8-2021

Factors Related to Cognitive Reserve in Healthy Older Adults

Ann Tram Nguyen

LOMA LINDA UNIVERSITY
School of Behavioral Health
in conjunction with the
Department of Psychology

Factors Related to Cognitive Reserve in Healthy Older Adults

by

Ann Tram Nguyen

A Dissertation Defense submitted in partial satisfaction of
the requirements for the degree
Doctor of Philosophy in Clinical Psychology

August 2021

Each person whose signature appears below certifies that this dissertation in his/her opinion is adequate, in scope and quality, as a dissertation for the degree Doctor of Philosophy.

_____, Chairperson
Grace J. Lee, Associate Professor of Psychology

_____
Colleen A. Brenner, Associate Professor of Psychology

_____
Nicole Gatto, Associate Professor of Public Health

_____
Kelly R. Morton, Professor of Psychology

ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to my dissertation chair, Dr. Grace J. Lee, for your unwavering guidance and support throughout my graduate studies. It was your kindness, reassurance, and belief in my abilities and potential for growth that helped me progress through these years. Your support and monitoring of my efforts and progress significantly contributed to my success. I thank you for taking the time to train me in your expertise on complex neuroimaging analyses during my first year and for your encouragement of me to reach new levels in research and writing.

I would like to thank my thesis committee members, Dr. Brenner, Dr. Morton, and Dr. Gatto, for their advice and direction in helping me complete this milestone. Your feedback in writing and insight in analyzing data has greatly contributed to my dissertation completion. Your kindness and understanding of me as an emerging scholar have nurtured my ability beyond what I thought possible.

I want to give my heartfelt thanks to my fiancée, Morgen Aita, for his unconditional love and support through my graduate studies. Without your understanding of my needs as a graduate student as well as partner, I would not have survived the emotional rigors of the program. You are my rock and I could not have been more blessed to walk beside you throughout our 8 years together, with 7 of those years being long distance. Thank you for always believing in me, lifting my spirit, and remaining by my side throughout the “good good” and bad.

I am grateful for my family, friends, and my colleagues who have supported me throughout my career. To my parents, Tin and Thang Nguyen, thank you for your enormous sacrifices so that your children can have a better future with freedom to pursue

their dreams. To my brother, Brian Loc Nguyen, your belief in my abilities and support throughout some of the most trying times in my academic career reminds me to wake up each day and continue the fight because *hard work beats talent every time*. You are the first testament to our parents' sacrifices and have allowed me to see that "doctor" is a title that is achievable in our family. To my inspiring friends, your time and companionship have helped me strive and achieve beyond my expectations. To my lab mates, thank you for your support and your help. From all of you, I realized that it is not the struggle that matters but what truly matters are the bonds and memories you create during the struggle.

Finally, I would like to thank all the faculty and staff in this program for your time, understanding, and support through this long endeavor in my career. I am most grateful for the safe space provided by the faculty to process and discuss sociopolitical events as well as the provision of numerous resources to help students cope with an uncertain future during the pandemic. I felt welcomed and driven for success since the fanfare of orientation day. With your day-to-day help and kind words during my years in the program, I felt proud to be part of this academic family.

CONTENT

FIGURES

Figures Page

TABLES

Tables Page

ABBREVIATIONS

CR	Cognitive Reserve
ApoE-4	Apolipoprotein E-4 gene
PPT	Physical Performance Test
TUG	Timed Up and Go
NART	National Adult Reading Test
AMNART	American National Adult Reading Test
CDC	Centers for Disease Control
U.S.	United States
NIH	National Institutes of Health
AD	Alzheimer's Disease
MCI	Mild Cognitive Impairment
fMRI	Functional Magnetic Resonance Imaging
PFC	Prefrontal Cortex
MMSE	Mini-Mental State Exam
IQ	Intelligence Quotient
VIQ	Verbal Intelligence Quotient
iADLs	Instrumental Activities of Daily Living
CEO	Chief Executive Officer
Allele Types	ε2, ε3, and ε4
AVLT	Auditory Verbal Learning Test
CDR	Clinical Dementia Rating
RAVLT	Rey's Auditory Verbal Learning Test

AHS2-CAN	Adventist Health Study-2 Cognitive and Neuroimaging
WAIS-IV	Wechsler Adult Intelligence Scale - 4th edition
TMT-A/B	Trail-making Test - Part A/B
BNT	Boston Naming Test
WMS-IV	Wechsler Memory Scale – 4th edition
LM	Logical Memory subtest
LLU	Loma Linda University
DOT	Dictionary of Occupational Titles
OCC	Occupational Complexity

