorate student and helping me to grow as a scientist. Thank you for providing me with the greatest opportunities I could only dream of having. This dissertation, and my academic career, would not have been possible without the support from you.

I would also like to thank the rest of my dissertation committee, Mick Rugg, Kristen Kennedy, and Jackie Nelson, for their time, expertise and guidance on this project. Thank you for being so supportive through the project.

Thank you to the past and current members of the Park Aging Mind Lab and the collaborators in the Dallas Lifespan Brain Study. The work in this dissertation would be impossible without your contribution.

Thank you to Eva Qin and Maggie O'Connell for your care and help in my years as a grad student. You are both brilliant and wonderful people. I feel fortunate to always have your support.

Thank you to Micaela Chan, Chris Foster, Melissa Rundle for your care and help. You were always there for me when I needed help, and I am so grateful for everything that I have learned from you.

Thank you to Sara Festini, Michelle Farrell, and Katie Munro. I am grateful just to have you in my life. You have always believed in me, even when I didn't believe in myself. Your love, support and encouragement have helped me to get where I am today. You all are the best.

An emotional thank you to my husband, Xueming (Jackie) He. Seven years ago, I met this wonderful man when I first came to this country. You are the best thing that ever happened to

me. You say never quit when I feel defeated; and you say you always believe in me and support me no matter what happens, when I feel stressed. Thank you for understanding of my pursuit for an academic career, and being encouraging through my years in graduate school. I will always love you.

Thank you to my family for all the love and support. An extra thank you to my Mom. You have always been my role model as an independent and successful woman in a male-dominated field. Thank you for always making sure I know how proud you are of me. I would like you to know that I have been so proud of you too.

November 2019

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The University of Texas at Dallas, 2019

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Cognitive aging research has traditionally studied the inevitable cognitive decline in older adults as a group. Recently, more research has recognized the importance of understanding the individual variability in cognitive aging trajectories. Some individuals show superior performance and better preservation of cognition relative to others at their age, termed "*prime"* agers in the present dissertation. By contrast, some individuals may exhibit substantial cognitive deficits and greater decline representing a suboptimal cognitive aging profile, termed "*nonprime"* individuals. Many neuroimaging research efforts have been made to explore the neural mechanisms associated with these individual differences. Two possible patterns of functional activity, youth-like activation and compensatory recruitment, have been proposed to be particularly related to individual variability in cognitive changes. However, there is still a lack of consensus on what brain activity patterns may represent optimal aging in *prime* individuals. The present dissertation investigated this question in two studies. Because one major source of difficulty in this topic is the challenge in identifying *prime* agers, Study 1 implemented an exploratory data-driven approach to classify participants based on their cognitive performance and longitudinal cognitive change across multiple cognitive domains. Using two waves of

longitudinal cognitive data (with a four-year interval) in episodic memory, inductive reasoning, working memory, processing speed from the Dallas Lifespan Brain Study, Study 1 in Chapter 2 examined the cognitive aging profiles in middle-aged, young-old and very old participants, and successfully identified two distinct cognitive aging profiles among participants, representing *prime* and *nonprime* individuals. Study 2 in Chapter 3 then utilized this classification of subgroups and compared their patterns of functional activity using a subsequent memory fMRI task collected at the second wave of DLBS. The analyses revealed several functional activity pattern differences between *prime* and *nonprime* individuals. First, *prime* individuals showed greater subsequent memory effect than *nonprime* individuals across core task-related regions associated with successful encoding. In addition, the higher subsequent memory effect in *prime* individuals, compared to *nonprime* individuals, was most evident in the young-old group, because *prime* agers exhibited better preservation of higher effect comparable to in younger adults, until very old age. In contrast, *nonprime* agers showed reduced subsequent memory effect starting in young-old age. Finally, *prime* young-old adults also recruited additional frontal regions, including left superior frontal and right orbitofrontal cortex, compared to young adults. This additional recruitment showed a trend of relationship to better memory performance, possibly suggesting a compensatory nature of this activation. In conclusion, the present dissertation demonstrated the use of a data-driven, multivariate approach and successfully identified *prime* and *nonprime* agers with distinct cognitive aging profiles. Comparison of their patterns of functional brain activity revealed that *prime* agers show a preservation of higher activation until very late in the lifespan and additional frontal recruitment in young-old age.

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CHAPTER 1

INTRODUCTION AND BACKGROUND

Aging has been historically characterized by substantial cognitive decline in many older adults (D. C. Park et al., 2002; Salthouse, 2003; Schaie, 1996), but recent literature has recognized the considerable inter-individual variability in the maintenance of cognitive ability throughout the lifespan (Goh, An, & Resnick, 2012; Hoogendam, Hofman, van der Geest, van der Lugt, & Ikram, 2014; Kramer et al., 2007; Lindenberger, 2014; Mella, Fagot, Renaud, Kliegel, & De Ribaupierre, 2018; Mungas et al., 2010; Nyberg, Lovden, Riklund, Lindenberger, & Backman, 2012; Royall, Palmer, Chiodo, & Polk, 2005; Wilson et al., 2002), suggesting that some people are more vulnerable to age-related cognitive decline while some may be resistant to cognitive change. As 20 percent of the total U.S. population will be over the age of 65 by 2030 (Ortman, Velkoff, & Hogan, 2014), there is a pressing need for promoting cognitive health and delaying age-related decline in older adults. Many interventional studies are targeting at improving older adults' cognition (Mewborn, Lindbergh, & Miller, 2017), and their success depends on a thorough knowledge of what constitutes "optimal aging" (Cabeza et al., 2018; Daffner, 2010; Nyberg et al., 2012; Nyberg & Pudas, 2018). In the present dissertation, individuals across the adult lifespan who have superior cognitive performance and better longitudinal preservation in cognition, relative to their peers, are termed as "*prime*" agers, representing a group of individuals exhibiting a more optimal cognitive aging profile. The overarching goal of the present dissertation aims to explore two challenging questions in this topic: (1) how can we identify *prime* individuals? and (2) how do they differ from other

individuals who represent average or nonprime trajectories of aging in brain functional activities?

Many research efforts have been made to identify and characterize individuals into groups who show "better" or "worse" patterns of cognitive aging (Albert et al., 1995; Baltes & Baltes, 1993; Depp & Jeste, 2006; Nyberg & Pudas, 2018). However, operationally identifying *prime* individuals with optimal aging has always been challenging (Bowling & Dieppe, 2005; Depp & Jeste, 2006; Fiocco & Yaffe, 2010; Rogalski et al., 2013; Rowe & Kahn, 1997). Previous studies have mainly classified individuals on their memory performance (Harrison, Weintraub, Mesulam, & Rogalski, 2012; Olaya et al., 2017; Pietrzak et al., 2015), or a coarse measure of mental status (e.g., Mini-mental State Exam; MMSE) (Han, Gill, Jones, & Allore, 2015). As a result, these studies divide individuals based on one specific cognitive domain. But cognition is comprised of multiple domains. An ideal classification should be holistic and comprehensive that summarizes cognitive aging status across domains, as one of the key elements proposed to define optimal aging conceptually is the preservation of functioning in "multiple cognitive domains" (Depp, Harmell, & Vahia, 2011). Particularly, in addition to memory, speed of processing (Salthouse, 1996b), inductive reasoning (Tucker-Drob, Johnson, & Jones, 2009), and working memory (Salthouse & Babcock, 1991) have also shown evidence of age-related decreases in cognitively normal older adults, and should be incorporated when identifying *prime* versus *nonprime* agers.

In the first study of this dissertation (Chapter 2), I will investigate cognitive aging as a broader system that reflects an integrated totality of cognitive performance and changes across multiple domains of the individual, using data from the Dallas Lifespan Brain Study (DLBS).

DLBS is a large-scale longitudinal study that aims to characterize cognitive and brain aging in cognitively normal individuals across the adult lifespan (aged 20-90 years old). It includes a cohort that is very well characterized in not only cognition but also other aspects that are related to aging, including brain function (Chan, Park, Savalia, Petersen, & Wig, 2014; Kennedy, Rodrigue, Devous, et al., 2012; H. Park, Kennedy, Rodrigue, Hebrank, & Park, 2013; Rieck, Rodrigue, Kennedy, Devous, & Park, 2015), brain structure (Song, Farrell, Chen, & Park, 2018), amyloid deposition (Farrell et al., 2017; Rodrigue et al., 2013; Song, McDonough, Liu, Lu, & Park, 2016), tau deposition, cerebrovascular assessment (Peng et al., 2018), genetic information (Rodrigue et al., 2013), and comprehensive surveys of psychosocial measures (Chan et al., 2018; Festini, McDonough, & Park, 2016).

I will take advantage of this rich dataset and the wide age range of participants. I will use a data-driven approach -- latent mixture modeling (Muthén, 2001; Ram & Grimm, 2009) -- that is specifically designed for separating individuals based on the heterogeneity in the data, and explore the differential cognitive aging patterns in this well-characterized cohort. Specifically, I will examine the longitudinal changes over four years in four cognitive domains – episodic memory, inductive reasoning, working memory, and speed of processing. Then, I will explore the existence of different subgroups in middle-aged (35-54 years old), young-old (55-69 years old) and very old adults (70-89 years old) based on their cognitive performance and longitudinal change in all four domains. These subgroups may reflect different cognitive aging profiles (e.g., *prime*, *average*, *nonprime*, etc). Finally, I will characterize and compare their longitudinal change in the four cognitive domains to further understand which of these cognitive domains contribute to distinct profiles between individuals. This data-driven approach may prove to be

useful for future studies to classify participants. A multivariate, unbiased approach may be particularly appropriate for aging and clinical research to develop classification with little *a priori* knowledge about the characteristics of subgroups.

Another puzzle in understanding optimal aging is what patterns of brain activation may be related to better cognitive aging. In the second study of the dissertation (Chapter 3), I will specifically investigate this question. I will relate the classification of cognitive aging profiles (obtained in Study 1 in Chapter 2) to brain functional activities to understand brain activity differences in individuals who have evidenced different cognitive changes.

One of the first findings in early neuroimaging studies of aging was that older adults who showed similar levels of task accuracy as young adults had decreased occipital activity as well as additional recruitment in prefrontal regions (Grady et al., 1994). Later research replicated the patterns of increased activity in prefrontal regions in older adults across a wide range of tasks and found that this additional recruitment was observed in older adults with better performance (Cabeza, Anderson, Locantore, & McIntosh, 2002; Eyler, Sherzai, Kaup, & Jeste, 2011; Reuter-Lorenz, Stanczak, & Miller, 1999). Based on these findings, researchers interpreted this increased prefrontal activation as a *compensatory recruitment*, often featured in high-functioning older adults, and suggested that such ability to recruit additional regions is indicative of successful adaptive aging (Cabeza, 2002; Craik & Rose, 2012; Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008).

In contrast to the compensation view showing age-related increases in activation, older individuals have also shown age-related decreases in task-related activation, which may reflect reduced neural responsiveness in older brains (H. J. Li et al., 2015). Presumably, older

individuals with little age-related change, structurally and functionally, are speculated to have better-preserved cognitive functions (Nyberg et al., 2012). Indeed, recent evidence has shown that older adults who maintained the ability to activate specific task-related regions as in young adults had better memory performance and little memory decline (Persson, Pudas, et al., 2011). Moreover, longitudinal fMRI evidence suggests that older individuals who declined in memory, not those who managed to maintain their memory, had increased prefrontal activity longitudinally (Pudas, Josefsson, Rieckmann, & Nyberg, 2018). Researchers have therefore proposed the concept of *brain maintenance* and suggested that "maintaining a youthful brain, rather than responding to and compensating for changes, may be the key to successful memory (cognitive) aging" (Nyberg et al., 2012; Nyberg & Pudas, 2018).

The majority of previous investigations on functional brain activity in older adults have interpreted their findings based on one of the two aforementioned views of successful brain aging (*compensatory recruitment*, *brain maintenance*). The two different accounts may seem contrary but are not necessarily contradictory, and may operate at different stages of the lifespan to cope with age-related changes (Cabeza et al., 2018). For example, the Scaffolding Theory of Aging and Cognition (STAC) suggests that the brain is a dynamic system with both positive and negative changes with age (D. C. Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014). As illustrated in Figure 1, as age increases, individuals are affected by depletion factors such as "neural challenges" and "functional deterioration". According to STAC, the individual variability in aging is, at least partly, a consequence of these changes: brains appearing to have low maintenance will perform worse than intact brains with better preservation. Critically, another important contributor to individual differences in cognitive aging is "compensatory

scaffolding" that represents the engagement of supplementary neural function in response to neural degradation. This compensatory support helps to counteract the adverse changes in the face of neural challenges and deteriorations with aging. Overall, STAC integrates these different perspectives and views the brain as a dynamically adaptive system and suggests that compensatory activation may counteract the effects of neural degrading and leads to better cognitive aging.

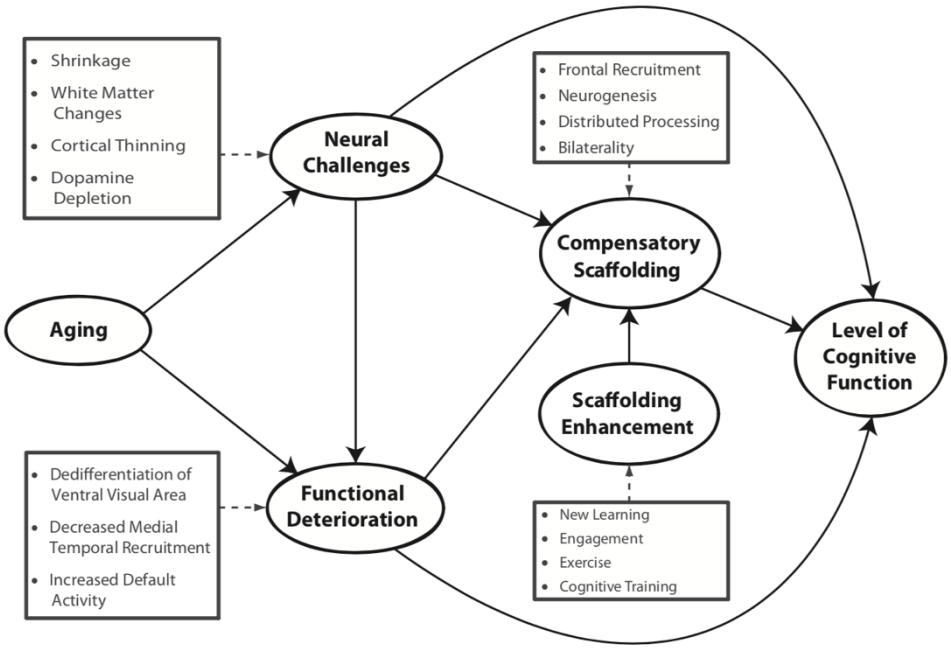

Figure 1. A conceptual model of the scaffolding theory of aging and cognition (STAC)

Therefore, to better understand the patterns of functional activity related to optimal cognitive aging, I will directly compare individuals with different cognitive aging profiles and examine whether there are distinguishable functional activity features related to successful cognitive aging. Taking the view of STAC, I suggest that optimal cognitive aging may be related to better preservation of youth-like activity pattern, while additional recruitment outside task-related regions may compensate and help with task performance in old age when brain

maintenance is reduced. I will use a subsequent memory task and compare the brain activity during successful encoding between individuals who established a superior pattern of cognitive aging and those who did not, as will be defined in Study 1 (Chapter 2), in middle-aged (35-54 years old at baseline), young-old (55-69 years old at baseline), and very old adults (70-89 years old at baseline). I will first focus on any brain activity difference in task-related regions of subsequent memory (Kim, 2011; Maillet & Rajah, 2014) and then explore activity differences outside the core task-related regions.

In summary, the present dissertation examines individual cognitive differences in aging and classifies individuals representing distinct cognitive aging profiles in middle-aged, young-old, and very old individuals (Study 1 in Chapter 2), and then relates the classification to differences in their brain activity (Study 2 in Chapter 3). Specifically, in Study 1 of Chapter 2, I explore a data-driven approach that holistically classifies cognitive aging based on cognitive performance and longitudinal change across multiple cognitive domains. Then, using the classification, I directly compare brain activity during successful encoding between individuals who have evidenced differential cognitive aging profiles, and examine what brain activity features may be related to successful cognitive aging in Study 2 of Chapter 3.

CHAPTER 2

USING A DATA-DRIVEN APPROACH TO CLASSIFY COGNITIVE AGING

2.1. Introduction

2.1.1. Overview of individual differences in cognitive aging

Cognitive aging research has been traditionally focusing on the inevitable cognitive declines in older adults, including slower speed of processing (Salthouse, 1996b), lower working memory (Salthouse, 1994), lower inductive reasoning ability (Tucker-Drob et al., 2009), and worse episodic memory (Ronnlund, Nyberg, Backman, & Nilsson, 2005). In these studies, the older population is often viewed as a homogeneous group whose mean performance is depicted as the representation of cognitive level in older adults and how it typically worsens with age.

Recently, studies have started to recognize the individual variability in age-related changes (Lindenberger, 2014; Rapp & Amaral, 1992). For example, Figure 2 illustrates the great inter-individual variability in longitudinal changes in memory (Nyberg, 2017). Each line represents an individual from the Betula study (Nilsson et al., 1997). The direction of the line represents if the individual has shown increases (going up) or decreases (going down) in their memory performance. The figure shows the mean change function (red curve) overlaid on individual patterns of change (black lines). The diverse patterns of the individual lines represent the massive inter-individual differences in the sample. This great variability in longitudinal change has also been reported in many independent samples with different measures of cognition (e.g., Baltimore Longitudinal Study of Aging (Goh et al., 2012); Seattle Longitudinal Study (Schaie, 1996); Religious Order Study (Wilson et al., 2002)), including the Dallas Lifespan Bran Study. The notion that cognitive aging does not follow homogenous declining trajectories

challenges the historical view of inevitable cognitive decline with age (Salthouse, 2010a), and offers the opportunity to explore factors that may contribute to different cognitive trajectories. Correctly characterizing and isolating the group of individuals presenting different cognitive aging profiles now becomes essential for ultimately understanding cognitive aging, and identifying modifiable factors that may lead to better cognitive aging.

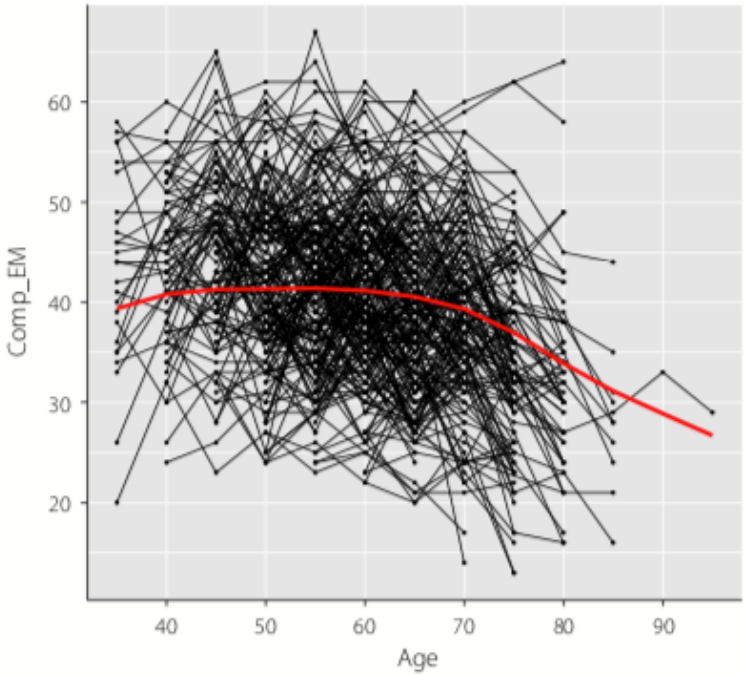

Figure 2. Illustration of mean change in episodic memory across the adult lifespan (red curve) and patterns of individual change (black lines) observed in the Betula study. Comp_EM=composite score of episodic memory (adapted from Nyberg, 2017).

However, there has not been a consensus on how to best separate individuals based on how their cognition changes with age. Thus, operationally identifying and studying different aging profiles has always been challenging (Fiocco & Yaffe, 2010; Rowe & Kahn, 1997). The proportion of individuals who may represent successful agers also varied dramatically across samples for this reason (Cosco, Prina, Perales, Stephan, & Brayne, 2014; Depp & Jeste, 2006).

2.1.2. Traditional approaches to classify different cognitive aging patterns

To study cognitive aging, some researchers use a cross-sectional design that collects data from individuals at different ages at the same time and examines the inter-individual differences to make inferences about age-related change. Cross-sectional classification of cognitive aging relies on the assessed performance at one time point and often defines superior agers, who appear to represent successful aging, based on the performance level relative to younger cohorts. An important assumption of such cross-sectional classification is that older adults performed the same as young adults when they were at the younger age and that the observed difference between older and younger groups reflects cognitive aging over the years. However, older people grew up in a very different socio-cultural and educational environment compared to the younger generation today, which may lead to different developmental trajectories beyond the effect of aging (Salthouse, 2014b). In addition, older adults recruited in healthy aging studies are often more selective, compared to young adults (Ronnlund et al., 2005; Singh-Manoux et al., 2012). Therefore, an optimal classification of agers who have better or worse cognitive aging trajectories should consider the intra-individual change that tracks their cognitive development related to aging using a longitudinal design where the same individual is tested repeatedly and compared to oneself.

Even among the studies using longitudinal data, various analytic approaches have been implemented when isolating individuals with different cognitive patterns (e.g., Australian Imaging, Biomarkers, and Lifestyle study (Pietrzak et al., 2015); Betula study (Josefsson, de Luna, Pudas, Nilsson, & Nyberg, 2012; Persson et al., 2005); Geneva Variability Study (Mella et al., 2018); Health Aging and Body Composition study (Yaffe et al., 2009)). Some researchers

took a theory-driven approach and separated individuals based on an *a priori* definition of successful or unsuccessful older adults by comparing their longitudinal cognitive change to zero (Mella et al., 2018; Persson et al., 2005; Yaffe et al., 2009). For example, Yaffe and colleagues (2009) studied 2509 older adults from the Health, Aging and Body Composition study over 8 years and separated participants into three groups based on the estimated rates of their longitudinal change in mental status: maintainers with 0 change or greater (30%), minor decliners with slopes less than 0 but no more than one SD below the mean change (53%), and major decliners with slopes more than one SD below the mean (16%). However, this approach relies on the prior knowledge of number of subgroups in the sample and the cut-off score for separating subgroups, which is inconclusive and even controversial in aging research.