ABSTRACT OF THE DISSERTATION

Factors Related to Cognitive Reserve in Healthy Older Adults

by

Ann Tram Nguyen

Doctor of Psychology, Graduate Program in Psychology
Loma Linda University, August 2021
Dr. Grace J. Lee, Chairperson

Background. Physical and cognitive impairments are two of the most prevalent age-related conditions, with evidence that both factors interact prior to or concurrently with the earliest detectable stages of cognitive impairment. Cognitive reserve (CR) allows an individual to cope more successfully with age-related brain and functional changes and is associated with better cognitive function and reduced risk of cognitive decline. However, it remains unclear to date the specific roles of individual markers of CR, and whether or not this relationship is modified by genetic risk (ApoE-4 genotype) and/or physical function. **Method.** We assessed cognitive functioning (global cognition, psychomotor speed, language, verbal memory, executive function) in 130 healthy older adults (43.1% males, 56.9% females, ranging in age from 60 to 96). We measured physical function using the Physical Performance Test (PPT) & Timed Up and Go (TUG) tests. CR is represented by years of education, estimated premorbid verbal intelligence (AMNART), and occupational complexity across three levels (with Data, People, and Things). Data was analyzed using a series of hierarchical multiple regression models. **Results.** Estimated premorbid verbal intelligence contributed independently to global cognition, language, executive function, and verbal memory, while years of education and

occupational complexity with data significantly contributed to the prediction of executive function only. Higher physical functioning enhanced the protective effect of estimated verbal intelligence on language. The presence of the ApoE-4 genotype significantly reduced the protective effects of occupational complexity with people on psychomotor speed, and marginally on global cognition. In contrast, the protective effects of occupational complexity with things on global cognition, language, and executive functioning was enhanced in individuals who are ApoE-4 carriers. **Conclusion.** Findings suggest that cognitive reserve represents a combination of factors that independently determine the threshold for competence within specific cognitive domains, and that these relationships may differ based on physical function and genetic risk. This investigation has the potential to shed light on various factors that can either increase or decrease risk of cognitive decline and highlight the need for cognitive and physical intervention in at-risk older adult populations.

CHAPTER ONE

INTRODUCTION

In the United States, the number of persons over the age of 60 is projected to more than double in approximately the next 30 years, increasing from 40.2 million in 2010 to 88.5 million in 2050 (U.S. Census Bureau, 2010), along with the number of Americans diagnosed with dementia (Centers for Disease Control [CDC] and Prevention and Alzheimer's Association, 2007). Due to advancements in medical and pharmacological interventions, the average life expectancy has risen to more than 78-years-old, placing members of the aging population at an increased risk of developing cognitive and neurological disorders, such as dementia (Murphy, Xu, Kochanek, & Arias, 2018). While global aging is a significant leap for humankind, longevity also presents growing economic, social, and public health concerns with additional needs in long-term care and specialized health care workers. With the longevity boom giving rise to increased age-related risk for pathological cognitive decline, finding ways to maintain or improve older adults' cognitive health and quality of life has become a public health priority (Hendrie et al., 2006). Despite cognitive aging research over the past 50 years and growing evidence of age-related cognitive changes in brain structure and function, there is a shift towards emphasizing the modifiable risk and protective factors that may mitigate cognitive decline in old age (Anderson & Craik, 2017). Additional research is needed to fully understand how the biological, physical, mental, and environmental components that accompany normal cognitive aging interplay and how specific patterns of cognitive changes may progress to pathologic aging to identify the risks and protective influences on cognition in old age.

The structure of this review will first describe patterns of normal cognitive aging, with a brief description of neuroanatomical (e.g., structural and functional) alterations seen in aging brains that may account for cognitive decline, followed by a review of specific cognitive domains that typically decline with age and the mechanisms that account for them. Secondly, the chapter will outline the changes in cognition that occur in pathological human aging beginning with Alzheimer's disease (AD), the most common cause of dementia in older adults, and briefly explore Mild Cognitive Impairment (MCI)—a preclinical stage of AD. Thereafter, the concept of cognitive reserve, referred to as the ability to resist or delay the deleterious effects of brain pathology, will be extensively reviewed. The associations between proxies of cognitive reserve, modifiable lifestyle factors (e.g., physical abilities), known genetic risk markers, and varying cognitive domains are provided. Finally, a brief discussion of the current limitations in cognitive reserve literature, the study's aims and hypotheses, and the important implications for the development of diagnostic tools and treatments are provided.