2.1.3. Latent mixture modeling explores different cognitive aging profiles

Some recent studies, on the other hand, used data-driven approaches that specifically explore whether subgroups of individuals could be identified representing statistically different cognitive aging profiles (Downer, Chen, Raji, & Markides, 2017; Han et al., 2015; Hayden et al., 2011; Olaya et al., 2017; Pietrzak et al., 2015). Mixture modeling (Muthén, 2001; Nagin, 1999; Ram & Grimm, 2009) is particularly designed for this purpose.

Mixture modeling refers to the family of exploratory techniques that discover the optimal clustering solution and classify individuals into different groups based on the heterogeneity in the data. Mixture modeling includes pattern mixture modeling (R. J. Little, 1993), group-based trajectory modeling (Nagin, 1999), latent variable mixture modeling (Muthén, 2001; Ram & Grimm, 2009), latent growth mixture modeling (Muthén & Muthén, 2000), etc. Mixture modeling is very appropriate for studies where the aim is to separate individuals, because its

main objective is to cluster participants into different groups based on the variability in the data distribution. For example, Figure 3a represents an observed distribution of longitudinal change scores, consisting of two hidden distributions with different means. Mixture modeling examines this possibility and looks for the best solution to separate the subgroups by specifying a latent class, *c*, where the group difference between *c*=0 and *c*=1 is maximized and the within-group variability is minimized. For example, in the case of a mixture modeling of longitudinal change, the class variable, *c*, may offer a two-class solution which suggests that it detects two groups of individuals whose longitudinal changes follow two different distributions with different center values: one group with change scores around zero, and a group with negative values (Figure 3b).

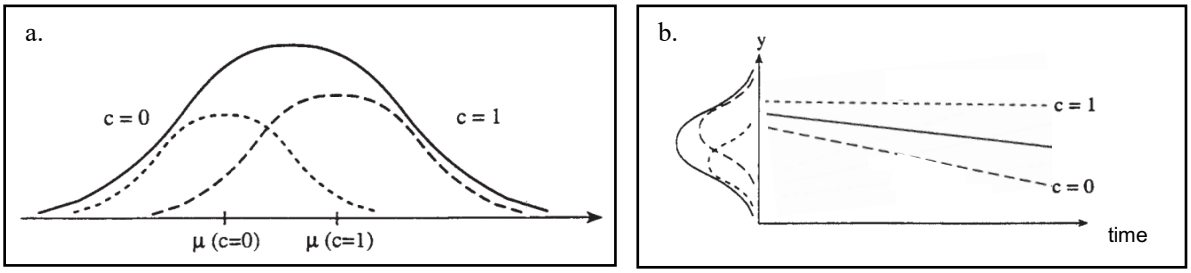

Figure 3. Illustration of mixture modeling. (a). Mixture modeling explores the presence of subpopulations within the whole population that is distinguishable and can be separated by a latent class variable, *c*. (b). Different distributions of longitudinal change scores may represent subpopulations with different developmental trajectories: class *c*=1 shows little longitudinal change whereas class *c*=0 shows a greater longitudinal decline.

Longitudinal studies using mixture modeling techniques have often identified two to five subgroups of individuals with different cognitive aging patterns (Downer et al., 2017; Han et al., 2015; Hayden et al., 2011; Mella et al., 2018; Olaya et al., 2017; Pietrzak et al., 2015; Zammit, Hall, Lipton, Katz, & Muniz-Terrera, 2018). For example, Hayden and colleagues (Hayden et al., 2011) studied 1049 older adults who were followed up to 15 years and classified three subgroups

based on a single measure of global function. They identified that the majority (65%) of old adults as a "slow decline" group that did experience some, but not substantial, cognitive decline, about 27% experienced moderate decline, and that 8% belonged to a group experiencing very rapid decline. Similarly, Pietrzak et al. (2015) followed 333 cognitively normal older adults for 54 months in the Australian Imaging Biomarkers and Lifestyle Study of Aging (AIBL), and also found three subgroups with different patterns of longitudinal change based on memory performance: subtly declining (30.9%), rapidly declining (3.6%), and stable (65.5%).

One feature of mixture modeling, as a data-driven approach, is that it explores the between-individual variability with no specific assumption regarding its heterogeneity. Traditional approaches separate individuals based on an *a priori* decision of the group number and the cut-off scores, and most studies examining cognitive aging divided participants into two to three groups (e.g., maintainer/decliner (Persson et al., 2005); successful/average/unsuccessful agers (Josefsson et al., 2012)). However, the number of meaningfully different subgroups may not be valid before exploring the data, particularly in an aging population (Ardila, 2007; Ylikoski et al., 1999). Mixture modeling allows for an unbiased examination of this heterogeneity and reveals whether the data indeed suggest meaningful differences between groups in the sample.

Another feature of mixture modeling is that it provides a person-oriented view of cognitive aging. That is to consider the structure and dynamics of behavior across different measures are, at least in part, specific to the individual (Bergman, 2001; Bergman & Magnusson, 1997). Traditional approaches, which are referred to as variable-oriented, are more appropriate in investigating theoretical questions regarding the relationships between variables. Mixture modeling, on the other hand, is a goal-directed process. Although it lacks mechanistic

implication, it identifies subpopulations at the individual level across variables (Bergman & Trost, 2006; von Eye & Bogat, 2006). In the current study, mixture modeling will classify participants simultaneously based on multiple variables, so it allows for classifications beyond the performance in a single cognitive domain, which offers a holistic profile of cognitive aging (Muthén & Muthén, 2000; Ram & Grimm, 2009). This is an important advantage of the current study as most research on optimal aging in older adults only based their classifications on either memory (Harrison et al., 2012; Olaya et al., 2017; Pietrzak et al., 2015) or a coarse measure of global mental function (Yaffe et al., 2009). Little is known as to the individual differences in cognitive aging when a wider range of cognitive measures is taken into account. The question was raised more than 25 years ago (Rabbitt, 1993) and still remains open now (Nyberg & Pudas, 2018), suggesting the need for investigation with a broader view of cognitive aging beyond a single cognitive domain.

Despite its strengths, mixture modeling is essentially an exploratory analysis. It may not be proper for hypothesis-driven studies where researchers have strong predictions for the number of groups or the separating patterns that ought to be observed. However, it is a suitable strategy for the current study where I aim to explore the DLBS longitudinal cognitive data and separate these individuals into different groups that may represent differential aging profiles. The Dallas Lifespan Brain study includes a cohort of individuals that are thoroughly studied with rich individual difference information in many aspects related to aging. An exploration of heterogeneity and the development of subgroups in this well-characterized sample will be beneficial for further examinations where other characteristics between groups can be compared (e.g., functional differences in Chapter 3).

2.1.4. Advantages of using structural equation modeling for mixture modeling

As already alluded to, mixture modeling can be conveniently integrated into structural equation modeling (Muthén, 2001; Muthén & Muthén, 2000). Structural equation modeling can directly model longitudinal change with all available information and, different from traditional approaches relying on repeated analyses, does not require all measures to be repeatedly administrated across different waves in the longitudinal tests. Particularly, structural equation modeling estimates *latent* scores, as opposed to *observable* scores, which represent variables that are not directly observed but inferred from available information. It can also account for invariance across time and reliability of the tests (T. D. Little, 2013). A recent study specifically compared latent scores and a composite of observable scores that both estimated longitudinal cognitive change in older adults, and found that latent modeling is better at providing accurate inferences of change estimates with lower type-I error rates, and that latent variables are especially necessary when lower-performing individuals had more missing values (Proust-Lima et al., 2019). Therefore, the current study adopts the latent change score model to estimate cognitive performance and change in all cognitive domains.

Another advantage of using structural equation modeling in longitudinal studies is that drop-out individuals can be included and help to generate more precise estimates of longitudinal change. A common issue in observational longitudinal studies is that people who drop out of the study may be different from those who stay to participate (Lindenberger, Singer, & Baltes, 2002; Schaie, Labouvie, & Barrett, 1973). Often, the drop-out participants are the low-performing individuals at baseline (Salthouse, 2014a) who may be at a higher risk for rapid cognitive decline. Conventional longitudinal analyses based on repeated comparison only allow for the

inclusion of remaining longitudinal individuals with complete data. This limits the interpretation of study findings, however, because the longitudinal participants may not be representative of the recruited sample, and the change score may be underestimated using such an elite sample. Structural equation model as a whole, and latent mixture modeling in particular, on the other hand, can use full information maximum likelihood estimation (R. J. Little & Rubin, 2019), which is a statistical method of estimating the parameters. It uses all available information – even the limited information from drop-outs -- to estimate a model that would most likely produce the estimates from the sample data that are analyzed. This method allows for the estimation to take into account the performance of drop-out individuals. When some cases (e.g., drop-out individuals) have missing values at a follow-up wave, the model factors the likelihood function so that it is computed separately for those cases (e.g., drop-out individuals) and those with complete data on both waves (e.g., remaining individuals). These two likelihoods are maximized together to eventually find the most precise estimates. This method of estimating the most precise parameters does not include an imputation of generated data. In most cases, structural equation modeling with maximum likelihood estimation is preferred to estimate the longitudinal change in a sample like DLBS with possible selective attrition (Newman, 2003). Therefore, in the first study in this chapter, I will implement mixture modeling using structural equation modeling (i.e., latent mixture modeling). Specifically, I will estimate participants' cognitive performance and change using latent change score model (McArdle, 2009) with maximum likelihood function, and then classify participants based on the heterogeneity in their latent scores of cognitive performance and change in all four domains (Muthén, 2001; Ram & Grimm, 2009).

2.1.5. Cognitive aging in middle-aged adults

Finally, aging is a continuous process throughout the lifespan, beginning in early to middle adulthood (Hartshorne & Germine, 2015; Salthouse, 2009). Many recent studies have suggested that the slope of cognitive change is nonlinear and varies across the lifespan. For example, cross-sectional studies suggest that different cognitive abilities peak at different ages (Hartshorne & Germine, 2015) and may follow different developmental trajectories (for a meta-analysis, see (Verhaeghen & Salthouse, 1997)). Longitudinal studies have also shown that older adults exhibited the largest decline (Hedden & Gabrieli, 2004; Schaie, 1994; Singer, Verhaeghen, Ghisletta, Lindenberger, & Baltes, 2003), compared to middle-aged individuals, even after adjustment for practice effects (Ronnlund et al., 2005). Therefore, the operational definition of optimal cognitive aging may be different at different ages (Garfein & Herzog, 1995; Salthouse, 2010b; Zelinski & Burnight, 1997). Optimally, studies should include participants across a wide age range and compare possible differences across the lifespan in cognitive aging profiles in middle-aged, younger older adults, and very old adults.

But few studies have studied a sample including middle-age adults regarding their longitudinal changes in different cognitive constructs (e.g., (Baltes & Lindenberger, 1997; Tucker-Drob, 2011; Zelinski, Gilewski, & Schaie, 1993)), and even fewer have examined their individual variability in cognitive aging. One study (Gunstad et al., 2006) used a cross-sectional design and also adopted a data-driven approach that classified middle-aged and old individuals based on their cognitive performance in multiple domains. They identified three clusters of cognitive performance profiles in both middle-aged and older groups and thus suggested that heterogeneity in age-related cognitive may begin to manifest in middle adulthood. However, this

study only investigated the cross-sectional performance level, and could not provide direct inferences for cognitive aging. The current study will use the two waves of longitudinal cognitive data from the Dallas Lifespan Brain Study and explore the differences and consistencies in identified cognitive aging profiles in middle-aged, young-old and very old adults (e.g., number of classes identified; distribution of class; contributing cognitive domain).

2.1.6. Summary

In Study 1 of this chapter, I will use a longitudinal design to examine cognitive changes over four years in four cognitive domains including episodic memory, inductive reasoning, working memory, and speed of processing. A data-driven latent mixture modeling will explore subgroups of individuals in middle-aged (35-54 years old at baseline), young-old (55-69 years old at baseline) and very old (70-89 years old at baseline) groups, based on their cognitive performance and change scores in all four domains. Due to the exploratory nature of the analyses, the prediction of results is tentative and made based on the similarity and differences between the current study and previous literature. Previous studies using mixture modeling in cognitive aging literature have detected two to five groups with different longitudinal change patterns (Mella et al., 2018; Olaya et al., 2017; Pietrzak et al., 2015). The DLBS data are different from other longitudinal datasets in a way that it has a relatively short period of testing interval (4 years) and includes a healthy sample. These factors may contribute to reduced variability in the data that leads to a smaller number of groups compared to other studies. I, therefore, hypothesize that the latent mixture modeling will reveal no more than three groups of individuals showing different longitudinal change pattern in this study: a group of *prime* agers who appear to have superior performance with cognitive maintenance, a group of *average* agers

who represent the general population with some performance variability across domains, and a group of *nonprime* agers who may present suboptimal profiles with lower performance and greater decline in most cognitive domains.

2.2. Methods

2.2.1. Participants

The study included all participants from the Dallas Lifespan Brain Study, aged from 20 to 89 years old at baseline. A total of 464 participants were initially tested. Four years later, 337 came back for the second wave (72.63% of the initial sample; 84.25% of those who could be contacted). Among the 127 drop-out participants, 18 were deceased, 46 could not be contacted, 29 were too busy, 33 withdrew from the study, and 1 was involved in a clinical trial.

All participants were recruited locally from the community and were right-handed with normal or corrected to normal vision. Participants were screened for neurological and psychiatric disorders, loss of consciousness for more than ten minutes, a history of drug or alcohol abuse, and a history of major heart surgery or chemotherapy within five years. This study was approved by The University of Texas Southwestern and The University of Texas at Dallas institutional review boards. All participants provided written informed consent and were debriefed according to human investigations committee guidelines.

2.2.2. Cognitive measures

Four cognitive domains were measured in the DLBS cognitive battery. The cognitive indicators used in the study are shown in Table 1. Specifically, to measure the speed of processing, participants completed Digit Comparison (Salthouse & Babcock, 1991) and Digit Symbol Substitution Test (Wechsler, 1997) in wave 1, and an additional measure from the NIH

Toolbox (NIHTB) Pattern Comparison (Casaletto et al., 2015) in wave 2. Working memory was measured by CANTAB Spatial Working Memory (Robbins et al., 1994), CANTAB Spatial Recognition Memory (Robbins et al., 1994), CANTAB Delayed Match to Sample (Robbins et al., 1994), Operation Span (Turner & Engle, 1989), and Letter Number Sequencing (Wechsler, 1997) in wave 1, and measured by CANTAB Spatial Working Memory (Robbins et al., 1994), Letter Number Sequencing (Wechsler, 1997) and the NIHTB List Sorting Task (Casaletto et al., 2015) in wave 2. Reasoning was measured by Raven's Progressive Matrices (Raven, Raven, & Court, 1998), ETS Letter Sets (Ekstrom, French, Harman, & Dermen, 1976), and CANTAB Stockings of Cambridge (Robbins et al., 1994) in both waves. Episodic memory was measured by CANTAB Verbal Recognition Memory (Robbins et al., 1994) with immediate free-recall and delayed recognition, and Hopkins Verbal Learning Test with immediate free-recall, delayed free-recall, and delayed recognition (Brandt, 1991) in wave 1. All these memory measures were also included in wave 2. Woodcock-Johnson III Memory for Names immediate and delayed recognition (Woodcock & Johnson, 1989) was added in the middle of wave 1 testing, and a subset of participants (N=158) had these measures in wave 1. An examination of missing values in longitudinal participants reveals missingness not completely at random (Little's MCAR: χ^2 =1174.08, p<.001). To address this issue, imputation was first conducted for the missingness in the longitudinal participants (about 4% of total data) (Rubin, 2004) and maximum likelihood estimation was used to precisely estimate latent factors for the whole sample (R. J. Little & Rubin, 2019). This procedure provides adequate information for full information maximum likelihood estimation while avoiding possible convergence failure (Enders & Bandalos, 2001; Newman, 2003).

Table 1. Cognitive measures used in the current study. Tasks/indicators in bold are included in both waves. Abbreviations are in parentheses.

Cognitive Domain	Wave 1	Wave 2
Processing Speed	**Digit Comparison (DC1)**	**Digit Comparison (DC2)**
	Digit Symbol Substitution Test (DS)	**Digit Symbol Substitution Test (DS2)**
		NIHTB Pattern Comparison (NIHPS2)
Reasoning	**Raven's Progressive Matrices (RAV1)**	**Raven's Progressive Matrices (RAV2)**
	ETS Letter Sets (ETSLS1)	**ETS Letter Sets (ETSLS2)**
	CANTAB Stockings of Cambridge (SOC1)	**CANTAB Stockings of Cambridge (SOC2)**
Working Memory	**Letter Number Sequencing (LNS1)**	**Letter Number Sequencing (LNS2)**
	CANTAB Spatial Working Memory (SWM1)	**CANTAB Spatial Working Memory (SWM2)**
	CANTAB Spatial Recognition Memory (SRM1)	NIHTB List Sorting Task (NIHLS2)
	CANTAB Delayed Match to Sample (DMS1)	
	Operation Span (OSPAN1)	
Episodic Memory	**Hopkins Immediate Free-recall (HOPF1)**	**Hopkins Immediate Free-recall (HOPF2)**
	Hopkins Delayed Free-recall (HOPDF1)	**Hopkins Delayed Free-recall (HOPDF2)**
	Hopkins Delayed Recognition (HOPDR1)	**Hopkins Delayed Recognition (HOPDR2)**
	WJIII Memory for Names Immediate (WJIM1)	**WJIII Memory for Names Immediate (WJIM2)**
	WJIII Memory for Names Delayed (WJD1)	**WJIII Memory for Names Delayed (WJD2)**
	CANTAB Verbal Recognition Memory	**CANTAB Verbal Recognition Memory**
	Immediate Free-recall (VRM1)	**Immediate Free-recall (VRM2)**

2.2.3. Data analysis

2.2.3.1. Estimate performance and longitudinal change for each cognitive domain

A latent change score model was used to estimate the longitudinal cognitive change in the sample. Figure 4 illustrates a simplified version of a latent change score model (McArdle, 2009; Raykov, 1992). The measurement (bottom) portion of the model specified for a given cognitive domain, Y, measured by multiple indicators (e.g., Ya, Yb, and Yc) on two occasions (Y1 and Y2). Each indicator was specified to load on the occasion-specific domain factor with a loading. Loadings of the same measure at different times set to equal. Cross-time residual autocorrelations were allowed for each indicator from a repeated task (Y1a and Y2a), but not depicted in diagrams for simplicity. In addition, when measures were from the same task (e.g., Immediate Free-recall and Delayed Free-recall in Hopkins Verbal Learning Test), I also

specified them to be correlated at each time point. Then, in the change score (top) portion of the model, a key latent factor, latent change score (Y Change), is constructed to represent the unexplained change in Y_2, which is allowed to be correlated with Y_1.

The current study modeled four cognitive domains (episodic memory, inductive reasoning, working memory, and speed of processing) simultaneously. The latent change score model was constructed and explored using Mplus Version 7.4 (Muthén & Muthén, 2012-2015). Maximum log-likelihood estimation was used, and goodness of model fit was examined based on comparative fit index (CFI), Tucker-Lewis Index (TLI), and root-mean-square error of approximation (RMSEA). A value greater than 0.9 for the CFI and TLI indicates a reasonable fit, as does an RMSEA less than 0.08. Given the sample size in this study, the complexity of the longitudinal model tested, and the sensitivity of chi-square test to sample size, it is recommended to not focus on the chi-square test but more on CFI, TLI, and RMSEA (Kline, 2015).

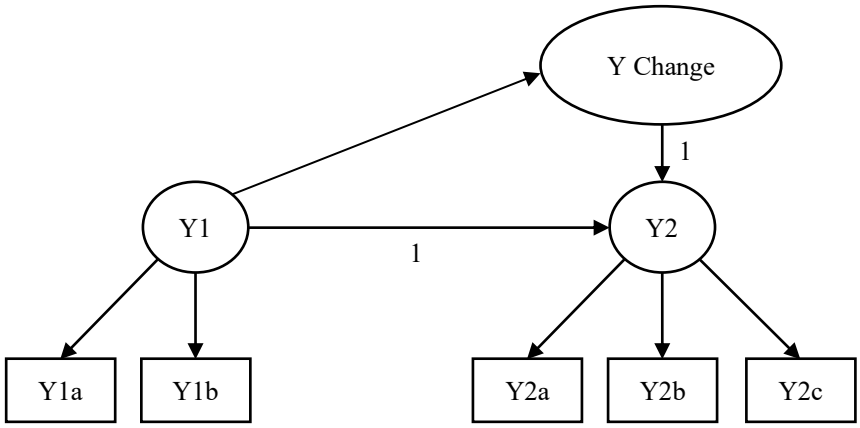

Figure 4. Latent change score model of cognitive domain Y.

2.2.3.2. Identify different cognitive aging profiles

Latent mixture models (Muthén, 2001; Muthén & Muthén, 2000) were used to examine the differential patterns of cognitive aging based on the estimates of cognitive performance and change in four cognitive domains. Individuals who completed both wave 1 and wave 2 were

included for the classification so I would not over-interpret the classification for drop-out individuals who did not provide any information regarding their aging trajectories and were no longer in this study. Latent mixture modeling was conducted for three age groups separately (middle-aged: 35-54 years old; young-old: 55-69 years old; very old: 70-89 years old) so the classification would not be primarily driven by age-related differences, which does not contribute to our understanding of unobserved heterogeneity in the sample. Adults below 35 years old were not included in this classification because these healthy young individuals are not expected to show "cognitive aging" over a relatively short period of four years.

Latent mixture modeling explored a *class* solution to explain the heterogeneity in cognitive performance and change patterns in all four cognitive domains. If the data suggested a subgroup showing a distinct pattern from the rest of the group, those individuals would be associated with a higher probability of belonging to a class that represents their cognitive aging profile. The final model with the optimal number of subgroups was iteratively determined based on suggested procedures for implementing mixture modeling analysis in Ram and Grimm (Ram & Grimm, 2009). Specifically, I looked for parameter estimates that were are out of bounds (e.g., negative variances), checked entropy, compared information criteria (e.g., Bayesian Information Criteria, Akaike Information Criteria), inspected likelihood ratio test results (e.g., Lo-Mendell-Rubin adjusted test), examined the number of members in the smallest class to avoid data over-extraction (Berlin, Williams, & Parra, 2014), and finally ensured that the selected model can provide empirical justification and interpretation for the data.

Post-hoc visualization of group patterns of cognitive aging profile determined the class labels (e.g., *prime*, *average*, *nonprime*). Finally, I compared the longitudinal change in four

domains between different classes to understand which cognitive domain played an important role in separating the individuals.

2.3. Results

2.3.1. Demographic and attrition information

Table 2 shows the demographic information of participants separated by age groups. Attrition analysis revealed no significant difference in age and sex, but drop-out participants were less educated. Moreover, participants who dropped out had significantly or marginally significantly lower performance in most cognitive measures, compared to those who continued to participate (Table 3). This further supports the *a priori* decision that drop-out participants should be included to avoid an underestimate of longitudinal change, and that maximum likelihood estimation should be used for more precise estimates.

Table 2. Demographic information of participants in different age groups.

	Young (reference) N=73	Middle-aged N=106	Young-old N=138	Very old N=147	*p*
Retention rate	0.64	0.75	0.77	0.71	.262
Baseline age range	20-34	35-54	55-70	70-90	<.001
Follow-up age range	25-38	40-59	59-74	74-93	<.001
Female (N)	46	61	91	89	.581
MMSE	28.73	28.67	28.51	27.91	<.001

2.3.2. Longitudinal estimates of cognitive performance and change

Before the latent change score model is specified, the construct reliability of all cognitive domains was first examined based on the Cronbach's α of each domain for each wave. All four domains had high internal reliability (processing speed: standardized Cronbach's α is .865 for

Table 3. Attrition analysis compares baseline characteristics in drop-out and remaining participants (see Table 1 for definitions of task abbreviation).

	Drop-out (N=127)		Stay (N=337)		
	Mean	SD	Mean	SD	*p*
Baseline age	57.66	20.05	58.55	17.38	0.638
Female (N)	71		216		0.105
Education	15.42	2.32	15.90	2.29	0.047
Blood Pressure (sys)	127.72	17.62	125.65	17.43	0.228
Blood Pressure (dia)	80.17	9.62	80.68	9.70	0.595
MMSE	28.33	1.23	28.42	1.24	0.487
DC	59.89	14.26	62.56	14.47	0.057
DS	51.89	13.89	54.65	13.67	0.041
RAV	0.74	0.17	0.81	0.14	<.001
ETSLS	14.83	6.31	16.95	6.32	0.001
SOC	7.91	2	8.49	1.93	0.002
LNS	10.24	2.68	11.08	3.14	0.003
SWM	34.19	22.27	31.39	22.06	0.194
SRM	16.1	2.61	16.81	2.06	0.003
DMS	34.48	3.5	34.69	3.58	0.548
OSPAN	12.41	7.17	14.46	7.98	0.005
HOPF	6.66	1.82	6.97	1.98	0.095
HOPDF	4.58	2.5	5.43	2.63	0.001
HOPDR	19.89	2.5	20.49	2.31	0.013
WJIM	49.71	11.77	51.97	10.81	0.123
WJD	18.03	8.74	20.68	8.92	0.023
VRM	6.73	1.89	7.12	1.97	0.037

wave 1 and .869 for wave 2; working memory: standardized Cronbach's α is .784 for wave 1 and .810 for wave 2; inductive reasoning: standardized Cronbach's α is .865 for wave 1 and .869

for wave 2; episodic memory: standardized Cronbach's α is .826 for wave 1 and .885 for wave 2). The latent change score model estimated four domains simultaneously. Figure 5 presents the specified multivariate latent change score model. Overall, this model was an excellent fit to the data, $\chi^2(417) = 899.826$, $p<0.001$, CFI=0.949, TLI= 0.943, RMSEA=0.050, 90% CI=[.045, .054], suggesting a good quality of cognitive constructs specified using this model.

Based on the estimates from the above model, Figure 6 depicts the longitudinal cognitive change in each cognitive domain using spaghetti plots. Each line in the graph represents one individual in the study. The starting point is the estimated wave 1 performance for that domain, and the ending point is the estimated wave 2 performance. The direction of the line represents the trajectory of the longitudinal change pattern. Lines are coded based on the retention status of the individual: black solid lines represent participants who continued to participate, and gray dashed lines represent participants who dropped out of the study. Visualization of the two types of participants also confirmed the finding that drop-out participants were more often to be low performing individuals at baseline. Across four cognitive domains, despite the visually overwhelming age-effects on cross-sectional and longitudinal differences, there is great individual variability that permits further investigation of possible heterogeneity using the latent mixture model.

2.3.3. Latent mixture modeling identified two different cognitive aging profiles

Latent mixture models were fit to classify individuals based on latent baseline and latent change scores, separately in middle-aged, young-old, and very-old adults. Explored models ranged from 1-class to 3-class solutions for all groups. Table 4 presents the model fit indices for the three models. For all three groups, the 2-class model was the best fit based on the

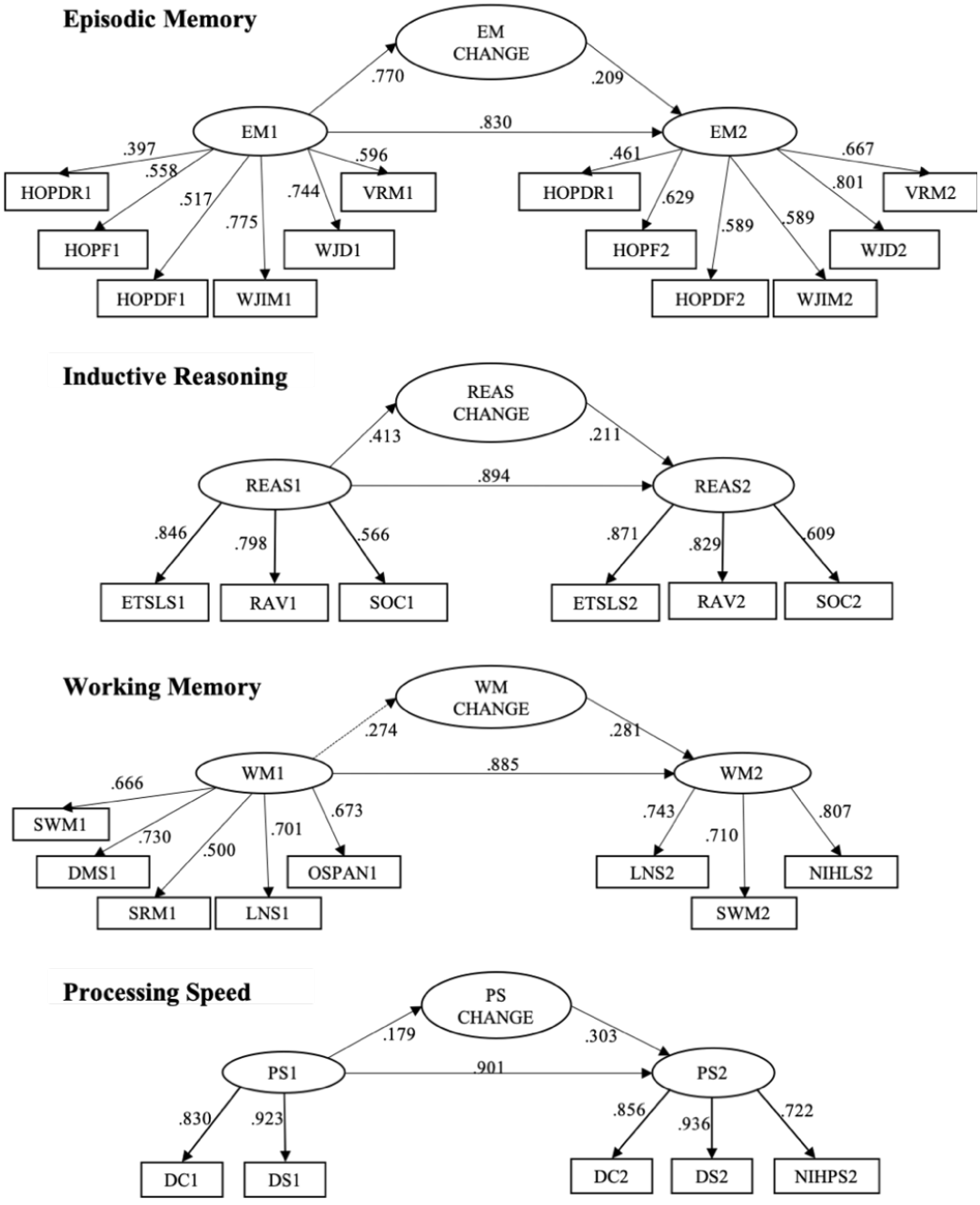

Figure 5. Latent change score model estimates cross-sectional performance and longitudinal change in four cognitive domains. All coefficients are standardized using the variance of the observed, outcome, and latent variables. In the measurement portion of the model (bottom), the coefficients between time 1 or time 2 latent factor and indicators represent the loadings of the variables to the construct. In the latent structural model (top), the path from time 1 factor to change factor was estimated while fixing the two paths to time 2 factor to be 1 (see Figure 4). Overall, this model was an excellent fit to the data, CFI=0.949, TLI= 0.943, RMSEA=0.050, 90% CI=[.045, .054], suggesting a good quality of constructs specified using this model.

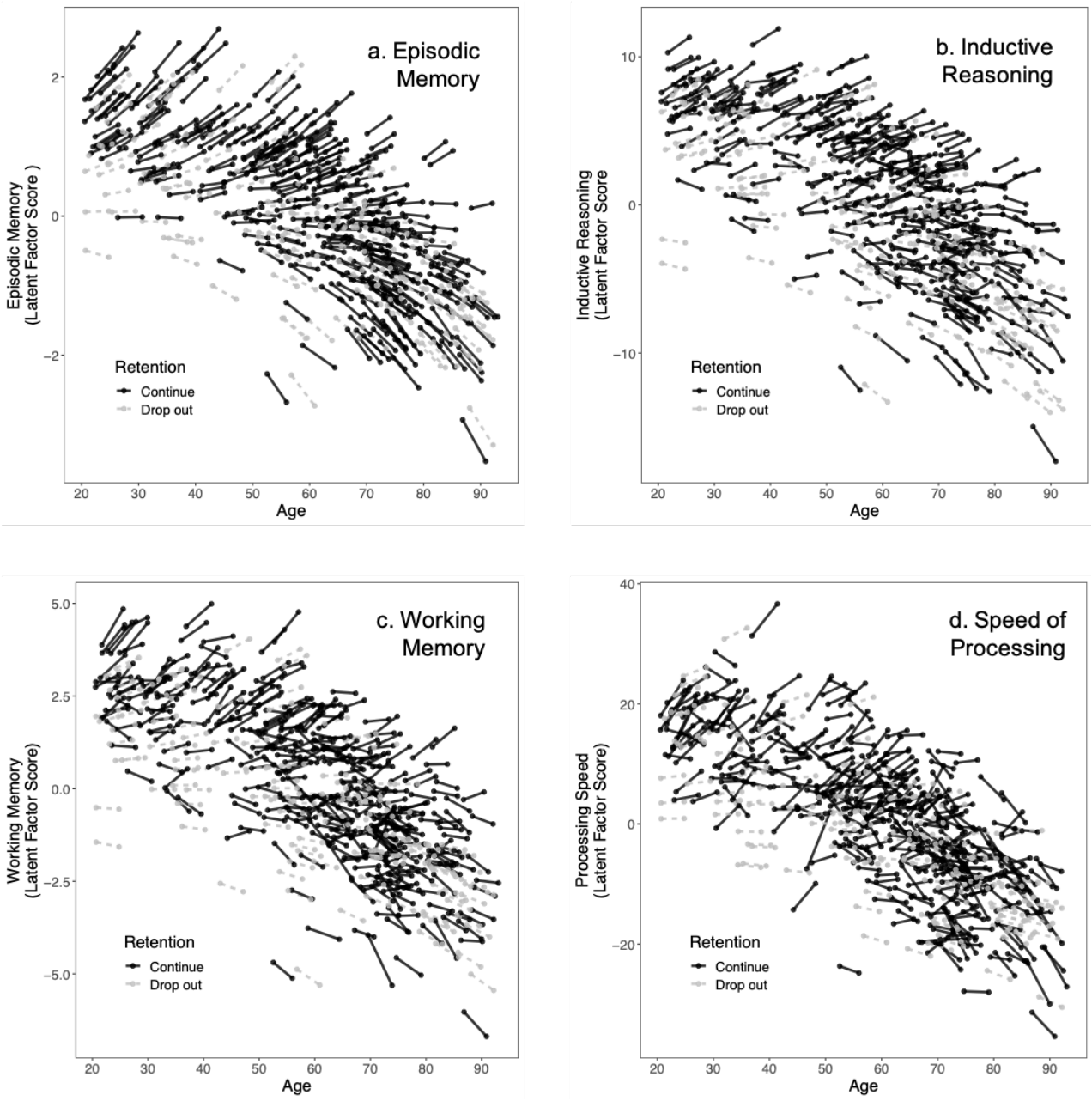

Figure 6. Spaghetti plot of longitudinal cognitive change over four years. The latent change score model uses the *fixed marker* approach so the unit of the specified latent variables is the same as the *marker* indicator. The *marker* indicator for each cognitive domain used is listed as follow: Episodic memory -- Hopkins Verbal Learning (Immediate Free Recall); Inductive reasoning -- ETS Letter Sets; Processing speed -- Digit Comparison; Working memory -- Letter Number Sequencing.

Table 4. Latent mixture model fit indices in three age groups. Two-class solution (in bold) was chosen for all three groups.

		One Class	**Two Classes**	Three Classes
Middle-aged (N=79)	Log-likelihood	-956.78	**-845.73**	-786.28
	BIC	1983.47	**1800.71**	1721.12
	Entropy		**0.90**	0.95
	BLRT (Lo-Mendell-Rubin) *p*		**0.57**	0.04
	Number of smallest class		**25**	1
Young-old (N=105)		One Class	**Two Classes**	Three Classes
	Log-likelihood	-1292.32	**-1105.02**	-1017.77
	BIC	2659.10	**2326.38**	2193.78
	Entropy		**0.93**	0.96
	BLRT (Lo-Mendell-Rubin) *p*		**0.04**	0.06
	Number of smallest class		**41**	11
Very old (N=105)		One Class	**Two Classes**	Three Classes
	Log-likelihood	-1731.01	**-1139.34**	-1068.14
	BIC	34541.87	**2395.02**	2294.51
	Entropy		**0.93**	0.96
	BLRT (Lo-Mendell-Rubin) *p*		**0.05**	0.32
	Number of smallest class		**51**	23

recommended procedure in Ram & Grimm (2009), confirming the existence of subgroups representing differential cognitive aging profiles in our sample across all age groups. Note that middle-aged data fit the 2-classification nicely (entropy = .90) but yielded a non-significant Bootstrapped likelihood ratio test (BLRT) indexed by Lo-Mendell-Rubin *p*-value ($p = .57$), which may suggest that both single and 2-class solutions could be appropriate for the data. In fact, the 3-class solution had a significant BLRT ($p = .04$) suggesting the data did show evidence of heterogeneity. However, one of the three classes had only one participant, which invalidated this solution (Berlin et al., 2014). Therefore, the final model was iteratively determined as the 2-class model. Figure 7 shows the distribution of the number of participants in each class for the

three groups. Specifically, in middle-aged adults, one class had 25 participants and the other had 54. In young-old adults, one had 41 participants, and the other had 64. In very-old adults, one class had 51 participants, the other had 54. The distribution of class was not statistically different among the three groups ($\chi^2 = 5.43$, $p = .066$), with a trend that the majority of younger groups (middle-aged, young-old) tended to be classified as class 1.

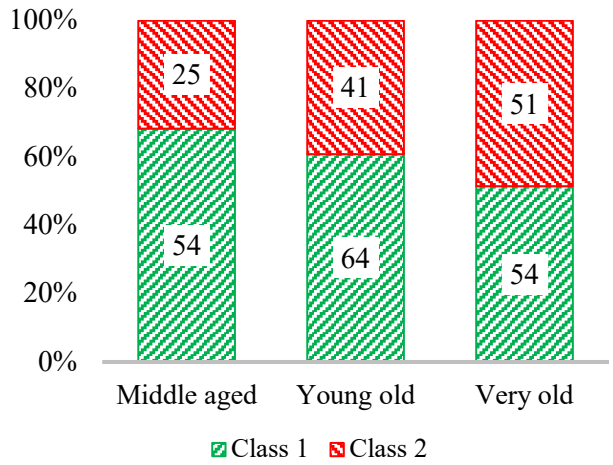

Figure 7. Distribution of class 1 and class 2 individuals in middle-aged, young-old and very old groups. The number represents the number of participants in each class for middle-aged, young-old and very old groups based on results from the latent mixture modeling.

I predicted in the introduction that one of the identified cognitive aging profiles may represent *prime* individuals who have superior and preserved cognitive function compared to their peers. To understand what patterns of cognitive aging each class represents (*prime* vs *nonprime*), I again used the spaghetti plot (as in Figure 6) to depict individuals using different colors representing the two classes. Figure 8 presents the cognitive performance for the two classes in four domains. Each line in the plot presents an individual in a young reference group

(blue), class 1 (green), or class 2 (red). Age groups are also depicted with different shades and shapes: young referenced with blue circles, middle-aged with squares, young-old with triangles,

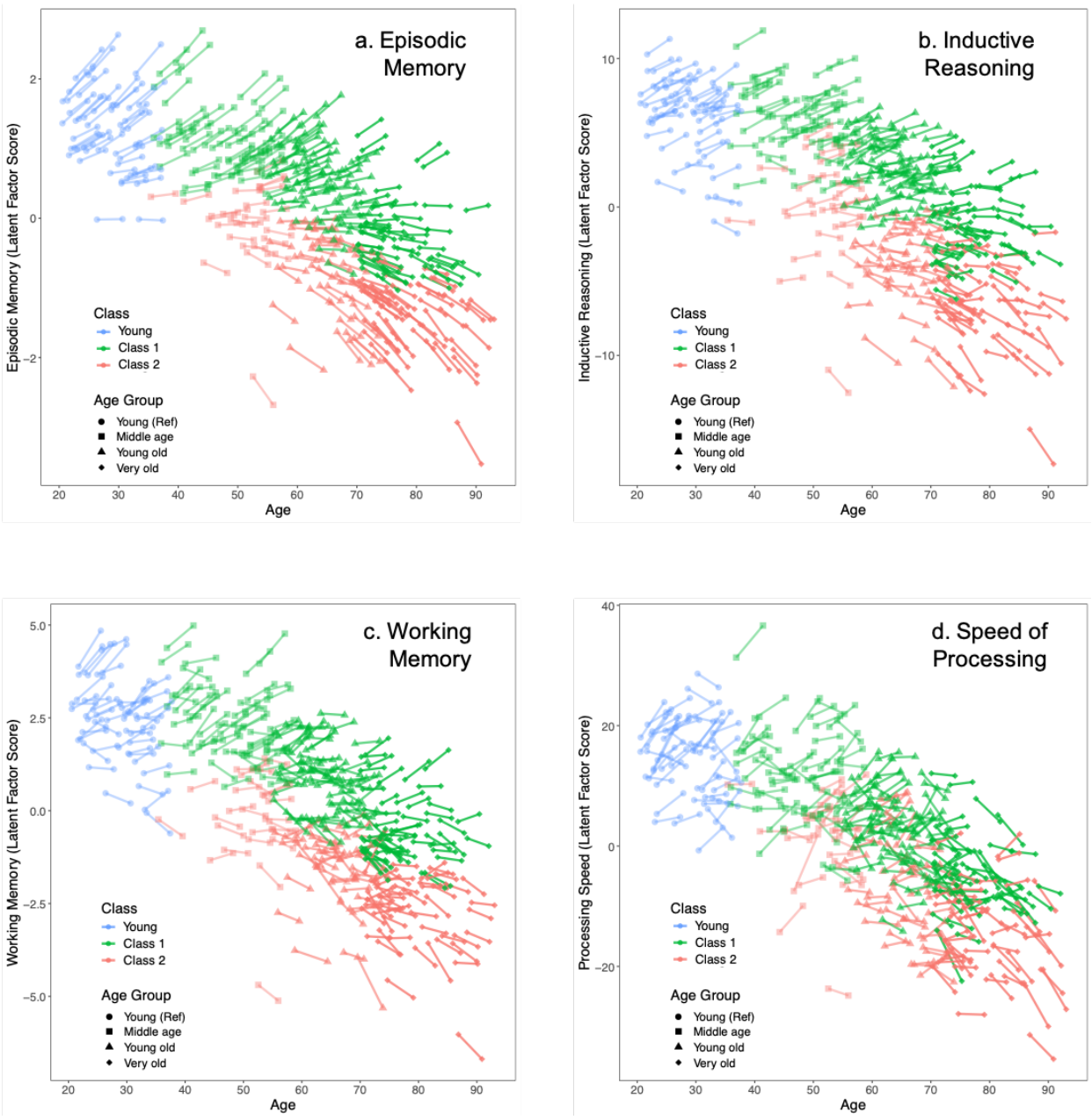

Figure 8. Spaghetti plot of longitudinal cognitive change over four years in two classes of individuals with visually distinct patterns of cognitive aging profiles. Age groups are depicted with different symbols.

and very old with diamonds. A surprisingly clear separation of the two classes suggests that most individuals in class 1 seem to have superior performance and better cognitive maintenance, compared to class 2 individuals. This observation is overall consistent in middle age, young-old and very old group. I hypothesized three groups may emerge and tentatively termed them as "*prime*", "*average*", and "*nonprime*" agers. The results showed a clear separation of two groups. Class 1 individuals who have superior cognitive aging profiles are labeled as "*prime*" agers. Class 2 individuals are termed as "*nonprime*" agers.