Normal Cognitive Aging Throughout the Lifespan

Age-Related Biological Brain Changes

The trans-National Institutes of Health (NIH) on cognitive and emotional health created a Critical Evaluation Study in 2005 that referred to cognitive health as not only the absence of disease but also the development and preservation of cognitive structures and functions that allow older adults to maintain their social connectedness, sense of purpose, ability to function independently, ability to functionally recover from illness or injury and to cope with residual functioning deficits (CDC, 2007). Changes in cognition

are a normal part of the aging process that is extensively documented in the scientific literature (Harada, Love, & Triebel, 2013). Cognitive abilities develop from infancy to young adulthood, peaking at different stages of adulthood and declining in older adulthood at varying rates, presenting an inverted "U-shaped" trajectory (Craik & Bialystok, 2006). As humans age, having cognitively intact abilities that allows one to communicate effectively, initiate and carry out daily activities as well as maintain one's independent functioning (e.g., managing finances, remembering to take medications on time, driving or taking public transportation, remembering to turn off the stove after use, learning how to use a new modern technological device) becomes a larger priority.

Normal cognitive aging is mainly understood in relative terms, such that cognitive changes are considered in comparison to one's same-age peers (Kravitz, Kim, Faust-Socher, Rogers, & Miller, 2008). "Normal aging" is a heterogeneous concept that consists of many biological (structural and functional) changes in the brain, in addition to cognitive, physical, and lifestyle changes (Anstey & Low, 2004; Christensen et al., 1999; Christensen, 2001; Drag & Bieliauskas, 2010; Ylikoski, Ylikoski, Keskivaara, Tilvis, Sulkava, & Erkinjuntti, 1999). During the lifespan, the human brain undergoes structural changes at both microscopic and macroscopic levels associated with the development of cognitive functions from infancy to adulthood, and cognitive declines from middle to later adulthood (Sullivan & Pfefferbaum, 2006). Structurally, brain size and volume increase between birth and adulthood due to the growth of synaptic connections between neurons (gray matter) and the myelination of nerve fibers, while later adulthood is associated with a 10% loss of brain volume by age 80 compared to young adults (Drachman, 2006). Specifically, gray matter volume increases until adolescence and

decreases in neuron number thereafter due to synaptic pruning, which may eventually lead to neuronal atrophy in old age (Craik & Bialystok, 2006; Draganski, Lutti, & Kherif, 2013). Myelination develops at a different rate in various regions of the brain, with the frontal cortex last to be fully myelinated into one's thirties. Consequently, the frontal cortex is also the region most vulnerable to myelin damage, exhibiting a "last in, first out" phenomena (Bartzokis, 2004), such that aging affects the frontal lobes first, where structural and functional declines are observed at a faster speed than the temporal, parietal, and occipital regions, particularly after the age of 70 (Craik & Bialystok, 2006; Drag & Bieliauskas, 2010). This concept is supported by findings of significant gray matter (Raz et al. 1997) and white matter (Head et al., 2004) changes in the frontal regions in older adults, suggesting that myelinated fibers in this area are most vulnerable to atrophy with age and damage (Craik & Bialystok, 2006; West, 1996). The hippocampus, involved in memory processes, is also another frequently studied region that shows structural changes in normal aging, such that atrophy in this region is associated with memory loss compared to the surrounding entorhinal cortex area (Head, Rodrigue, Kennedy, & Raz, 2008; Morrison & Hof, 1997; Raz 2005; Raz, Gunning-Fixon, Head, Dupuis, & Acker, 1998). Additionally, select subcortical structures, such as the basal ganglia and thalamus, are vulnerable to age-related atrophy (Lezak, Howieson, Loring, & Fischer, 2004).