Finally, I illustrated the cognitive aging profiles of the identified classes (Figure 9). The group means of longitudinal change, as standardized z-scores, for all four domains were depicted together for visualization of differential longitudinal change profiles in class 1 and class 2. In middle-aged adults, class 1 had better change scores in all domains, especially in episodic memory, inductive reasoning, and working memory, which particularly separated them form the class 2 individuals. In young-old adults, class 1 also had high change scores in episodic memory and reasoning. Their superior pattern of longitudinal change was comparable to, if not better than, the class 2 of the middle-aged group. Lastly, both classes in very old age showed low longitudinal scores in all domains, suggesting the inevitable worsening cognition in advanced age across all domains. Particularly, class 2 of the very old age group had a substantially worse profile of low change scores in memory and reasoning.

2.3.4. Comparison of cognitive change in four cognitive domains between classes in three age groups

In addition to the characterization of the two cognitive aging profiles in three age groups separately, in post hoc exploration, I compared the mean longitudinal change in the four

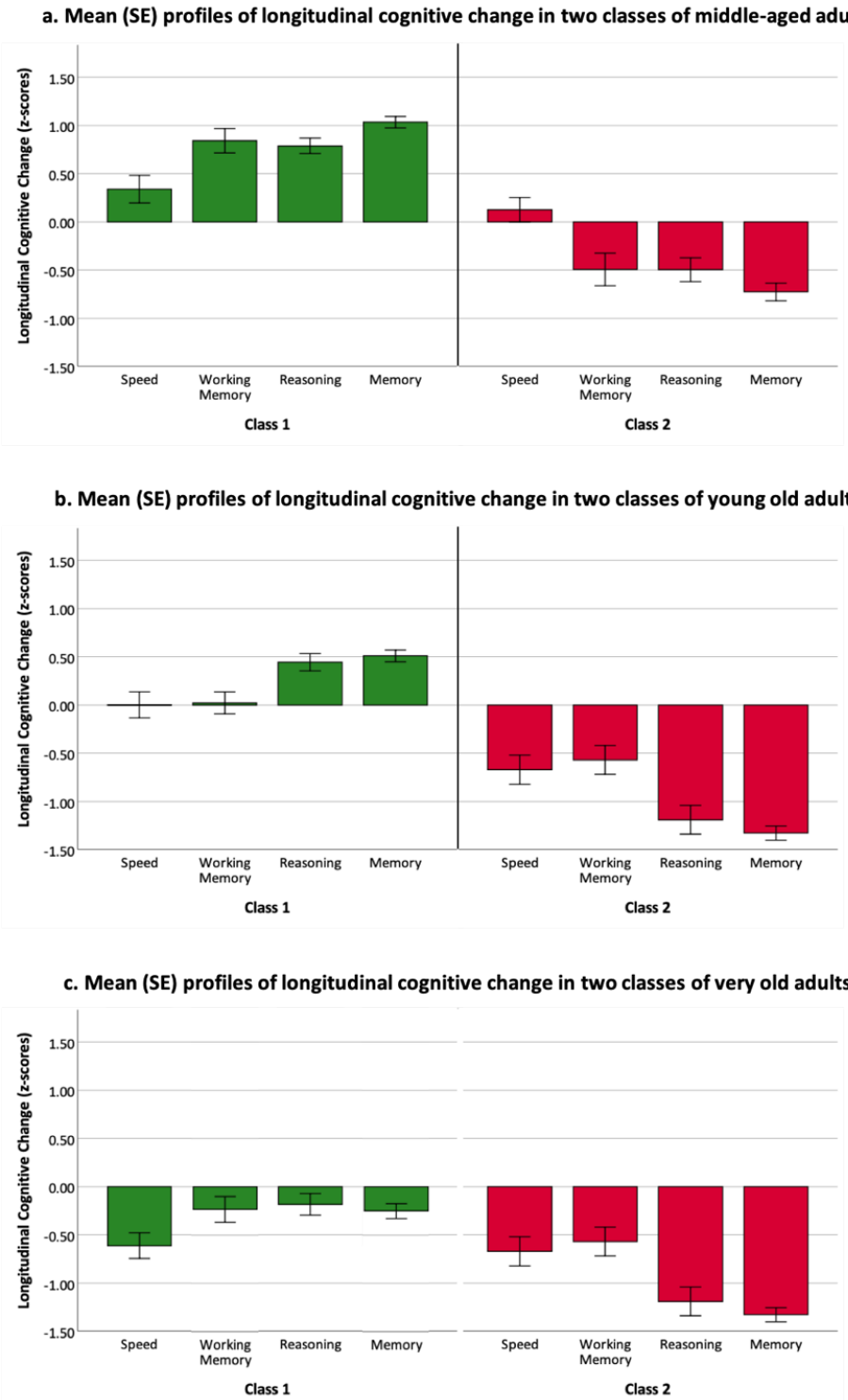

Figure 9. Cognitive aging profiles of class 1 (*prime* agers, green) and class 2 (*nonprime* agers, red) in middle age (a), young-old age (b), and very old age (c).

cognitive domains between the two classes of individuals in each age group (Figure 10). This analysis examined what cognitive domains have indeed contributed to the holistic classification. The results suggested that episodic memory and inductive reasoning showed significant differences in longitudinal change between class 1 (*prime* agers) and class 2 (*nonprime* agers) in

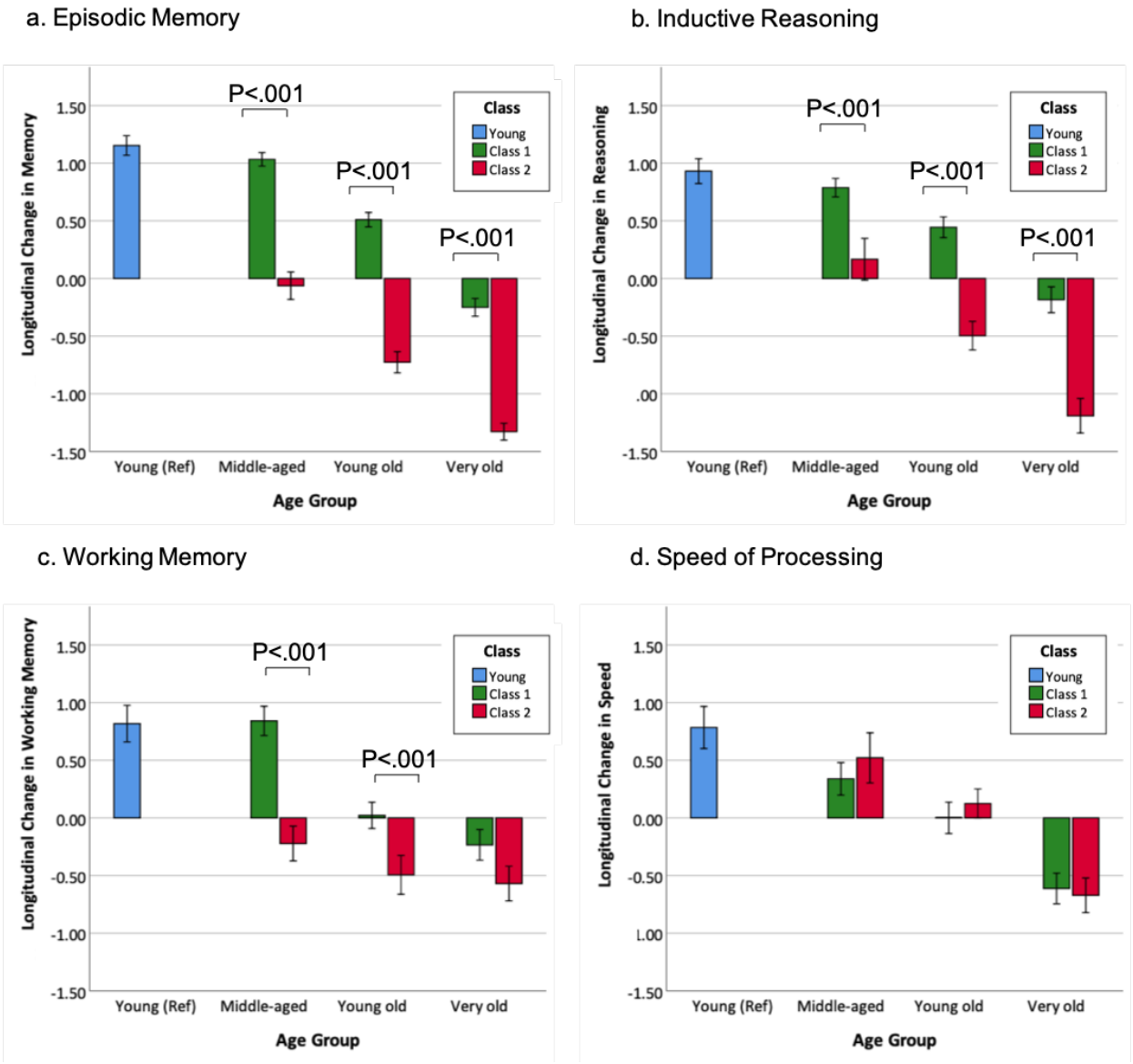

Figure 10. Longitudinal cognitive change (z-score) over four years in two classes of individuals. Mean change in the young group presented as a reference.

all three groups (episodic memory: middle age, t=-9.307, p<.001; young-old, t=-11.59, p<.001; very old, t=10.167, p<.001; inductive reasoning: middle age: t=-3.143, p=.003, young-old: t=-6.296, p<.001, very old: t=-5.410, p<.001), suggesting their predominant role in the holistic classification of *prime* versus *nonprime* agers across the adult lifespan. The differences between the two classes in the two domains also seem to reflect the high practice effect in *prime* agers who benefit more from the repeated exposure of the same tasks used. Working memory presented a diminishing effect in separating *prime* and *nonprime* agers from significant differences between classes in middle age (t=-5.002, p<.001) and young-old (t=-2.627, p=.010) adults, to nonsignificant difference in very old adults (t=-1.676, p=.097). Speed of processing, on the other hand, did not show any significant change difference between classes for any age group (p's>.47).

2.4. Discussion

2.4.1. Potential of using mixture modeling to identify subgroups in aging populations

The purpose of this study is to use a data-driven approach to classify individuals with different cognitive aging profiles. Two classes were identified based on four different cognitive domains (episodic memory, inductive reasoning, working memory, and processing speed), representing *prime* agers, defined as individuals who had superior cognitive performance and better cognitive preservation relative to their peers, and *nonprime* agers in the current study.

Identifying individuals showing optimal aging has been well recognized as one of the challenges in the field. Previous studies have often identified *prime* individuals (also referred to as successful agers (Driscoll et al., 2008), super-agers (Rogalski et al., 2013), etc. in other studies) using a traditional approach where either cut-off scores or the number of participants

needs to be predefined. Those approaches are also based on one cognitive domain or a single measure, which cannot capture the complex picture of cognitive aging (Gunstad et al., 2006). The current study implemented latent mixture modeling on a wide range of cognitive measures and successfully isolated individuals, offering some demonstration of this viable approach for the development of a person-oriented, holistic identification of *prime* individuals with optimal aging. As illustrated in this study, this approach is data-driven and does not require a specific operational definition of the subgroups before exploring the data. Thus, it may be very useful when the definition of subgroups is unknown or controversial, which is a common challenge in aging and some clinical population.

Future studies may continue exploring this approach in different samples with different cognitive measures, particularly in studies where the purpose is to identify a subgroup of diverging participants. The current study only included cognitively normal individuals. Presumably, in samples with larger variance (e.g., where clinical groups may also be present), latent mixture modeling is more powerful in detecting systematic differences underlying subgroups and can offer unbiased insights into the data.

2.4.2. Longitudinal changes in episodic memory and inductive reasoning, but not speed, as primary contributors in separating cognitive aging profiles

Episodic memory showed significant differences in longitudinal change between *prime* individuals with optimal cognitive aging and *nonprime* agers through the lifespan, confirming the validity of using the stability of episodic memory as a marker of overall cognitive status in many studies (Nyberg & Pudas, 2018). Inductive reasoning also had similar effects, where *prime* agers in all three groups had better longitudinal change scores than *nonprime* agers. Both

cognitive domains require complex mental processes and may be particularly sensitive in revealing individual differences in cognitive aging trajectories.

On the other hand, changes in speed of processing were not different between *prime* and *nonprime* agers. This is likely because speed of processing is one of the most vulnerable cognitive domains affected by aging: an early meta-analysis on cross-sectional studies suggested that speed drops approximately 20% by age 40 (Salthouse, 1982), suggesting an inevitable performance decrease starting early in lifespan. The majority of individuals experienced the inevitable decline in speed, which limits its variability and its ability to separate participants, even in middle-aged adults.

Moreover, tests of processing speed often require less strategy and rely on maximum processing capacity, and thus may be less affected by practice effects. In fact, practice effects could be one of the contributors to the superior trajectory of *prime* agers for episodic memory and inductive reasoning in middle-aged and young-old groups (Figure 8) (Salthouse, 2010b), given that same measures were used for these two domains. Therefore, speed of processing may be precisely revealing the expected age-related cognitive decline, whereas domains of episodic memory and inductive reasoning may also capture cognitive resilience in some individuals who can benefit more from practice effects.

Additionally, the difference in working memory change between *prime* and *nonprime* individuals seemed to be diminishing in advanced age, revealed by the finding that the significant difference in middle-aged and young-old groups became nonsignificant in the very old group. This may reflect a consistent decrease in working memory in very old age across individuals (Salthouse, 1994), possibly due to diminished frontal function with aging (Hedden &

Gabrieli, 2004; Nyberg et al., 2010). Like speed, the inter-individual variability in working memory change may also be limited in advanced age. In addition, speed and working memory have both been suggested underlying age-related worsening in many other cognitive domains (Salthouse, 1994, 1996a). Our study suggests that it may be less informative about individual differences in cognitive aging than other higher-order domains (e.g., reasoning, memory) that are more reflective of the functioning and mentality of the individual overall.

2.4.3. Limitations

One limitation of the study is that it is exploratory, and thus findings are mostly descriptive. Inferences from the results are limited. However, as not many studies have used this approach to examine the patterns in cognitive aging, this is one of the first efforts to use a longitudinal design to examine differential cognitive aging patterns in middle-aged, young-old and very old adults. In fact, this approach has revealed interesting cognitive aging profiles, and can also be further explored to understand how different profiles may be related to other individual difference variables.

Although tempting to consider the classified individuals as "successful" versus "unsuccessful" agers, it is important to note that all participants were functioning independently, and the two classes may be indistinguishable in everyday settings. Also, the classification is based on latent scores which only reflect how they performed relative to others. Therefore, I refrain from defining these individuals as "successful/unsuccessful" agers, which may limit the interpretation of what being a class 1 (or class 2) member means.

In the present study, the baseline performance and longitudinal change were not independent. Although this is expected as high-performing individuals often present better

cognitive stability (Tuokko, Garrett, McDowell, Silverberg, & Kristjansson, 2003), it is hard to disentangle the sources that protect one from showing cognitive decline. For example, a high-performing individual may exhibit little longitudinal cognitive change simply because he/she is good at the task and thus able to master the particular task better at the second time, despite age-related cognitive decline. This should be acknowledged in the present study where longitudinal change score was allowed to correlate with baseline performance for more precise estimates in the latent change score model. But in studies focusing on isolating the individual difference in longitudinal change beyond cross-sectional performance, researchers may consider using the baseline performance as covariates to control for its effect.

Finally, the present study only included two waves of longitudinal testing. It is vulnerable to common issues in longitudinal designs such as regression toward the mean, inability to test nonlinear change, and practice effects. Indeed, we observed better performance at time 2 in middle-aged and young-old groups, particularly for episodic memory and inductive reasoning. Thus, it is possible that *prime* agers showed a better aging trajectory because they benefited more from practice effects (rather than due to their resistance to age-related decline). Although it would still reflect interesting inter-individual differences, the interpretation of *prime* and *nonprime* agers would be different. Nevertheless, the present study adopted latent change score model that is specifically designed for two waves of longitudinal testing. It overcomes some flaws of two-wave longitudinal data by using latent constructs. Ideally, three or more waves of data will allow for examinations of nonlinear trajectory, as well as change estimates after the second time point, since practice effects are most pronounced in the early phase of repetitive testing (Bartels, Wegrzyn, Wiedl, Ackermann, & Ehrenreich, 2010). As the DLBS project is

currently collecting wave 3 data, future studies may use the same technique and examine whether an additional pattern of cognitive aging may emerge with a longer interval and more reliable estimates.

CHAPTER 3

BRAIN ACTIVITY DIFFERENCES BETWEEN PRIME AND NONPRIME INDIVIDUALS

3.1. Introduction

Many individual difference factors may be related to disparate trajectories in cognitive aging, and the research progress on identifying these factors has been accumulating. Studies have examined demographic, psychosocial, genetic, and neurological features related to different cognitive trajectories in aging (Rogalski et al., 2018; Yaffe et al., 2009). For example, carriers of APOE e4 have been found to show greater cognitive decline (Albrecht et al., 2015). Neuroanatomical features, such as thicker anterior cingulate and less hippocampal atrophy, are also linked to better cognitive performance in older adults (Gefen et al., 2015; Gorbach et al., 2017; Harrison et al., 2012; Raz, Gunning-Dixon, Head, Dupuis, & Acker, 1998; Rogalski et al., 2013; Salthouse, 2011). White matter hyperintensities and worse network integrity are also linked to worse cognitive aging (Persson et al., 2005; Wang et al., 2017). The neocortical deposition of AD biomarker (e.g., amyloid and tau) are also related to cognitive deficits and accelerated age-related decline in memory (amyloid: (Farrell et al., 2017; Hedden, Oh, Younger, & Patel, 2013); tau: (Maass et al., 2018; Sperling et al., 2019)). One key question remaining open is whether *prime*[1] and *nonprime* individuals have differential patterns of functional brain activity.

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[1] As defined in Study 1, *prime* agers refer to individuals who have superior performance and better longitudinal change scores relative to their peers. Operationally, *prime* and *nonprime* individuals were classified in Study 1, using a data-driven, holistic approach (latent mixture modeling) based on cognitive performance and change scores in four cognitive domains (episodic memory, inductive reasoning, working memory and speed of processing).

3.1.1. Baseline fMRI activity predicting longitudinal cognitive change

Some studies attempted to understand the role of brain activity in cognitive aging by using baseline fMRI activity to predict cognitive change, but the directionality of the findings has been inconsistent (Bookheimer et al., 2000; Hantke et al., 2013; Leal, Landau, Bell, & Jagust, 2017; Lind et al., 2006; Woodard et al., 2010). Bookheimer et al. (2000) found individuals with APOE e4 allele had greater memory-related activation in multiple regions and that this pattern of greater brain activation was predictive of memory decline in the next 2 years. Similarly, Leal et al. (2017) found that higher hippocampal activation was related to greater amyloid accumulation that was predictive of greater clinical decline. Both suggest that higher baseline activity may be related to an adverse longitudinal change in cognition.

On the other hand, Lind et al. (2006) studied 18 normal older participants with APOE e4 allele and found that reduced functional activity during encoding in the left inferior parietal region was related to longitudinal cognitive decline, suggesting that insufficient functional activity, rather than higher activity, may be predictive of worse cognitive outcome in older adults. Hantke et al. (2013) using two memory tasks (semantic memory, episodic memory) found that greater functional activation was predictive of better longitudinal cognitive stability for both memory tasks. Woodard et al. (2010) using a semantic memory task also found that higher fMRI activity during the task was predictive of less cognitive decline longitudinally and that the magnitude of task activation was a stronger predictor than hippocampal volumes.

Functional MRI may be a promising tool to detect early abnormalities in the brain and relate to longitudinal cognitive change (Sperling, 2011; Wagner, 2000), but baseline neural activity can only offer limited information of the brain before age-related changes in cognition

occur. A thorough exploration of functional brain activity related to better cognitive aging should examine brain functional activation in people who have already shown evidence of better or worse cognitive aging.

3.1.2. FMRI activity differences in individuals with different cognitive trajectories

Some previous studies related retrospective longitudinal change to functional activity differences to examine patterns of functional activation features in people exhibiting different longitudinal cognitive trajectories. For example, Persson et al. (Persson et al., 2005) used a semantic categorization task and found that the individuals who had lower baseline performance and greater memory decline over ten years had higher activity in the right prefrontal regions during semantic processing. In addition, they also found smaller hippocampal volumes and decreased anterior white matter integrity in these declining older adults. Overall, the study suggested evidence of increased functional activation in declining older adults, which may reflect structural disruptions and functional upregulations in frontal regions.

However, Pudas and colleagues (Pudas et al., 2013) using a face-name associative learning task and found that older adults who managed to maintain their memory ability across 15-20 years (referred to as successful older adults in the study) had higher hippocampal activity, compared to both average older adults and young adults, during the encoding block. They also found the same pattern in four prefrontal clusters where successful older adults had the highest functional activity (Figure 11a). This finding suggests the importance of recognizing the individual differences in cognitive aging when examining brain function in older adults.

Two longitudinal fMRI studies attempted to examine how brain functional changes may correspond to cognitive changes. They compared brain activity in individuals with different

longitudinal cognitive trajectories and found longitudinal functional reduction in hippocampal activation (O'Brien et al., 2010) and increased PFC recruitment (Pudas et al., 2018) related to cognitive decline in declining older adults. Specifically, O'Brien and colleagues (2010) studied 51 non-demented older adults using a face-name associative memory encoding task. Researchers contrasted the activation during novel versus repeated trials, and found that older individuals with rapid longitudinal decline had higher hippocampal activation at baseline, but a greater loss of hippocampal activation over time, compared to those who maintained their cognition. A recent longitudinal fMRI study (Pudas et al., 2018) in older adults also used a face-name associative encoding task and analyzed the activation during encoding block. They reported that declining older adults recruited additional PFC regions over time as their memory worsened and their hippocampus shrank. Interestingly, this pattern of results was seemingly inconsistent with their finding in 2013 (Pudas et al., 2013) where it was the maintaining individuals with less cognitive decline who had higher frontal activity. The authors noted that the longitudinal findings were found in a set of prefrontal regions outside the memory network which were not activated in the task in wave 1 (Figure 11b). They, therefore, interpreted this follow-up finding as functional re-organization in those additional frontal regions which may represent a compensatory response in attempt to cope with age-related cognitive decline. However, whether this altered activation in frontal regions is indeed beneficial was not directly investigated in the study, and this question still remains highly controversial.

3.1.3. Brain maintenance and functional compensation in high-performing individuals with better cognitive aging

Several accounts have been proposed to help interpret the findings of the patterns of functional activity related to better cognitive aging (Morcom & Johnson, 2015; Nyberg et al., 2012; Nyberg & Pudas, 2018; D. C. Park & Reuter-Lorenz, 2009). Two major views, brain maintenance (Nyberg et al., 2012; Nyberg & Pudas, 2018) and compensation (Cabeza, 2002; Davis et al., 2008), interpret the brain activity related to optimal cognitive aging from different perspectives and have suggested different brain function patterns are expected in individuals with better cognitive aging (Morcom & Henson, 2018; Nyberg et al., 2010).

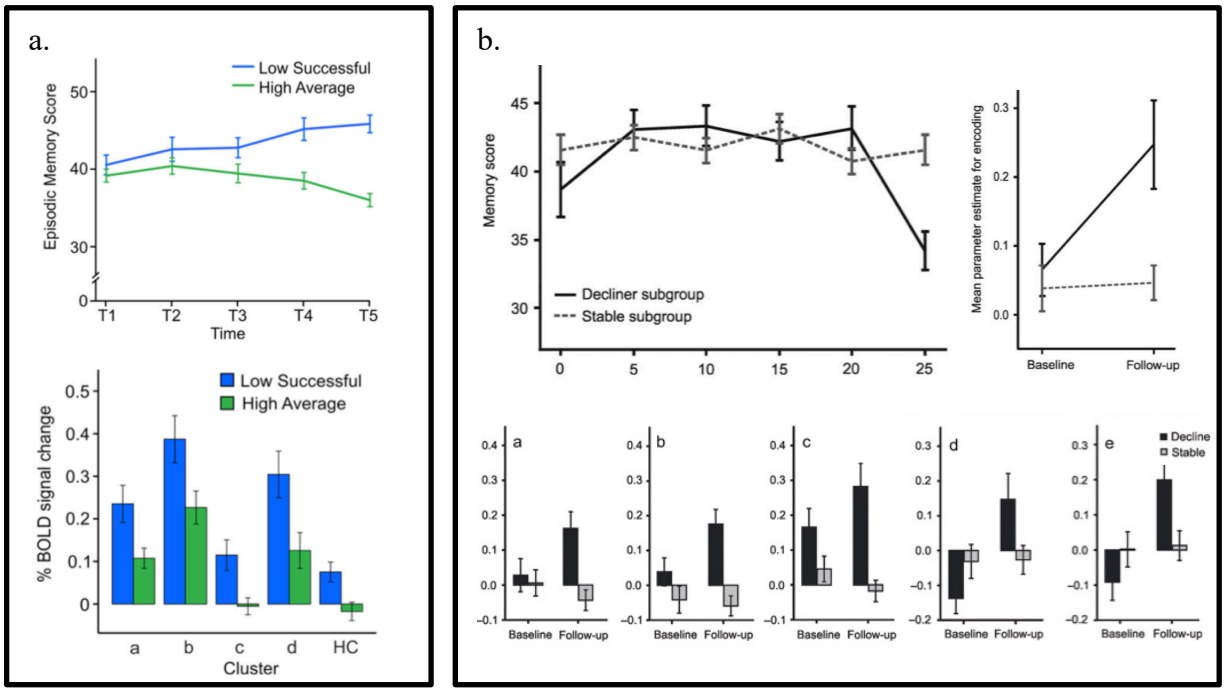

Figure 11. Better cognitive aging (less memory decline) was associated with evidence of increased (a) and decreased (Pudas et al., 2013) (b) prefrontal activity during encoding (Pudas et al., 2018).

3.1.3.1. Brain maintenance

The theory of brain maintenance suggests that cognitive performance difference is largely due to the between-subject variability in "brain maintenance", or the presentation of a lack of brain pathology. The theory suggests that "the individual differences in the manifestation of age-related brain changes and pathology allow some people to show little or no age-related cognitive decline" (Nyberg et al., 2012). Studies have shown that older adults tended to have reduced task-related activity in temporal and occipital regions, compared to younger adults (H. J. Li et al., 2015; Maillet & Rajah, 2014), and that this reduction was associated with age-related grey matter changes and white-matter hyperintensity (Nordahl et al., 2006). On the other hand, older adults also exhibited greater difficulty to suspend task-unrelated activity, compared to young adults (Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007). Moreover, high-performing older adults had comparable functional activation and deactivation as in younger adults (Duverne, Habibi, & Rugg, 2008; Nagel et al., 2009; Samu et al., 2017), supporting the idea that maintaining youth-like activation patterns may be a sign of optimal brain aging.

Stronger evidence comes from longitudinal studies. Persson et al. (Persson, Pudas, et al., 2011) found that the reduction in hippocampal activity was only found in individuals who had memory declines, but not in those whose memory was stable over 20 years. Nyberg et al. (Nyberg et al., 2010) found that older adults' brain function decreased longitudinally in frontal regions, suggesting that aging was associated with under-recruitment, not over-recruitment, of the frontal cortex, and questioned the findings of compensatory over-recruitment in high-performing older adults.

Another observation in older adults is reduced neural specificity or selectivity (Carp, Park, Polk, & Park, 2011; Dennis & Cabeza, 2011; Koen & Rugg, 2019; D. C. Park et al., 2004; J. Park, Carp, Hebrank, Park, & Polk, 2010; Voss et al., 2008). For example, an early study found that ventral visual cortex, which selectively responded to certain categories of visual stimuli (e.g., face, house, word) in young adults, showed reduced differences in activity when responding to different visual categories in older adults (D. C. Park et al., 2004). Recent studies suggest that reduced neural distinctiveness in older adults is also evidenced in MTL and striatum (Dennis & Cabeza, 2011) and in PFC (Morcom & Friston, 2012) for memory tasks, and that the greater regional distribution of brain activity in older adults, indicating reduced functional specificity, was associated with poorer memory performance (Morcom & Friston, 2012). The idea of reduced functional specificity may reflect the general broadening of responsive neurons, or it may be due to decreased activity of the category-sensitive neurons (J. Park et al., 2012). The former may be presented as a diffused increased in activity outside the task-related regions suggesting neural inefficiency. This increased activity reflects a general elevation of signals in response to multiple task conditions that do not typically involve these regions in young adults. And the latter may be presented as a decreased activity in task-related regions, suggesting reduced neural reactivity and responses. Both may be observed in the same task (Koen & Rugg, 2019; J. Park et al., 2012), and both are in agreement with the conceptual idea of brain maintenance that aging is accompanied by a series of brain changes, a lack of which may suggest better brain maintenance in successful aging.

3.1.3.2. Compensatory recruitment

In contrast, several cognitive neuroimaging theories of aging have proposed that there is age-related increase in functional brain activity in high-performing older adults that is compensatory for age-related degradation, emphasizing that such adaptive changes in brain function are favorable to better cognitive aging (Cabeza, 2002; Cabeza et al., 2018; Davis et al., 2008; Reuter-Lorenz et al., 1999). For example, the scaffolding theory of aging and cognition (STAC, (D. C. Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014)) suggests that brain is an adaptive system with neuroplasticity. Older adults are often affected by age-related neural degradation, including neural challenges (e.g., shrinkage, cortical thinning, white matter changes, etc.) and functional deterioration (e.g., decreased neural specificity, decreased functional recruitment, dysregulation of the default mode network). Critically, older adults may also exhibit "compensatory scaffolding" which represents the adaptive changes with age in brain function that may counteract the adverse effects of neural challenges and functional deterioration. For example, high-performing older adults may exhibit additional recruitment of novel prefrontal areas, which allows them to overcome atrophy to meet task demands (Cabeza, 2002). Moreover, studies have found decreased activation in posterior regions along with increased activation in frontal regions, and posited the theory that older adults may shift their functional reliance from posterior regions to anterior regions (Davis et al., 2008), which is believed to be one of the compensatory mechanisms underlying increased prefrontal activity. The STAC model integrates both the "negative" and the "positive" changes with age and suggests that functional compensation (only) occurs when brain integrity is reduced, proposing different and

complementary roles of brain maintenance and compensation in helping older adults to preserve cognitive function in aging.

Consistent with the compensatory view of age-related changes in functional activation, researchers have reported increased functional activity in cognitively normal individuals harboring early markers of AD and suggested that the activation was a compensatory response to the neural insults from pathology. For example, cognitively healthy older adults with elevated amyloid and tau burden (Elman et al., 2014; Huijbers et al., 2019; Mormino et al., 2012) or subjective memory complaints (Hayes et al., 2017; Rodda, Dannhauser, Cutinha, Shergill, & Walker, 2009) had increased hippocampal and/or prefrontal activity during encoding, compared to controls. This increased activity was beneficial for participant's memory performance. This pattern of increased activity was interpreted as a functional compensation in response to early deficits in these individuals helping them stay cognitively healthy and may diminish as AD progresses (Delli Pizzi, Punzi, Sensi, & Alzheimer's Disease Neuroimaging, 2019; Foster, Kennedy, Horn, Hoagey, & Rodrigue, 2018).

Altogether, the evidence of compensatory recruitment in older brains suggests that increased activity reflects brain adaption in relatively high-functioning older adults in response to inevitable age-related changes. Therefore, increased functional activation, particularly in prefrontal regions, may be a beneficial feature related to successful aging and help older adults to maintain cognitively better.

3.1.4. Factors to consider when examining functional activity related to cognitive aging

3.1.4.1. Age as a potential moderator of what activity pattern is expected

The majority of previous investigations on brain activation and successful aging of prime individuals have interpreted their findings based on one of the two aforementioned views (*brain maintenance*, *compensatory recruitment*). Although seemingly contrary to each other, they are not necessarily contradictory, and may operate concurrently to cope with age-related changes (Cabeza et al., 2018; D. C. Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014). *Prime* agers may indeed rely on better maintenance of youth-like activity pattern, while additional recruitment may also be compensatory in nature and helpful when their brain maintenance is reduced (Burianova, Lee, Grady, & Moscovitch, 2013; Duzel, Schutze, Yonelinas, & Heinze, 2011). Resisting age-related decline ideally relies on an intact brain with no neurodegeneration and thus no compensation, though this is less likely with increasing age. Middle-aged brains may be relatively well-preserved and rely on brain maintenance to perform well. Therefore, a youth-like pattern of brain function may be sufficient for *prime* agers in middle age. However, in older adults, age-related neurodegeneration may be so prevalent that additional recruitment is more beneficial than no recruitment. Even then, the compensation may still only be partially effective (Cabeza & Dennis, 2012). Successful cognitive aging in older age may require better adaption and re-organization by compensatory upregulating.

However, little is known about how functional activation may differ in *prime* and *nonprime* individuals across the lifespan, as only a few fMRI studies have included middle-aged adults (Ankudowich, Pasvanis, & Rajah, 2017; Ankudowich, Pasvanis, & Rajah, 2016; de Chastelaine, Mattson, Wang, Donley, & Rugg, 2015; Grady et al., 2006; Kennedy, Boylan,

Rieck, Foster, & Rodrigue, 2017; Kennedy et al., 2015; H. Park et al., 2013; Rieck, Rodrigue, Boylan, & Kennedy, 2017; Rieck et al., 2015; Vidal-Pineiro et al., 2018). Even fewer has investigated the specific functional activity related to successful encoding (de Chastelaine et al., 2015; de Chastelaine, Mattson, Wang, Donley, & Rugg, 2016; Kwon et al., 2015; H. Park et al., 2013; Vidal-Pineiro et al., 2018), a critical mental process of memory that is particularly vulnerable to aging.

For example, de Chastelaine et al. (de Chastelaine et al., 2015) used an associative memory task and found increased frontal recruitment during successful associative encoding in older adults, but not in the middle-aged, and that the increased recruitment was related to better memory performance in these older adults. This suggests that the additional frontal recruitment may not occur until later in the lifespan, and this recruitment may be compensatory for older adults. Similarly in a recent study (Vidal-Pineiro et al., 2018), researchers examined the activity related to subsequent associative memory success and found that middle-aged and high-performing old individuals showed similar brain activity as in young adults, whereas low-performing old adults showed reduced activation in frontal regions. On the other hand, Park et al (H. Park et al., 2013) studied a subset of participants from the Dallas Lifespan Brain study and found, for negative subsequent memory effect (i.e., forget > high-confidence remember), age-related decrease was particularly evident in low memory performers beginning in middle age, whereas high memory performers did not show these differences until old age, suggesting the importance of studying middle-aged adults in revealing different functional trajectories with age.

3.1.4.2. Different interpretations for different regions

The interpretations of functional results are also largely dependent on the region of findings. It is especially critical when inferring activity differences related to better outcomes of cognitive aging. Pudas and colleagues (2013) found that maintainers, who were defined as individuals with minimal longitudinal declines, had greater activity in prefrontal and hippocampal regions, compared to decliners. However, in their follow-up study (Pudas et al., 2018) with longitudinal fMRI data, they found the seemingly-opposite pattern: decliners had longitudinal functional increases in prefrontal activity, whereas the maintainers showed stability in activity magnitude with a similar level as observed in younger adults. This interesting inconsistency may be due to the difference in regions where the observation was detected. Although both effects were found in prefrontal regions, the recent study (Pudas et al., 2018) specifically noted that the findings were outside typical mnemonic regions. The regions activated in decliners in wave 2 also did not show significant activation in wave 1, suggesting that this region may be additionally recruited in decliners, in an attempt to compensate for their lower level of activity in task-related regions.

The role of a region during a task is essential to understand the meaning of any significant observation in task-related functional MRI. Analyzing task-related and task-unrelated regions separately is not only helpful but necessary for an appropriate interpretation of what the activity differences actually reflect.

3.1.4.3. Brain-behavioral correlation

In addition to the age of participants and the region of findings, the interpretation of functional differences in successful and unsuccessful aging is closely related to whether the

activity is beneficial for task performance. Increased functional activity in low-performing older adults may be interpreted as inefficient and detrimental neural over-recruitment because it was not observed in maintainers (J. Park et al., 2012). However, it is also possible that the increased activity is compensatory in nature: cognitively declining individuals are the ones in need of such compensation but the attempted compensation could not offset the age-related deficits (Cabeza & Dennis, 2012). Careful investigations should not only compare declining and maintaining individuals, but also examine how the activity is directly related to task performance. One way to help interpret the brain functional activity is to examine the relationship between activity magnitude and task performance. This examination is particularly critical for activations that are outside task-related regions because the function of the activation may be unclear. For example, recruitment outside task-related regions that is beneficial to task performance may suggest "compensatory upregulation". Additional recruitment outside task-related regions that is harmful to task performance, although not diagnostic, may suggest "decreased inhibition", "decreased neural efficiency", or "loss of neural specificity", reflecting age-related neural deficits.

But as pointed out in a recent review (Cabeza et al., 2018), the examination of brain-behavior correlation across participants often faces what is known as Simpson's paradox -- the relationship among subgroups may be different (Kievit, Frankenhuis, Waldorp, & Borsboom, 2013), and the examination of the brain-behavior correlation often ignores this potential problem. Researchers should consider the possibility that brain-behavioral relationship may be dependent on the behavior: low-performing individuals may show a positive brain-behavioral correlation attempting to utilize brain compensation, whereas the relationship may not be present or even opposite in high-performing individuals. Therefore, the present study will consider this

possibility and examine whether the brain-behavioral correlation differed in *prime* and *nonprime* individuals. If the evidence suggests a significant difference in the pattern of brain-behavioral correlations, the relationships should be interpreted separately (Cabeza et al., 2018).

Another way to separate brain activation that are truly helpful in task performance from those that are unrelated is using an event-related design that could separate trials with better performance and worse performance. One example of studying memory encoding is a subsequent memory paradigm (e.g.,(Gutchess et al., 2005)). In subsequent memory tasks, participants are presented with stimuli in the scanner and usually instructed to make a judgment related to some features of the stimulus so that they fully encode the stimulus. After they come out of the scanner, they complete a memory recognition test for the encoded stimuli. Researchers can then back trace participants' successful and unsuccessful encoding trials based on the accuracy of participants' responses. This bypasses Simpson's paradox and allows for separate analyses on successful encoding and unsuccessful encoding, and more importantly, on distinguishable brain activities only involved during successful encoding that indeed support better task performance.

3.1.5. Summary

The present study compares the functional activation between individuals exhibiting different cognitive aging profiles, defined in Study 1 in Chapter 2 as *prime* and *nonprime* individuals, in middle, young-old and very old age. *Prime* individuals refer to participants with superior cognitive performance and relatively less longitudinal decline over past four years in multiple cognitive domains (episodic memory, inductive reasoning, working memory, and processing speed). *Nonprime* individuals, on the other hand, overall present a suboptimal

cognitive aging pattern over past four years with worse performance and greater longitudinal decline across cognitive domains. In the present study, I compare functional brain activity in these *prime* and *nonprime* individuals in order to explore patterns of brain activation specifically related to better cognitive aging in middle, young-old and very old age. I use a subsequent memory task that separates successful encoding and forgotten trials. Functional imaging analyses will focus on the subsequent memory effect (high-confidence remembered > forgotten) which is the classic contrast of this paradigm representing the specific activation that distinguishes successful encoding from unsuccessful encoding. Additionally, the present study also explores the negative subsequent memory effect (forgotten > high-confidence remembered) as a secondary analysis, which contrast is less investigated but may show inter-individual differences between high and low performing individuals (H. Park et al., 2013). The study specifically examines three questions: (1) are there activity differences during successful encoding (subsequent memory effect) between *prime* and *nonprime* individuals in core regions related to successful memory encoding? (2) is the subsequent memory effect in *prime* and *nonprime* individuals different from healthy young adults? and (3) is there any additional recruitment outside core regions?

Successful encoding usually activates temporal regions in the memory network (hippocampus, fusiform gyrus) and occipital regions in tasks with visual stimuli (Eichenbaum, 2017; Gutchess et al., 2005; Kim, 2011) (Figure 12). In the present study, to examine the task-related effects, I focus on the regions common to participants, regardless of age, and compare the activity between *prime* and *nonprime* individuals in those regions for middle-aged, young-old and very old adults. To explore additional recruitment outside task-related regions, I explore

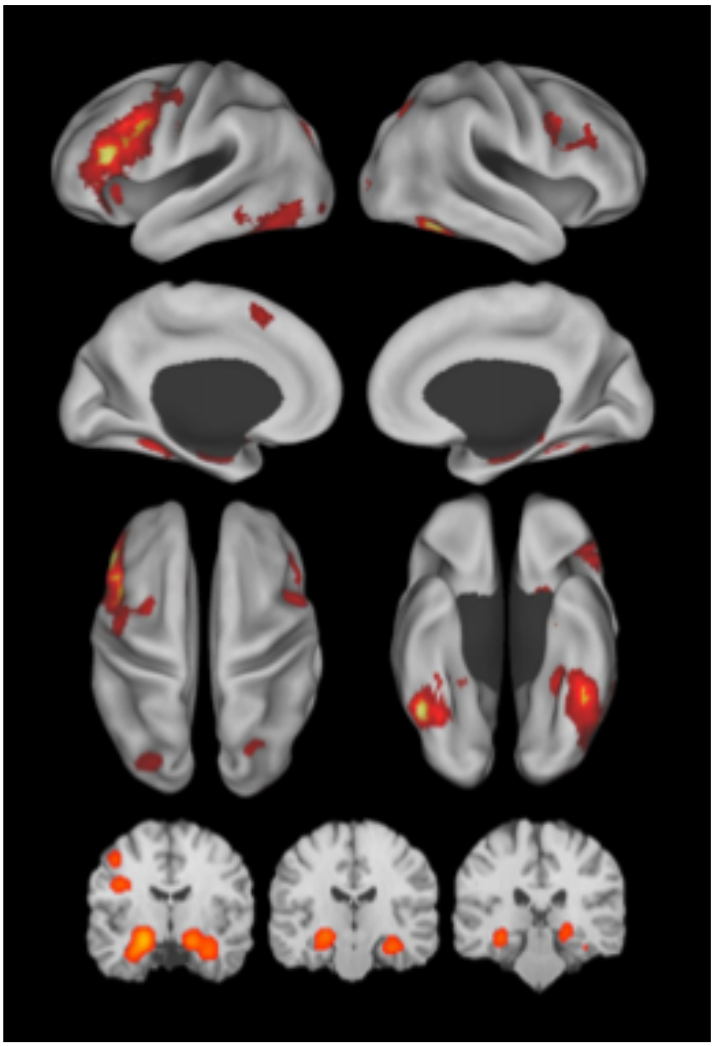

Figure 12. Regions found in (Kim, 2011) that are related to subsequent memory effect.

activity differences in the whole brain between *prime* and *nonprime* individuals in middle age, young-old age and very old age. Prefrontal regions may be a great source of compensation because it is involved with executive control and working memory (Yuan & Raz, 2014). This allows this region to be flexibly helpful with a wide variety of tasks. Older adults may also show decreased activation in the occipital and medial temporal lobe (fusiform gyrus, bilateral

parahippocampal gyri, hippocampal regions) (H. J. Li et al., 2015; Maillet & Rajah, 2014; Spreng, Wojtowicz, & Grady, 2010).

I hypothesize that *nonprime* individuals who have shown suboptimal changes in cognition over four years may present decreased subsequent memory effect in task-related regions, particularly in temporal regions, reflecting the importance of preserving youth-like patterns of brain activation in successful aging. There may be additional recruitment outside task-related regions in middle-aged and young-old *prime* individuals who have shown better cognitive aging profile, compared to *nonprime* and young adults. Greater recruitment outside task-related regions may be positively correlated with subsequent memory performance, suggesting its compensatory nature.