Beyond these structural changes, the cerebrovascular system also changes across the lifespan, with evidence of decreases in resting blood flow (metabolic rate of oxygen consumption), vascular reactivity to different chemical modulators (Gazzaley & D'Esposito, 2005), and functional blood flow seen in neuroimaging studies, particularly

to the prefrontal and temporal lobes (Krausz, Bonne, Gorfine, Karger, Lerer, & Chisin, 1998). Researchers have used functional imaging, such as fMRI, to measure brain activity by detecting blood flow alterations. As an individual engages in a cognitive task, blood flow increases in certain brain regions specific to the task, and these areas are illuminated on functional imaging scans (Salat, 2011). Researchers have consistently found that older adults are less lateralized relative to younger adults, such that they presented with increased bilateral frontal activation while their younger adult counterparts showed lateralized activation when completing the same cognitive tasks (Bäckman et al., 1997; Cabeza et al., 1997; Cabeza, 2002; Cabeza, Daselaar, Dolcos, Prince, Budde, & Nyberg, 2004; Craik, Klix, & Hagendorf, 1986; Mattay et al. 2002; Reuter-Lorenz et al., 2000). For example, on a verbal working memory task, younger adults activated the left prefrontal cortex (PFC) while older adults bilaterally activated both the left and right prefrontal cortex (Reuter-Lorenz et al., 2000). This bilateral activation is thought to represent a compensatory mechanism whereby the right hemisphere is over-activated to compensate for declining cognitive resources in the left PFC. These findings are in support of the Functional Compensation Theory that proposes that older adults recruit additional alternate brain regions as compared to younger adults in completing the same tasks in order to offset neurocognitive decline, particularly when engaged in demanding and complex cognitive tasks as normal aging limits the amount and efficiency of cognitive resources (Drag et al. 2010).

Neuropsychological Age-Related Cognitive Changes

In conjunction with structural and functional changes, age-related cognitive changes significantly impact global functioning, with the most significant age-related cognitive declines observed in the domains of memory, processing speed, and executive functioning (Rogers, Kang, & Miller, 2007; Zelinski, Dalton, & Hindin, 2011). Similar to how age-related changes in brain structure and function are not uniform across the whole brain, decline is not universal across cognitive domains or older adults but varies with some domains declining at a faster rate than others (Glisky, 2007). Although these domains decline at different rates, many of these basic and complex cognitive abilities are not independent of one another and function as a connected network (Zelinski et al., 2011).

Cognitive decline is typically gradual and not clinically significant until after age 60 (Schaie, 2005). Access to levels of cognitive processes develop near the extremes of aging; children are able to optimally access lower cognitive processes (e.g., object-naming, semantic language, word-finding, episodic recollection) and gradually build to higher levels (e.g., speech and language processing, decision making, executive control) as cognitive systems differentiate into specific subdomains (Glisky, 2007). In contrast, as we age, older adults are able to access higher conceptual levels but progressively lose access to the lower-level cognitive processes, such as semantic language (Baltes, Cornelius, Spiro, Nesselroade, & Willis, 1980; Burke, MacKay, & James, 2000). Thus, cognitive-developmental processes occur similarly in old age as in youth but in reverse.

Age-related changes in cognitive functioning can be assessed by tests of global functioning, such as the Mini-Mental State Exam (MMSE) or by neuropsychological tests

designed to measure specific cognitive domains (Folstein, Folstein, & McHugh, 1975). Many neuropsychological tests measure specific cognitive domains of intelligence. It is widely agreed that intelligence can be divided into two general categories—crystallized and fluid intelligence (Drag & Bieliauskas, 2010). Crystallized intelligence refers to skills and knowledge that are familiar, stable, can potentially improve through the life course due to experience, and is maintained until the 60s or later (Horn, 1970; Horn & Donaldson, 1976). Verbal knowledge is an example of crystallized intelligence (Harada, 2013). Fluid intelligence refers to the ability to problem-solve, reason, and adjust to unfamiliar situations independent of what is learned (Harada, 2013) and consists of six primary cognitive domains, including attention, executive functioning, memory, processing speed, language, and visuospatial functioning (Drag & Bieliauskas, 2010). Fluid intelligence tends to be more affected by the aging process than crystallized abilities (Rogers et al., 2007). A brief overview of the cognitive changes in each domain and its subcomponents are provided below to highlight age-related brain structural effects. At a group level, there is a decline between one and two standard deviations (15–30 IQ points) in fluid-type abilities between the ages of 20–70.7. Thereafter, the average decline in fluid abilities accelerates to about 0.5 of a standard deviation per decade (Anstey & Low, 2004).

Processing Speed

Processing speed is defined as the rate of mental quickness, perception, and execution of decisions (Salthouse, 1996). Processing speed is found to increase from infancy to young adulthood but decline from the 30s and thereafter (Corral, Rodriguez, Amenedo, Sanchez, & Diaz, 2006), with a 20% drop in processing speed by the age of 40 and approximately 40-60% reduction by the age of 80 (Christensen, 2001). The age-related slowing of processing speed presents itself especially when older adults are engaged in complex tasks that require speed in response time, such as noticing and responding to changing road conditions while driving, understanding and remembering new and large amounts of information simultaneously, being able to "think on the spot," and quickly retrieve a specific word during a conversation (Zelinski et al., 2011). For example, the average 25-year-old can copy 71-to-75 symbols on a 120-second timed task of graphomotor speed, whereas the average 70-year-old only copies 47-to-52 symbols in the same amount of time (Wechsler, 2008).

Several longitudinal studies have revealed that processing speed is the cognitive domain most sensitive to aging and a primary mediator of age-related cognitive changes in other domains (Bryan, Luszcz & Crawford, 1997; Fillit et al., 2002; Salthouse, 1996; Sliwinski & Buschke, 1999), also known as the "processing speed hypothesis." According to this theory, processing speed is hypothesized to represent a bottleneck or primary factor that contributes to many of the age-related deficits in other cognitive domains, including declines in verbal and visual memory, abstract reasoning, naming, and verbal fluency (Harada et al., 2013). For example, Bryan et al. (1997) found that once processing speed was controlled for in the analyses, declines in verbal fluency among

healthy older adults dissipated, leading researchers to arrive at two assumptions: 1) verbal fluency and other language-related tasks are preserved in later life, and, 2) age-related cognitive declines are due more to problems with processing speed rather than language deficits. Older adults that exhibited slowed processing speed have also performed poorly on tests of visuospatial functioning (Harada et al., 2013). Thus, older adults may perform poorly because specific cognitive tasks rely on fast processing speed.

The processing speed hypothesis has been extensively supported by research; however, several longitudinal studies have shown that the hypothesis may better explain between-group differences rather than intra-individual differences in cognitive aging, such that as processing speed declines with age, declines in other cognitive domains may be independent of these processing speed deficits (Sliwinski & Buschke, 1999; Zimprich, 2002).

Language

Different types of language processes involved in both crystallized and fluid intelligence are generally found to be resistant to age-related cognitive decline and even show improvements into the 70s as older adults increase their vocabulary (Park & Reuter-Lorenz, 2009). Semantic memory, a system of general word knowledge, has been consistently found to be preserved in healthy old age (Burke & Shafto, 2011). Specifically, abilities associated with vocabulary and grammar show a minimal loss from age 70 and on (Salthouse, 1996). However, older adults present with declines in verbal fluency, perhaps due to slower reaction times, but are also prone to more errors naming objects within categories (Salthouse, 2010; Singh-Manoux et al., 2012). Specifically,

older adults report word-finding difficulties and are more likely to experience a “tip of the tongue” phenomenon when attempting to recall familiar words, such as names of people or objects (Burke & Shafto, 2008). Such words and information are typically not lost from memory but can be retrieved later either spontaneously or with cues, suggesting difficulties with retrieval (related to executive dysfunction) rather than language abilities.

Memory

Memory difficulty is the most common complaint amongst older adults, with 22-56% of community-dwelling older adults endorsing some aspect of memory lapse (Rogers et al., 2007). Several researchers have posited that memory is a domain that is also significantly influenced by a number of other processes, such as processing speed, working memory, executive control processes, sensory abilities (i.e., changes in vision and hearing), and the use of higher-order strategies to improve learning, memory and retrieval (Isingrini & Taconnat, 2008). Declines in memory typically emerge after age 40 (Corral et al., 2006), with gradual and progressive decline with advanced age (Schaie, 1994). Subcomponents of memory show different rates of normal age-related decline, with some aspects notably declining faster than others, such as working memory (Salthouse & Babcock, 1991), select aspects of long-term memory (i.e., declarative memory) (Drachman, 2006; Rioux et al., 1995; Zec, 1995), and prospective memory (Zimmerman & Meier, 2006).