3.2. Methods

3.2.1. Participants

The fMRI data were collected during the second wave of DLBS data collection. These individuals also completed the same subsequent memory task during the first wave of data collection four years earlier with a different set of scene pictures. As introduced earlier, the purpose of the present study is to characterize functional activity features in people who have already shown evidence of different cognitive trajectories. Therefore, the present study using the classification from Study 1 in Chapter 2 specifically examines the functional activation at time 2. Initially, 464 participants were recruited at baseline in DLBS. Four years later, 337 participants came back for the second wave of DLBS testing. Among them, 297 DLBS participants completed the fMRI scan with the scene-encoding task. The three age groups in Study 1 in Chapter 2 also applied in Study 2 in this chapter. Among all participants, six did not have any

forgotten trials and were removed from analyses. One participant that had extremely low memory performance (high-confidence false alarm rate = 0.625; high-confidence hits rate = 0.302) was also removed. Table 5 shows the demographic information of participants.

Table 5. Age, sex and education information of participants.

	Young reference N=41	Middle-aged N=71	Young-old N=96	Very old N=82	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*p*
Mean Age (at MRI)	31.29 (4.29)	51.25 (5.74)	66.73 (4.50)	80.17 (5.49)	<.001
Sex (Female%)	70.7%	57.7%	65.5%	63.4%	.547
Education (yrs)	16.79 (2.04)	16.08 (2.22)	15.90 (2.15)	15.25 (2.47)	.004

3.2.2. MRI acquisition

Participants were scanned using a 3T Philips Achieva scanner with an 8-channel head coil. High-resolution anatomical images were collected with a T1-weighted magnetization-prepared rapid gradient-echo sequence with 160 sagittal slices, field of view (FOV) = 204 × 256 × 160 mm; voxel size: 1 × 1 × 1 mm^3; time to repetition: 8.1 milliseconds (ms); echo time: 3.7 milliseconds; flip-angle: 12°. Blood Oxygen Level Dependent (BOLD) fMRI data were acquired using a T2* weighted echo-planar imaging sequence with TR/TE/flip-angle=2000ms/25ms/80° and FOV = 220 x 220 mm^2. In each volume, 43 interleaved axial slices were acquired parallel to the AC-PC line covering the whole brain, voxel size 3.4 × 3.4 × 3.5

mm^3. Five additional volumes collected at the beginning of each run for T1 stabilization were discarded.

3.2.3. FMRI task

Participants viewed 96 pictures of outdoor scenes and responded if there was water in the scene by pressing yes/no button. Half of them contained water and half did not. Stimuli were presented using E-prime software (Psychology Software Tools, Pittsburgh, PA, USA). Each picture was presented for 3s in an event-related design with jittering range from 4 to 14 seconds (Figure 13a).

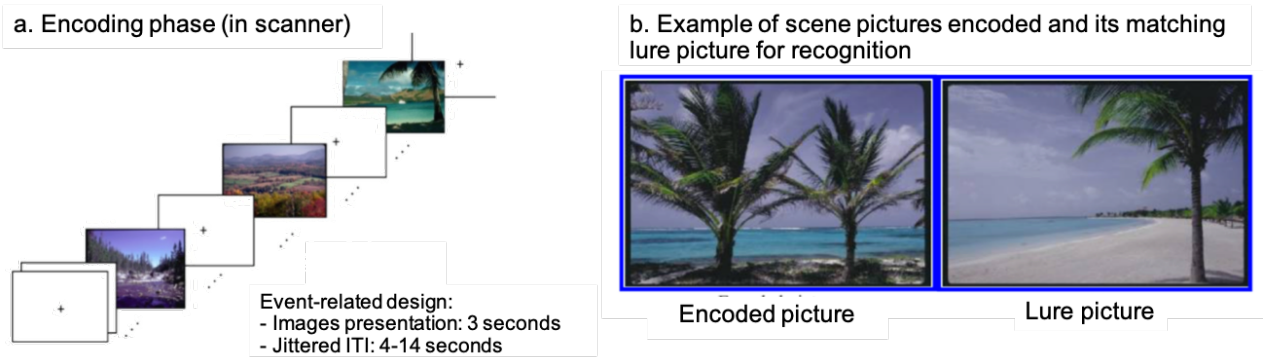

Figure 13. (a). Presentation of the scene pictures in the scanner during the encoding phase. (b). Example of encoded and matching lure pictures.

Approximately 20 minutes after the end of the presentation of the pictures, a recognition test was administered outside of the scanner. Participants were presented with a total of 192 pictures, 96 were target pictures that were presented in the scanner and 96 were lure pictures that were closely matched to the target pictures for similar content and composition (e.g., both the target and the corresponding lure consisted of ocean with palm trees; Figure 13b). Participants were instructed to indicate whether they remembered seeing the exact picture by making one of three judgments: 1. “high-confidence remember” indicating that the participant was confident the

same picture was presented; 2. “low-confidence remember” indicating that the participant remembered seeing the picture with low confidence; 3. “new item” indicating that the participant judged that it was a new picture not previously presented. This recognition task was self-paced with a maximum of 4s for each trial.

This subsequent memory task was also one collected in the baseline of DLBS so all participants have performed this task four years ago in wave 1. For this reason, we used a different set of pictures in wave 2 for all participants so that none of the scene pictures were presented before in either encoding or recognition in wave 1. This avoids possible memory for pictures from last wave while the task procedure was not unfamiliar to participants.

3.2.4. FMRI data processing

Statistical Parametric Mapping (SPM12, University College London, UK) was used for imaging processing and data analysis. For preprocessing, functional images were corrected for motion and realigned to the mean image across all the runs for each participant, which was then used for co-registering the anatomical scan. The anatomical scan was segmented to allow the estimation of deformation parameters for different tissues. Next, all functional images were co-registered to the MNI template via the anatomical image. Finally, spatial smoothing was implemented with a full-width-half-maximum (FWHM) kernel of 8mm. Artifact Detection Tools (ART) was used to detect outliers due to movement or signal intensity spikes (Mazaika, Whitfield, & Cooper, 2005). Time points of movement outliers were dummy coded in the first-level analysis and used to regress out the artifact. Runs that had more than 15% outlier volumes (~17 vol) due to intensity shift (>3% deviation from the mean in global intensity) or motion (>2mm motion displacement would be excluded. Participants with more than one run (out of

three) excluded would be removed from the analyses. None of the runs in any participants were removed based on this criterion.

At the individual level, a canonical hemodynamic response function was modeled by convolving the signal time course with the stimulus event. Eight nuisance regressors were included: six movement regressors, one artifact regressor, and the difference in the mean signal across runs. An autoregressive model, AR(1), was used to estimate and correct for the temporal autocorrelation. Additionally, the residual variance for each GLM was calculated for each individual. This measure reflects the remaining variance in the functional signal that is not attributable to the model and is the largest variance contributor (Friedman, Glover, & Fbirn, 2006; Suckling et al., 2008). It includes, in addition to random error, unexplained variance related to regional variability across the brain within individuals. Given the spatial heterogeneity of this measure, it is suggested to take additional efforts to account for its variability and use this piece of information in the second level statistics (Gonzalez-Castillo, Chen, Nichols, & Bandettini, 2017). Therefore, I calculated the regional residual variance for each ROI and included as an additional covariate in the supplementary analyses. The present study focused on a primary contrast of interest of subsequent memory effect (i.e., activity during high-confidence remembered greater than forgotten trials). A secondary negative subsequent memory effect (forgotten > high-confidence remembered) was also examined.

3.2.5. FMRI data analysis

3.2.5.1. Define task-related regions

Task-related regions were first defined. For subsequent memory effect and negative subsequent memory effect, two second-level general linear models (GLM) were created

separately in all participants with age as a covariate. The resulting images represent task-related regions underlying the specific processing (subsequent memory, negative subsequent memory) controlling for age. A voxel-wise correction with family-wise error (FWE) rate at $p < .05$ was used to define task-related ROI. The significant clusters were used as the masks for the task-related regional of interest (ROI) analyses.

3.2.5.2. Task-related ROI analysis

ROI analysis was performed in each of the task-related clusters. The mean activity estimate within each ROI was extracted. The analysis of covariance (ANCOVA) examined the effect of class (*prime*, *nonprime*), age (middle-aged, young-old, and very old), and their interaction while controlling for sex and education. Then, to compare the activity to young individuals in *prime* and *nonprime* individuals, two sets of ANCOVA was performed in *prime* and *nonprime* individuals separately that examined the specific difference between young and the other age group while controlling for sex and education.

3.2.5.3. Whole-brain analysis

In addition to ROI analysis, a whole-brain analysis explored if there were any activity differences between *prime* and *nonprime* individuals that may exist outside the core task-related regions. For any significant cluster that does not overlap with task-related ROI, the regional activity in *prime* and *nonprime* individuals was compared with young adults. Then, brain-behavioral correlations were performed to help interpret the meaning of the activity difference.

3.3. Results

3.3.1. Behavioral performance of subsequent memory task

Mean memory performance of each age is presented in Table 6. Participants overall performed similarly on the accuracy in recognizing the old pictures. There was only a trend of significance in the ability to distinguish new pictures: older adults less often correctly identified

Table 6. Behavioral performance of subsequent memory task in different age groups.

		Young reference N=41	Middle-aged N=71	Young-old N=96	Very old N=82	
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*p*
Old item	Hits	0.709 (0.154)	0.714 (0.146)	0.719 (0.136)	0.708 (0.145)	.954
	High confidence	0.410 (0.124)	0.502 (0.137)	0.546 (0.152)	0.523 (0.155)	<.001
	Low confidence	0.299 (0.024)	0.212 (0.121)	0.173 (0.123)	0.184 (0.121)	<.001
	Misses	0.289 (0.153)	0.282 (0.145)	0.276 (0.136)	0.275 (0.136)	.948
New item	Correct Rejection	0.473 (0.189)	0.501 (0.166)	0.491 (0.161)	0.441 (0.164)	.073
	False Alarm	0.525 (0.188)	0.492 (0.166)	0.494 (0.160)	0.549 (0.163)	.077
d': ZPr(HiC-hit) – ZPr(HiC-FA)		0.796 (0.465)	0.793 (0.428)	0.731 (0.330)	0.511 (0.310	<.001

new pictures as new (p = .073) but were more likely to falsely recognize new pictures as old (p = .077). To measure subsequent memory behavior, two indicators were used. First, to parallel the approach taken in the fMRI analyses, *d*' of high confidence trials was calculated from the z-transformed proportion of high-confidence remembered trials versus the proportion of high-confidence false alarms (H. Park et al., 2013). An analysis of variance (ANOVA) test showed significant differences in *d*' (ZPr(HiC-hit) – ZPr(HiC-FA)), which occurred because very old adults differed from the other three groups (p's <.05), despite equivalent performance in all other three age groups (p's >.1). Figure 14 presents the subsequent memory behavior, indexed by d' as

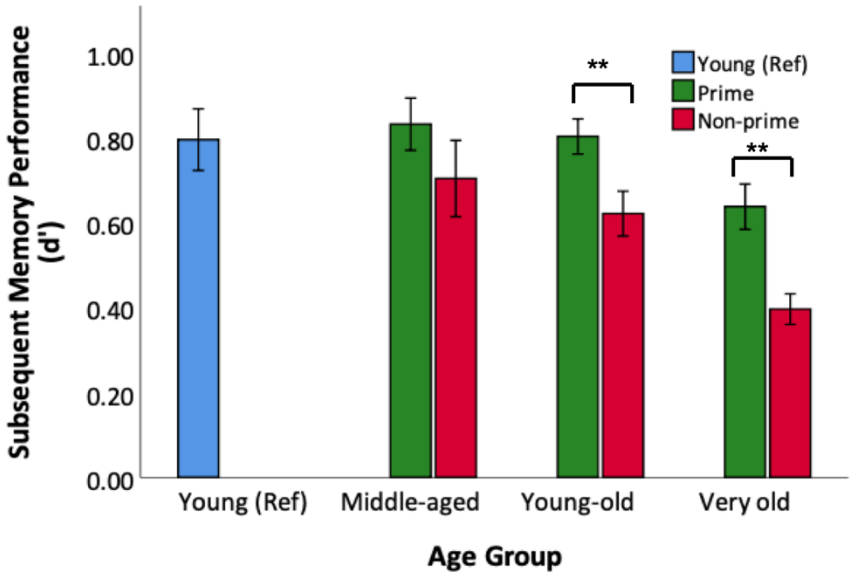

Figure 14. Subsequent memory performance in *prime* and *nonprime* agers in different age groups. ** p <.01.

a function of *prime* and *nonprime* agers in different age groups. The difference in memory performance was significant between *prime* and *nonprime* agers in both young-old and very old groups (p's < .05). In the secondary analyses where negative subsequent memory effect (subsequent forgetting effect) was examined, miss rate was also examined as an additional behavioral indicator of subsequent forgetting performance.

3.3.2. Brain activity differences of subsequent memory effect

3.3.2.1. Define task-related activity

In all participants, four regions related to subsequent memory were identified using the contrast of high-confidence remember greater than forget. Regions included the left and right fusiform/parahippocampal, and left and right lateral/mid occipital regions (Table 7; Figure 15).

3.3.2.2. Subsequent memory effect differences between *prime* vs *nonprime* individuals

To compare the subsequent memory effect between *prime* and *nonprime* individuals in

Table 7. Four subsequent memory effect regions.

Regions	Peak Coordinates (x y z)	*p* (FWE)	t	Cluster Size
Left fusiform/parahippocampal gyrus	-30 -40 -19	<.001	9.07	300
Right fusiform/parahippocampal gyrus	33 -34 -22	<.001	9.5	195
Left lateral/mid occipital cortex	-36 -88 20	<.001	6.11	81
Right lateral/mid occipital cortex	39 -82 14	<.001	6.72	92

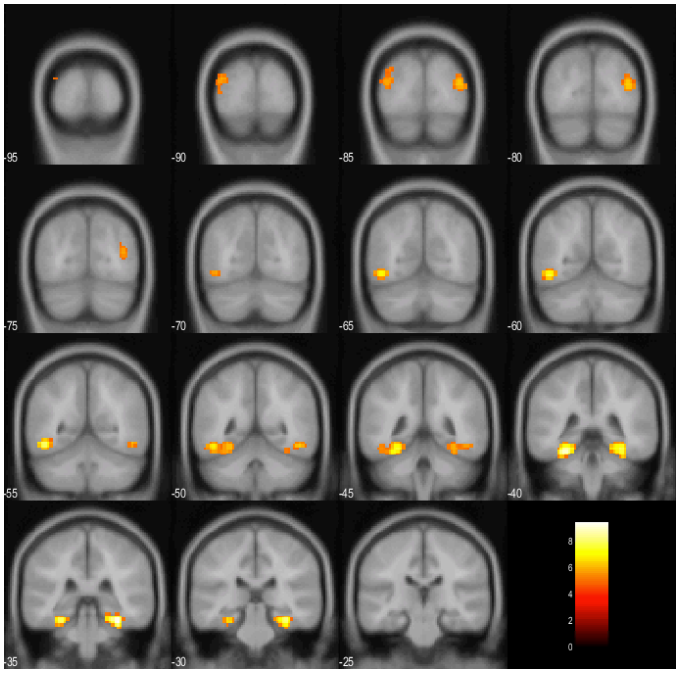

Figure 15. Brain regions showing significant subsequent memory effect (high-confidence remember > forget). Voxel-wise FWE corrected at $p < .05$.

middle-aged, young-old and very old adults, an ANCOVA was performed for each ROI to test the effects of age (middle-aged, young-old, very old), class (*prime*, *nonprime*), and their interaction while controlling for sex and education. Overall, *prime* individuals had higher subsequent memory effect, compared to *nonprime* individuals, and this difference in temporal

clusters was most evident in young-old adults (Figure 16). Specifically, left fusiform showed a significant main effect of *class* ($F(1, 241)= 7.073$, $p=.008$) where *prime* individuals had higher activation than *nonprime* individuals, and a significant age x class interaction ($F(2, 241)=5.026$, $p=.007$) such that the activation difference between *prime* versus *nonprime* individuals was most evident in young-old group. Right fusiform showed a similar but weaker pattern of results with a marginally significant interaction between age x class ($F(2, 241)=2.43$, $p=.09$) that *prime* individuals in young-old age had greater subsequent memory effect than *nonprime* individuals. Left lateral/middle occipital cluster showed a significant age effect ($F(2, 241)=4.585$, $p=.011$), revealing that older adults had reduced occipital effect, and a marginally significant class effect ($F(1, 241)=3.337$, $p=.069$) such that *prime* individuals overall had greater subsequent memory effect than *nonprime* individuals. There was no significant age x class interaction ($p=.511$). Lastly, right lateral/middle occipital cluster also showed a significant age effect ($F(2, 241)=4.74$, $p=.01$) with older groups showing decreased subsequent memory effect, and a significant class effect ($F(1, 241)=6.053$, $p=.015$) with *prime* individuals showing greater subsequent memory effect. There was no significant age x class interaction in the right occipital either ($p=.201$).

Then, I repeated all analyses to additionally control for regional residual variance for each ROI. Including regional residual variance did not change results for the left and right fusiform/parahippocampal gyrus. For the occipital clusters, the marginally significant effect of class in the left lateral/middle occipital region became non-significant, but the non-significant interaction in the right lateral/middle occipital region became significant. Overall, the pattern of results remained unchanged: *prime* individuals had greater subsequent memory effect across core task-related regions, and this difference was most evident in young-old adults.

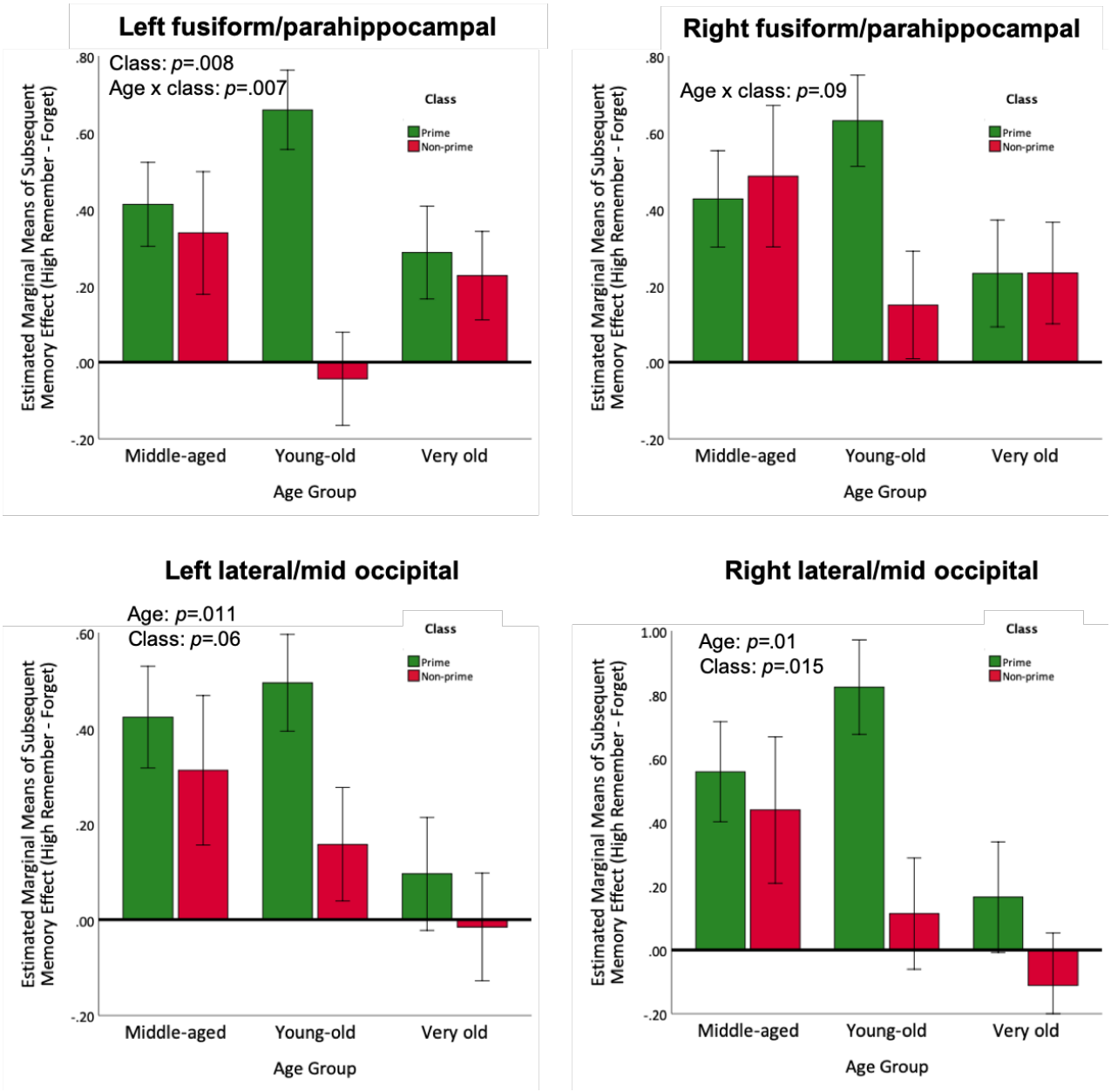

Figure 16. Estimated marginal means of subsequent memory effect, adjusted for sex and education, in *prime* and *nonprime* individuals (defined in Study 1 in Chapter 2) in middle-aged, young-old, and very old adults for four task-related ROIs.

Finally, to offer an overall representation of activity differences, an ANCOVA examined the mean subsequent memory effect in all task-related voxels for the effect of age, class, and their interaction while controlling for sex and education. I found a significant main effect of class

($F(2, 241)=5.330$, $p=.022$) that *prime* individuals had greater subsequent memory effect across task-related voxels than *nonprime* individuals. I also found a significant class x age group interaction ($F(2, 241)=3.574$, $p=.03$) that occurred because the higher subsequent memory effect difference was most evident in young-old individuals (Figure 17).

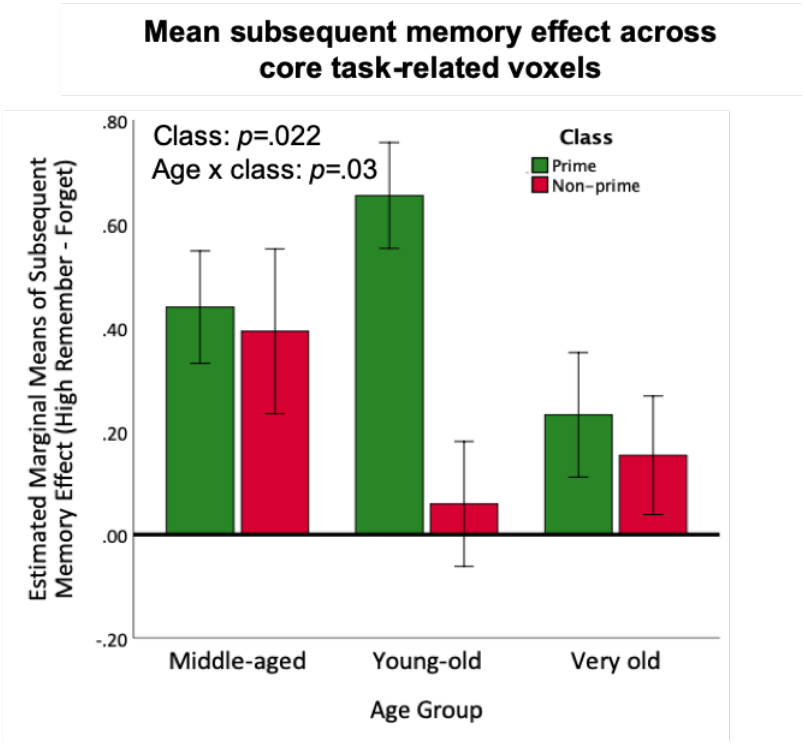

Figure 17. Mean subsequent memory effect across task-related voxels in *prime* and *nonprime* individuals (defined in Study 1 in Chapter 3) in middle-aged, young-old, and very old adults for four task-related ROIs.

3.3.2.3. Subsequent memory effect differences compared to young adults

Next, to answer the question of whether the activation in *prime* and *nonprime* individuals is different from young adults, the subsequent memory effect in middle-aged, young-old and very old adults was compared to the young reference group using ANCOVA while controlling for sex and education, for *prime* and *nonprime* individuals separately. I specifically focused on

the tests with the young reference group as it is the only relevant comparison. The results showed that *prime* individuals demonstrated youth-like activation until very old age, whereas *nonprime* individuals showed the difference starting in young-old age (Figure 18). Specifically, for left

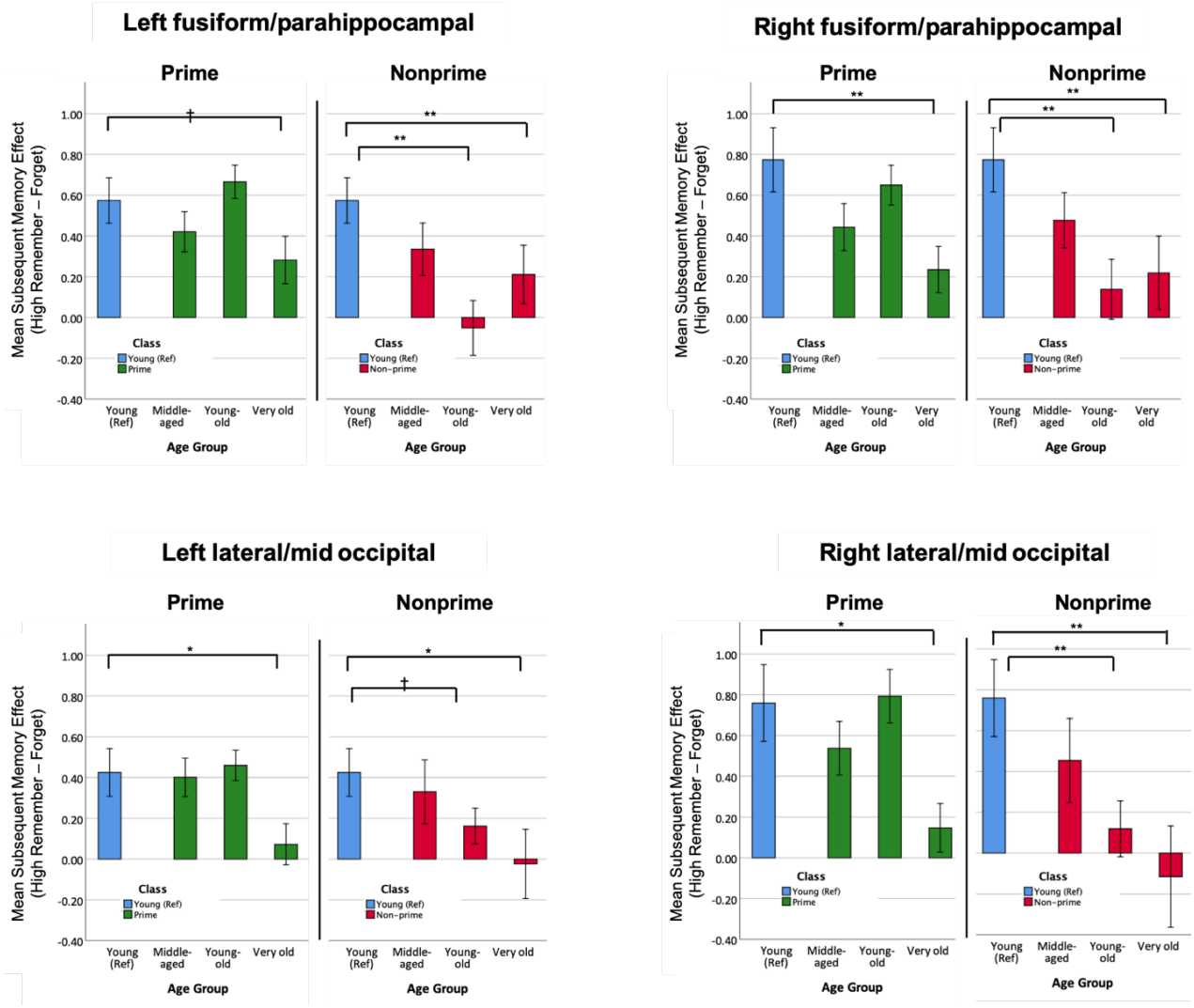

Figure 18. Mean subsequent memory effect in middle-aged, young-old and very old group, compared to the young reference group, separately for *prime* and *nonprime* individuals. † $p<.1$. * $p<.05$. ** $p<.01$.

fusiform/parahippocampal gyrus, the analyses of *prime* individuals revealed a tendency of reduced subsequent memory effect only in very old group comparing to the young reference

group (p=.097). *Nonprime* individuals, however, showed a significant reduction in both young-old (p=.003) and very old groups (p=.007) compared to young adults. A similar pattern was also found for right fusiform/parahippocampal gyrus: the analysis of *prime* individuals revealed significant reduction in subsequent memory effect only in very old group, compared to young (p=.008), whereas *nonprime* individuals showed significant reduction in both young-old (p=.003) and very old adults (p=.007). The two occipital regions also revealed the same patterns: in the left lateral/middle occipital region, very old group were the only group that showed significantly reduced effect, comparing to young (p=.025). In *nonprime* individuals, in addition to the very old group who had significantly reduced subsequent memory effect (p=.005), young-old also had marginally significant reduction compared to young adults (p=.056). For the right lateral/middle occipital region, in *prime* individuals, only the very old group had significant lower subsequent memory effect compared to young (p=.016), whereas *nonprime* individuals showed significant reduced effect in both young-old (p=.008) and very old groups (p=.001) compared to young adults. All results remained unchanged when the regional residual variance was also included.

3.3.2.4. Result summary of ROI analysis

In summary, *prime* individuals overall had higher subsequent memory effect than *nonprime* individuals. Across all core regions supporting successful encoding, results showed a consistent pattern that *prime* individuals were featured with maintenance in youth-like pattern of significant subsequent memory effect until very old age. *Nonprime* individuals showed reduced effect starting at a younger age in late adulthood.

3.3.2.5. Whole brain exploration of subsequent memory effect differences

To explore activity differences between *prime* and *nonprime* individuals which may be outside task-related regions, whole-brain analyses were performed in middle-aged adults, young-old adults, and very old adults contrasting the subsequent memory effect in *prime* and *nonprime* individuals. The only group where the significant effect was observed is in the young-old group, where six clusters showed significantly higher subsequent memory effect in *prime* individuals than *nonprime* individuals, after FWE cluster-wise correction at $p < .05$. Five cortical clusters are illustrated in Figure 19, primarily overlapping with regions that have been previously reported to be associated with subsequent memory or memory processing in general (Kim, 2011). Some of these clusters were also identified in the ROI analysis (e.g., left and right occipital, left fusiform), and some are novel clusters outside the core task-related regions, including frontal regions (e.g., left inferior frontal, left superior frontal, right orbitofrontal cortex).

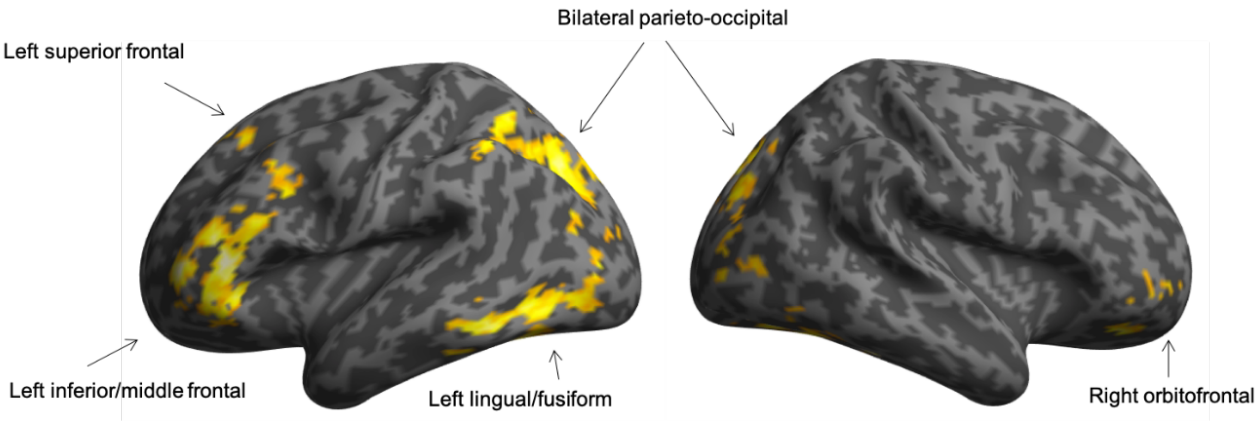

Figure 19. Five cortical regions show significant subsequent memory effect in *prime* individuals than *nonprime* individuals in young-old adults. Cluster wise FWE corrected at $p<.05$.

To specifically examine outside task-related regions, before comparing the activity differences in these clusters, the voxels belonging to task-related regions (identified in the previous section) were masked out. This removed 199 voxels in the left lingual/fusiform cluster,

reducing its cluster size from 886 to 687 voxels, and 64 voxels in the bilateral occipital cluster, reducing its size from 1389 to 1325 voxels. Then, to better interpret the activity differences between *prime* and *nonprime* young-old adults revealed in the whole brain analysis, their subsequent memory effect was compared to the young reference group. The results showed that *prime* young-old individuals appeared to have additional recruitment than young adults in left superior frontal cortex (p=.009; Figure 20a) and marginally in the right orbitofrontal cortex (p=.079). Importantly, the brain-behavioral correlation between activation magnitude and *d*' suggested a trend that individuals with greater additional recruitment seemed to have a better subsequent memory (left superior frontal: r=.182, p=.078, Figure 20b; right orbitofrontal: r=.234, p=.022). These two prefrontal regions were distant from the core task-related regions, suggesting that there may be additional frontal recruitments outside task-related regions in *prime* young-old adults, and that the individuals who were able to recruit these regions had better subsequent memory performance.

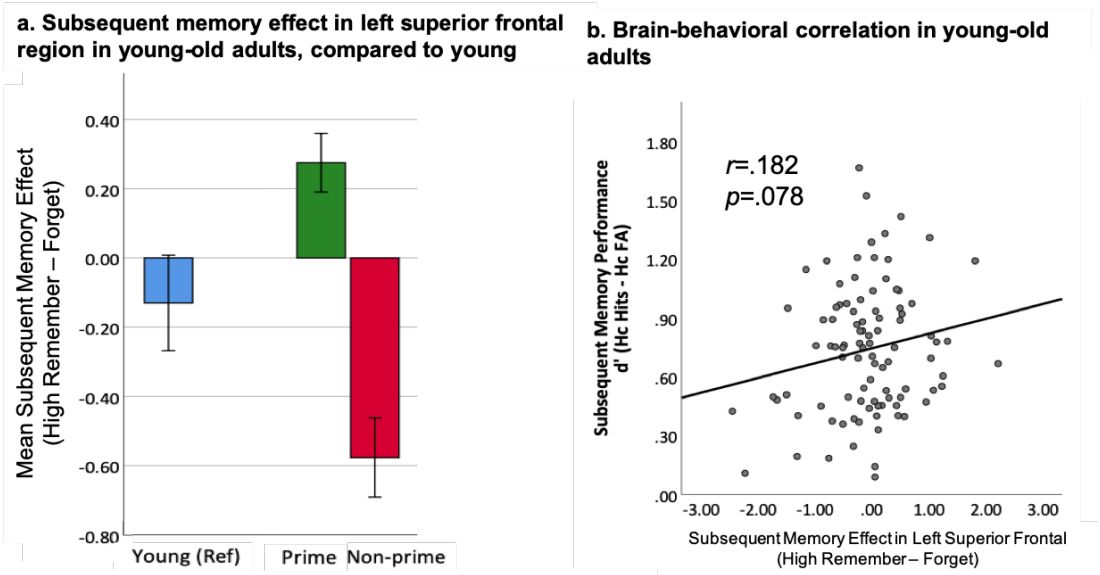

Figure 20. (a). Subsequent memory effect in *prime* and *nonprime* young-old individuals differ from young adults. (b). Additional recruitment showed a trend of association with better subsequent memory performance in young-old individuals.

In the other four clusters (left lingual/fusiform, left inferior/middle frontal, left and right parieto-occipital, cerebellum), *prime* individuals showed comparable activations as in young adults (p's >.1), whereas *nonprime* individuals showed reduced activation (p's <.003). This pattern is consistent with the observation in task-related regions, suggesting the importance of preservation of functional activation in *prime* adults in young-old age.

I did not find any region that showed significantly greater activation in *nonprime* individuals compared to *prime* individuals. And no significant activity differences between *prime* and *nonprime* individuals was found in other two age groups.

3.3.3. Activity analysis of negative subsequent memory effect

In addition to subsequent memory effect, I also explored activity differences between *prime* and *nonprime* individuals for negative subsequent memory effect. The negative subsequent memory effect reflects regions showing lower activation during encoding of high-confidence remembered items than forgetting items, representing suppression of certain regions during successful encoding. Across all participants, seven clusters were identified mainly covering large areas in the default mode network (Figure 21).

Regions	Peak Coordinates (x y z)	*p* (FWE)	t	Cluster Size
DMN regions (left/right precuneus, cingulate, middle frontal)	6 -64 35	<.001	11.86	6734
Right angular gyrus/superior temporal	51 -52 35	<.001	12.08	2255
Left angular gyrus/superior temporal	-60 -58 23	<.001	9.66	1810
Right inferior frontal	54 17 -1	<.001	8.68	417
Left inferior frontal	-51 11 -1	<.001	6.93	285
Right inferior temporal	54 -7 -37	<.001	9.76	238
Left inferior temporal	-51 -7 -37	<.001	6.93	114

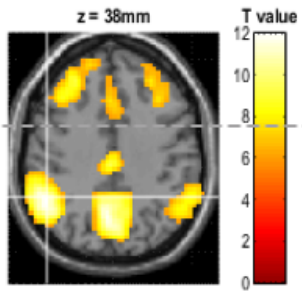

Figure 21. Brain regions showing significant negative subsequent memory effect (forget > high-confidence remember). Voxel-wise FWE corrected at $p < .05$.

Then, for each cluster, the negative effect in *prime* and *nonprime* individuals was compared. The results showed that, in the midline DMN region, there was a significant age x class interaction ($F(2, 241)=4.649$, $p=.01$; Figure 22a) because *nonprime* individuals of young-old age had greater negative effect ($p=.011$) than *prime* individuals. This pattern was unexpected and warranted a further brain-behavioral analysis. The activity magnitude in the DMN cluster and the subsequent memory index, *d*', showed no significant relationship ($r=.097$, $p=.347$). Using the behavioral measure of subsequent forgetting (miss rate), the analysis revealed a negative relationship between negative subsequent memory effect and miss rate ($r=-.237$, $p=.02$; Figure 22b), suggesting that this over-suppression was more frequent in individuals with higher miss rate and may reflect maladaptive suppression related to worse subsequent memory performance. Additionally, the left inferior temporal region showed a significant age x class interaction ($F(2, 241)=3.853$, $p=.023$) such that the *nonprime* individuals in the middle-aged group failed to show disengagement, but the comparison to young adults suggested neither class showed statistically significant differences from young adults (p's>.1).

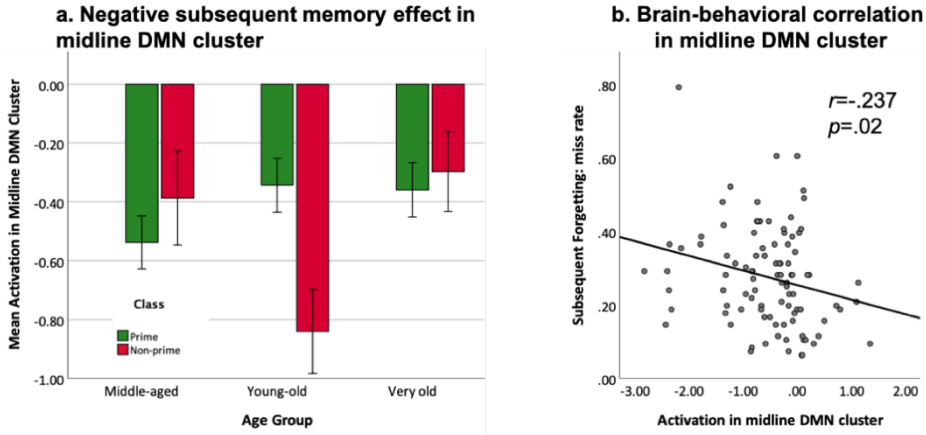

Figure 22. (a). Negative subsequent memory effect of *prime* and *nonprime* individuals in middle-aged, young-old and very old adults in the midline DMN cluster. (b). Brain-behavioral correlation in the DMN cluster. Greater negative subsequent memory effect in the midline DMN cluster was related to higher miss rate. Removing the potential outlier who had the highest miss rate did weaken the relationship but did not change the significance ($r=-.212$, $p=.040$).

Finally, the whole-brain analysis for negative subsequent memory effect did not find any cluster showing differences between *prime* and *nonprime* individuals in any age group.

3.4. Discussion

This study using a subsequent memory fMRI task found that *prime* individuals overall showed higher activation than *nonprime* individuals in task-related regions including left and right temporal and occipital regions. The *prime* individuals showed better preservation of high task-related activation until very old age. The *nonprime* agers, on the contrary, showed reduced task-related activation starting in young-old age. Additionally, the present study also found evidence of additional neural recruitment outside the core task-related regions in young-old *prime* individuals: *prime* adults recruited additional prefrontal regions, including the left superior frontal cortex and right orbitofrontal cortex, and individuals with greater activation had better subsequent memory performance, suggesting a compensatory nature of this frontal recruitment. Overall, the findings suggest that higher activation during successful encoding, both within task-related regions and in additional frontal regions, was present in *prime* individuals with less retrospective decline.

3.4.1. Fusiform, parahippocampal, and occipital regions in successful encoding

The present study used a subsequent memory task to investigate brain activity patterns that are sensitive to successful encoding. Some researchers have explored functional activities during encoding between older individuals with different cognitive aging trajectories (e.g., Persson et al., 2011; Pudas et al., 2013; Pudas et al., 2018), but those studies did not separate successful encoding from unsuccessful encoding. Activities during unsuccessful encoding may not involve the mental processes leading to memory, but may be more reflective of general

perceptual processing of the stimuli. As I alluded to in the introduction, those studies may be limited in the interpretation of differences in functional brain activity between individuals because the nature of the compared activation is unclear. The present study specifically focused on subsequent memory effect that distinguishes successful and unsuccessful encoding. The results, in fact, converge with those previous findings and clearly presents functional activity differences between *prime* and *nonprime* individuals highlighting the importance of functional integrity in core memory regions in aging.

The present study found subsequent memory effect in left and right temporal and occipital clusters including fusiform, parahippocampal and lateral/middle occipital regions, which are essential for successful encoding in the across lifespan sample. The results suggest the higher-order visual processing, particularly involved in occipital regions (Grill-Spector, Kourtzi, & Kanwisher, 2001), is essential for successful memory of the pictorial stimuli in this study. Moreover, parahippocampal gyrus and fusiform gyrus have both been linked to successful memory encoding, particularly for colorful visual information and environmental information (Aguirre, Detre, Alsop, & D'Esposito, 1996; Gutchess et al., 2005). It has been frequently reported that fusiform and parahippocampal activation is critical for subsequent memory during processing of pictorial stimuli in young adults (Kim, 2011). A meta-analysis on the age-related differences in subsequent memory effect showed age equivalent activation in young and old adults in medial temporal lobe and left fusiform gyrus (Maillet & Rajah, 2014). Similarly, Park et al. (2013) used a subset of DLBS participants and also found left parahippocampal and fusiform areas were among the subsequent memory effect regions common to all individuals from young to old age. Overall, our study substantiates prior findings that activity in temporal

regions including fusiform and parahippocampal gyrus is commonly critical for successful encoding regardless of age.

3.4.2. People who aged better longitudinally have higher task-related activations

The direct comparison between *prime* and *nonprime* agers revealed a pattern that *prime* individuals overall had higher activation than *nonprime* individuals, particularly in young-old adults. Higher task-related neural activity has been found positively correlated with cognitive performance cross-sectionally (Eyler et al., 2011). And typical aging is often accompanied by age-related loss of neural responses or neural modulation, particularly in temporal and occipital regions (Koen & Rugg, 2019; S. C. Li, Lindenberger, & Sikstrom, 2001; McDonough, Cervantes, Gray, & Gallo, 2014). The present study demonstrated that this age-related neural decline may not be universal in older adults and that people with less longitudinal cognitive decline have higher activations than those with suboptimal patterns of cognitive aging.

Typical age-related decline in decreased functional activation may reflect age-related adverse effects of accumulated neural depletion factors on functional alterations. For example, gray matter atrophy , white matter integrity (Lucas, Wagshul, Izzetoglu, & Holtzer, 2019; Webb, Rodrigue, Hoagey, Foster, & Kennedy, 2019), amyloid deposition (Kennedy, Rodrigue, Devous Sr, et al., 2012; Song et al., 2016), decreased dopamine availability (Backman, Lindenberger, Li, & Nyberg, 2010) have all been liked to age-related differences in brain activity differences. These factors may also contribute to differences in cognitive aging trajectories, directly or indirectly through brain function (Hedden & Gabrieli, 2004; Nyberg & Pudas, 2018). As a consequence, higher task-related activation may reflect better maintenance in structural integrity

(Nyberg et al. 2012; Cabeza et al., 2018) and is prevalent in individuals who also present better cognitive aging profiles.

3.4.3. High functional activation in *prime* individuals until very old age

By examining fMRI data in a large sample across the adult lifespan, the present study provides evidence that better cognitive aging is associated with better preservation of patterns of higher task-related activation. This conclusion is supported by two interconnected findings. First, *prime* agers demonstrated task-related activations at a similar magnitude as in young adults, until very old age. On the contrary, *nonprime* agers showed reduced task-related activation starting in young-old age. This finding suggests that expected age-related functional reduction is delayed in *prime* individuals, compared to *nonprime* individuals. The task-related activation appears to be well preserved throughout most of the adult lifespan in individuals showing better cognitive aging trajectories. Second, *nonprime* young-old individuals also showed loss of activations widely outside task-related regions where *prime* individuals had comparable activations as in young adults. This pattern is also consistent with the prediction of brain maintenance theory (Nyberg et al., 2012; Cabeza et al., 2018) that the inability of recruiting proper activation is likely a consequence of age-related detrimental changes in the whole brain, not necessarily specific for a particular region.

The importance of preserving high brain functional activation in older individuals has been suggested previously. Park et al. (2013) used a subset of participants that were included in this study and focused on the age-related differences in young, middle-aged, and old adults. They found that low-performing middle-aged adults started to show reduced deactivation for negative subsequent memory, whereas high-performing adults only showed the reduction when they were

at older age. Pudas et al. (2013) used a memory task and found successful older adults, defined by maintaining high memory performance over 15-20 years, had comparable medial temporal activation as in young adults, whereas the average older adults who showed typical memory decline had reduced activation. A longitudinal examination of functional activity changes also found that it was the declining older adults with greater memory decline showed greater activation reduction in the hippocampus with age (Persson, Kalpouzos, Nilsson, Ryberg, & Nyberg, 2011). The current study further provides stronger evidence of such characteristics by presenting a clear consistency across task-related regions of successful encoding (e.g., left and right temporal and occipital regions), as well as some extended clusters outside task-related regions.

3.4.4. Compensatory recruitment in frontal regions

In addition to the preservation of high task-related activation similar to young brains, the present study also showed some preliminary evidence that may be suggestive of neural compensation in *prime* individuals at young-old age. In two prefrontal clusters (left superior frontal and right orbitofrontal regions), *prime* individuals had additional recruitment, compared to young adults. Critically, individuals who additionally recruited the activation tended to show better subsequent memory, suggesting that the use of the additional regions indeed helped their memory performance.

The critical role of the prefrontal lobe in brain compensation has been well documented. An early review examined 47 neuroimaging studies and found that greater frontal activation was one of the most evident patterns related to better cognitive aging in older adults (Eyler et al., 2011). Prefrontal regions are actively involved in cognitive control processes that contribute to a

wide range of cognitive tasks, including memory encoding (Badre & Wagner, 2007). It has been suggested that individuals who showed the least parahippocampal activation recruited the most frontal regions (Gutchess et al., 2005) and the prefrontal functional capacity may be a mediator of encoding quality in aging (de Chastelaine et al., 2016), as it is one of the particularly vulnerable regions affected by age-related detrimental effects (Fjell et al., 2014; Rabbitt, 2005). The ability to activate additional prefrontal regions should be recognized as an important feature of desired activation patterns in *prime* individuals.

3.4.5. Age as a potential moderator of what functional activity pattern is expected in successful aging

Another important feature of the present study is that it relates the brain activity pattern to cognitive aging across the adult lifespan. It was suspected that functional characteristics related to better cognitive aging may depend on age. Indeed, the findings suggest that preservation of sufficient functional activation likely becomes most critical in young-old adults (55-69 years old as baseline age in the present study), and the pattern of compensatory recruitment also emerges in the same age.

Middle-aged brains are likely relatively spared from age-related detrimental changes and present high levels of functional brain activity with little need for compensation. But as age increases, individual differences in preserving proper brain function become critical. Studies have suggested the ability to resist functional and structural decline relies on neural plasticity and cellular repair which may offset age-related pathology (Cabeza et al., 2018). For individuals who can no longer withstand the increasing neural deterioration, functional activity deficits in task-related regions may start to be present. Not coincidently, this is also when compensatory

responses start to emerge, probably to cope with functional deteriorations according to the STAC model (D. C. Park & Reuter-Lorenz, 2009). The present study suggests that young-old age (55 to 69 years old at baseline in the study), which represents the start of late adulthood, is when this critical divergence begins. Finally, very old brains likely lose the brain structural integrity, regardless of being a *prime* or *nonprime* individual, possibly due to "wear and tear" at cellular levels at an advanced age (Nyberg et al., 2012). Therefore, there is little neural resource for preserving high brain function or recruiting additional neural function.

Previous studies on functional neuroimaging of aging often focus on functional activity changes as a function of age. The present study suggests that the individual difference in functional change is not exclusively related to age, but also a reflection of whether one is considered as a *prime* or *nonprime* individual, highlighting the importance of recognizing the individual differences in cognitive aging when examining brain function in older adults.

3.4.6. Limitation and future direction

One limitation of the present study is that functional inferences are based on a cross-sectional comparison across age groups, which assumes that older groups had similar brain activation as the young when they were younger. However, studies using an across-lifespan sample sometimes have more selective older participants (Fjell et al., 2014; Rugg, 2016) who may represent a group of higher functioning individuals and would have exceeded the young reference individuals when they were younger. In that case, the inferences may reflect sample differences rather than developmental changes. In fact, the present study was not designed to provide direct proof regarding *brain maintenance* or *compensation* argument. Instead, it explores what brain activity may be specifically present in individuals with better cognitive aging and

found higher subsequent memory effect as well as additional frontal recruitment in *prime* individuals, which findings are better interpreted in the context of *brain maintenance* and *compensation* theories. Future studies may use longitudinal designs to examine the relationship between functional and cognitive changes in the same individual for a more definitive inference.

Additionally, one interpretation of the results is that middle-aged adults have relatively better brain structure which enables better preservation of higher brain function and requires little need for compensation for age-related neural pathology. The current dissertation did not directly investigate the role of neural pathology, but used age as a proxy of the overall status of brain structure. Future studies may investigate specific moderators (e.g., hippocampal atrophy, (Persson et al., 2005)) that may determine the efficacy of brain maintenance and compensation.

Another caveat to the interpretation of the findings is that individual differences in non-neural factors, such as cerebrovascular reactivity, may be a confounding cause of the subsequent memory effect differences, as cerebrovascular reactivity is an important non-neural determinant of BLOD signal that changes with age (Liu, Jill, & Lu, 2019). For this particular reason, I refrained from directly contrasting between age groups and considered an additional covariate, signal residual variance, that is evidenced to reflect inter-individual biological variances like vascular differences (Gonzalez-Castillo et al., 2017; Kazan et al., 2016). The potential influence of cerebrovascular differences is also a common issue in most prior studies examining age-related effects on fMRI activation. Future studies should consider incorporating measures of CVR that may correct for its effect on BOLD signal (Liu et al., 2019; Tsvetanov et al., 2015).

As an investigation of functional differences between *prime* and *nonprime* individuals, the present study explored multiple regions in three age groups for each hypothesized question.

Although the regions investigated for each question should not be considered independent from each other, the conduction of multiple tests may still increase the Type I errors. This is partially addressed by performing an additional analysis for all task-related voxels, which nevertheless presented a consistent pattern similar to the regional results. However, the results should be interpreted with the acknowledgement of the potential multiple comparisons problem.

Finally, it is important to note that the present study is correlational. The findings illustrate the patterns of brain activation that is present in individuals who have accomplished optimal cognitive aging retrospectively. It does not directly examine causation between brain and behavior. It is possible that functional activity patterns reflected a "snapshot" of neural functional features which indeed led to better cognitive outcomes. It is also possible that cognitive changes over the past years resulted in alterations in strategy, motivation, etc., which could also reflect in brain activity.

CHAPTER 4

CONCLUDING REMARKS

As 20 percent of the total U.S. population will be over the age of 65 by the year 2030 (Ortman et al., 2014), a better understanding of the patterns of functional brain activity that are associated with successful aging has become increasingly necessary. It has become critically important to recognize what brain activity pattern is characteristic of individuals who show better trajectories of cognitive aging. The present dissertation investigated the brain activation features in *prime* individuals, who are defined in the present dissertation as individuals with superior cognitive performance and less longitudinal decline relative to their peers across multiple cognitive domains. The results from this dissertation heighten our understanding of the patterns of brain activity that are related to successful aging in many ways:

First, Study 1 in Chapter 2 used a data-driven approach to identify individuals with distinct cognitive aging profiles based on cognitive performance and longitudinal change across multiple domains over four years. Although the existence of heterogeneity in cognitive aging has been well acknowledged, how to best distinguish individuals remains a complex issue (Nyberg & Pudas, 2018; Pruchno & Carr, 2017). Study 1 in Chapter 2 offered a novel and unique way to capture the heterogeneity in cognitive aging, which may be a useful method to classify individuals into *prime* and *nonprime* agers in future research. The use of a multivariate, unbiased approach may be particularly appropriate for aging and clinical research to develop classification with little *a priori* knowledge about the characteristics of subgroups.

Second, Study 2 in Chapter 3 clearly demonstrated that *prime* individuals with less longitudinal cognitive decline exhibited better preservation of high brain activation until very old

age. On the contrary, *nonprime* agers showed reduced activation starting in young-old age. Previous literature on successful aging has largely been limited to brain function in older adults in contrast to young adults (Nyberg & Pudas, 2018; Mailet & Rajah, 2014). The present dissertation is one of the first efforts to use a lifespan sample to investigate brain activity features in successful agers who longitudinally aged better. The present dissertation suggested that the divergence of brain activation emerges in young-old adults. The longitudinal examination of cognitive change allows for a more confident classification of successful cognitive aging. The inclusion of participants with a wide age range helps to connect the existing observations in different age groups, and may reconcile some inconsistency in the literature.

Third, Study 2 in Chapter 3 provided evidence of additional recruitment in frontal regions in *prime* individuals. Importantly, these regions were outside the core task-related regions, and individuals who recruited the regions to a higher degree had better subsequent memory. This is congruent with the historical views that the core source of neural compensation is frequently localized to the prefrontal cortex (Maillet & Rajah, 2014; Reuter-Lorenz & Park, 2014). Notably, some recent research has questioned the notion of neural compensation: some suggested no evidence of greater frontal activation longitudinally (Nyberg et al., 2010), and some questioned the interpretation of increased frontal activation (Morcom & Henson, 2018). Future studies with longitudinal neuroimaging data should examine the within-individual change in frontal activation, and between-individual differences related to better or worse cognitive aging. Nevertheless, the present study provides evidence of both preservation of youth-like activation and functional compensation in the same group of *prime* individuals, echoing the notion that the

two theories represent complementary, not competing, functional patterns related to superior cognitive aging (Cabeza et al., 2018; Park & Reuter-Lorenz, 2009).

Finally, the present dissertation provides further characterization of functional brain patterns that represent successful cognitive aging. In the aging literature, much is known about structural brain aging, and researchers have agreed on the significant contribution of structural brain integrity to individual differences in cognition. However, functional contributors to differential cognitive aging has been controversial (Morcom & Henson, 2018; Nyberg et al., 2010). This dissertation links the heterogeneity in cognitive aging to differences in brain function. Although an ideal investigation would implement a longitudinal design that follows individuals to track the brain function and cognitive development simultaneously, the present study provides important evidence that both brain maintenance and compensation characterize desired brain activation patterns that may be associated with better cognitive aging.

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Zelinski, E. M., Gilewski, M. J., & Schaie, K. W. (1993). Individual differences in cross-sectional and 3-year longitudinal memory performance across the adult life span. *Psychol Aging, 8*(2), 176-186. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8323722

BIOGRAPHICAL SKETCH

Xi Chen was born in Beijing, China and grew up in Beijing. Xi entered Beijing Normal University as a physics student. She developed a strong interest in psychology during her first year of college. Xi then transferred to a psychology major and received her BS in Psychology. While in college, she was primarily interested in research regarding cognition and aging. Xi moved to Dallas, Texas to begin her graduate school as a master's student at The University of Texas at Dallas in 2012. In 2014, after receiving her MS in Applied Cognition and Neuroscience, she joined the Park Aging Mind Lab as a PhD student, investigating age-related cognitive and neural changes in cognitively normal adults.

CURRICULUM VITAE

Xi Chen

EDUCATION

University of Texas at Dallas
Ph.D. Cognition and Neuroscience, in progress
M.S. Applied Cognition and Neuroscience, 2014

Beijing Normal University
B.S. Psychology, 2012

RESEARCH INTERESTS

I am interested in the individual differences in brain structure, brain function, and cognition, particularly memory function, that are associated with normal aging, as well as preclinical AD.

- What are normal (and pathological) age-related changes in brain function?
- How do individual differences in brain structure and function contribute to cognitive aging?
- Are there detectable alterations in brain and behavior in preclinical AD, compared to healthy older adults?

PEER-REVIEWED PUBLICATION

Chen, X., Farrell, M. E., Moore, W., & Park, D. C. (2019). Actual memory as a mediator of the amyloid-subjective cognitive decline relationship. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 11,* 151-160. doi.org/10.1016/j.dadm.2018.12.007.

Chen, X., Zhang, M., & Liu, X. L. (2019). Retrieval practice facilitates judgments of learning through multiple mechanisms: simultaneous and independent contribution of retrieval confidence and retrieval fluency. *Frontiers in Psychology, 10*, 987. doi.org/ 10.3389/fpsyg.2019.00987.

Farrell, M. E., **Chen, X.**, Rundle, M. M., Chan, M. Y., Wig, G. S., & Park, D. C. (2018). Early detection of longitudinal amyloid-related cognitive decline in middle-aged and initially amyloid-negative adults. *Neurology. 91*(19), e1809-1821. doi.org/10.1212/WNL.0000000000006469.

Zhang, M. [#], **Chen, X.**[#], & Liu, X. L. (2018). The confidence in accuracy moderates the benefits of the testing effect. *Memory*, 1-7. doi.org/10.1080/09658211.2018.1529796.

Peng, S-L., **Chen, X.**, Li, Y., Rodrigue, K. M., Park, D. C., & Lu, H. (2018). Age-related changes in cerebrovascular reactivity and their relationship to cognition and hypertension: a four-year longitudinal study. *NeuroImage, 174,* 257-262. doi.org/10.1016/j.neuroimage.2018.03.033.

Vis, J. B., Peng, S. L., **Chen, X.**, Li, Y., Liu, P., Sur, S., ... & Lu, H. (2018). Arterial-spin-labeling (ASL) perfusion MRI predicts cognitive function in elderly individuals: A 4-year longitudinal study. *Journal of Magnetic Resonance Imaging*. doi:10.1002/jmri.25938.

Song, Z., Farrell, M. E., **Chen, X.**, Park, D. C. (2018). Longitudinal accrual of neocortical amyloid burden is associated with microstructural changes of the fornix in cognitively-normal adults. *Neurobiology of Aging*. doi.org/10.1016/j.neurobiolaging.2018.02.021.

Chen, X., Hertzog, C., & Park, D. C. (2017). Cognitive predictors of everyday problem solving across the lifespan. *Gerontology*. *63*(4), 372-384. doi:10.1159/000459622.

Farrell, M. E., Kennedy, K. M., Rodrigue, K. M., Wig, G., Bischof, G. N., Rieck J. R., **Chen, X.**, Festini, S. B., & Park D. C. (2017). Association of longitudinal cognitive decline with amyloid burden in middle-aged and older adults: evidence for a dose-response relationship. JAMA Neurology. doi:10.1001/jamaneurol.2017.0892.

CONFERENCE ORAL PRESENTATIONS

Chen, X., & Park, D. C. (2019). Brain activity differences in successful and unsuccessful agers. Society for Neuroscience, Chicago, USA.

Chen, X. (2019). Mechanisms underlying subjective memory complaints. Dallas & Austin Area Memory Meeting, Dallas, USA.

Chen, X., Jingting, Z., Farrell, M. E., & Park, D. C. (2018). Subjective memory complaints reflect functional deficits in the hippocampus and elevated amyloid burden in cognitively normal adults. Alzheimer's Association International Conference, Chicago, USA.

Chen, X., Farrell, M. E., & Park, D. C. (2017). Actual memory decline mediates the effect of amyloid burden on subjective memory in cognitively normal adults. Alzheimer's Association International Conference, London, UK.

Chen, X. (2017). Cognitive Predictors of Everyday Problem Solving across the Lifespan. Developmental, Cognitive and Social/Personality Brownbag Series, Dallas, USA.

[#] equal contribution as a co-first author

Chen, X., Festini, S. B., McDonough, I. M., & Park, D. C. (2016). Cognitive Change Across the Lifespan: Four-year longitudinal findings in the Dallas Lifespan Brain Study (DLBS). International Psychonomic Society Meeting, Granada, Spain. Presented by Festini, S. B.

SELECTED POSTER PRESENTATIONS

Chen, X. & Park, D. C. (2019). Brain activity differences between successful and unsuccessful agers. Alzheimer's Association International Conference, Los Angeles, USA.

Chen, X., Jingting, Z., Farrell, M. E., & Park, D. C. (2019). Subjective cognitive decline reflects actual memory decline and functional deficits in the hippocampus. Dallas Aging and Cognition Conference, Dallas, USA.

Chen, X., Jingting, Z., Farrell, M. E., & Park, D. C. (2019). Independent contributions of hippocampal activity, amyloid burden, and retrospective decline to subjective memory decline. Human Amyloid Imaging, Miami, USA.

Munro, C. E., **Chen, X.,** Rundle, M. M., Cullum, C. M., Rodrigue, K. M., & Park, D. C. (2019). ApoE4 as a moderating factor between mild traumatic brain injury and tau deposition in the temporal cortex. Human Amyloid Imaging, Miami, USA.

Chen, X., Jingting, Z., Farrell, M. E., & Park, D. C. (2018). Subjective memory complaints reflect worse actual memory and functional deficits in the hippocampus. Organization for Human Brain Mapping, Singapore.

Chen, X., Jingting, Z., Farrell, M. E., & Park, D. C. (2018). Effects of amyloid deposition and hippocampal activation on subjective memory complaints. Human Amyloid Imaging, Miami, USA.

Farrell, M. E., **Chen, X.**, Rundle, M. M., Chan, M. Y., Wig, G. S., & Park, D. C. (2018). Early detection of longitudinal amyloid-related cognitive decline in middle-aged and initially amyloid-negative adults. Human Amyloid Imaging, Miami, USA.

Chen, X., Jingting, Z., Farrell, M. E., & Park, D. C. (2018). Effects of amyloid deposition and hippocampal activation on subjective memory complaints. Human Amyloid Imaging, Miami, USA.

Chen, X., Festini, S. B., McDonough, I. M., Park, D. C., & Hertzog, C. (2017). Change in processing speed predicts change in other cognitive domains: Four-year longitudinal findings in the Dallas Lifespan Brain Study (DLBS). Dallas Aging and Cognition Conference, Dallas, USA.

Festini, S. B., **Chen, X.**, & Park, D. C. (2017). Busyness and brain structure: Middle-aged adults show strongest relationship between busyness and cortical thickness. Cognitive Neuroscience Society Annual Meeting, San Francisco, USA.

Chen, X., Festini, S. B., McDonough, I. M., & Park, D. C. (2016). Cognitive Change Across the Lifespan: Four-year longitudinal findings in the Dallas Lifespan Brain Study (DLBS). Cognitive Aging Conference, Atlanta, USA.

Peng, S-L., **Chen, X.**, Li, Y., Rodrigue, K., Cheng Y., Park, D. C., & Lu, H. (2016). Longitudinal relationship between cerebrovascular reactivity and processing speed in young and elderly individuals. The International Society for Magnetic Resonance in Medicine Annual Meeting, Singapore, Singapore.

Farrell, M. E., **Chen, X.**, Festini, S. B., & Park, D. C. (2016). What predicts cognitive decline over 3.5 Years in healthy adults? Age or Amyloid? Cognitive Aging Conference, Atlanta, USA.

Song, Z., Farrell M., **Chen, X.**, & Park, D. C. (2016). Longitudinal accrual of amyloid is associated with degradation of white matter tracts connected to the hippocampus in cognitively-normal adults. Human Amyloid Imaging, Miami, USA.

Farrell, M., Festini, S. B., **Chen, X.**, & Park D. C. (2016). Regional differences in the progression of amyloid accumulation and cognitive consequences in healthy adults across the lifespan. Human Amyloid Imaging, Miami, USA.

Chen, X., Farrell, M. E., Festini, S. B., McDonough, I. M., Rieck, J. R., & Park, D. C. (2015). Cognitive predictors of everyday problem solving across the lifespan. Dallas Aging and Cognition Conference, Dallas, USA.

AWARDS and GRANTS

PhD Research Small Grant, University of Texas at Dallas (2019)
AAIC Travel Fellowship, Alzheimer's Association (2018)
Competitive Student Scholarship, University of Texas at Dallas (2012-2013)

PROFESSIONAL SKILLS

R, Mplus, SPSS, SPM, FreeSurfer, FSL, MATLAB, MRIcron, E-prime