Working Memory

Several studies have suggested that working memory—the ability to actively manipulate information while it is in temporary storage—is essential in understanding the trajectory of cognitive aging, as it appears to be among the most sensitive to decline in old age relative to other cognitive functions (Hertzog, Dixon, Hultsch, & MacDonald, 2003; Iachini, Iavarone, Senese, Ruotolo, & Ruggiero, 2009; Rogers et al., 2007). Working memory is subject to developmental change in early and late-life (Mayer & Moreno, 1998) as it is found to peak from infancy to young adulthood and gradually decline in old age at varying rates, presenting an inverted "U-shaped" developmental trajectory (Craik & Bialystok, 2006; Diamond, 2006). Working memory is especially important in the childhood and adolescent years as it significantly influences academic outcomes in English and mathematics (Gathercole, Pickering, Knight, & Stegmann, 2004) and is linked to key learning outcomes as information needs to enter into working memory to be stored in long-term memory (Cowan & Alloway, 2009). As people age and reach late adulthood, older adults are found to perform more poorly on tests of working memory than their younger counterparts (Brickman, Habeck, Zarahn, Flynn, & Stern, 2007; Voineskos et al., 2012).

Aging greatly affects working memory due to its significant demands on cognitive resources, as it requires greater efforts in information processing in addition to basic storage (Drag & Bieliauskas, 2010). Deficits in working memory are commonly due to reduced ability to inhibit and efficiently process information (Salthouse & Babcock, 1991), allowing irrelevant information to enter into one's working memory (Zec, 1995). For example, individuals' working memory can be affected by distractions,

such that when older adults are asked a distracting question while looking at a telephone number, they may have difficulty recalling the number. Increases in working memory impairments occur with age as the tasks requiring active participation of working memory become more complex (Drag & Bieliauskas, 2010). That is, older adults may not have difficulties remembering a few items on a grocery list but may struggle to calculate prices and navigate around the store to find the next item on a list (Dobbs & Rule, 1989).

Long-term Memory

Long-term memory is often divided into declarative memory and procedural memory. Declarative (or explicit) memory consists of knowledge of facts, objects, and events that can be consciously learned, recalled, or "declared (Rogers et al., 2007) and can be further subdivided into episodic and semantic memory, with select aspects of declarative memory more so impacted by the aging process. Additionally, declarative memory formation generally consists of three main processes: encoding (learning), storage (retention/consolidation), and recall (retrieval).

Episodic memory. Episodic memory—the ability to recall past personal events related to a specific time and place—has been consistently shown to decline with age (Rogers et al., 2007). Individuals rely on episodic memory to think back to a specific time—Tulving referred to this as "mental time travel" (Tulving, 2002). Problems with episodic memory, particularly recent episodic memory, may involve a deficiency in encoding, storage, and retrieval (Glisky, 2007). At the input level, aging can affect older adults' abilities to encode new information (Delis, Kramer, Kaplan, & Ober, 2000;

Haaland, Price, & Larue, 2003). Older adults yield weaker scores on a variety of learning and memory tests compared to younger adults. Generally, they have more difficulty remembering newly presented information, such as a word list, details of events, or the context in which something occurred (Darowski, Helder, Zacks, Hasher, & Hambrick, 2008; Zelinski et al., 2011). This problem may be due to the fact that older adults have greater difficulty implementing encoding and learning strategies, as they encode information in a less meaningful or efficient way with less elaboration or rehearsal, resulting in less distinctive memory traces that are similar to others in the memory system. Hence, interfering with subsequent memory processes, such as later retrieval of previously learned and stored information after a delay (Economou, 2009; Craik, 1983; Haaland et al., 2003; Price, Said, & Haaland, 2004). For example, many common daily memory lapses experienced by older adults, such as forgetting where one has parked their vehicle, are due to poor encoding. Neuroimaging studies utilizing functional magnetic resonance imaging techniques (fMRI) have also shown age-related decreases in functional activity in the prefrontal cortex at encoding stages, which has been associated with poorer subsequent memory performance (Cabeza, 2001; Daselaar, Veltman, Rombouts, Raajimakers, & Jonker, 2003).

At the *storage and consolidation* level of episodic memory processing, medial temporal lobe structures such as the hippocampus are involved. Storage consists of the integration and binding of various aspects of information into a composite memory trace; memory problems can arise when information is not entirely bound to its spatial and temporal context (Glisky, 2007). Finally, at the *retrieval* level, older adults appear to have the most difficulty on cognitive tests with spontaneous/free recall, and, to a lesser

degree, difficulty in cued recall, but minimally in recognition memory; however, these are dependent on encoding as mentioned previously (e.g., well-learned information is easier to recall). Retrieval is sensitive to the aging process, as the self-initiated task of searching one's cognitive library in recall is mentally taxing for older individuals who already have limited resources (Craik, 1986). However, when environmental support or cues are provided at the encoding and retrieval stages, the resource demands of encoding and retrieval are minimized. Evidence from neuropsychological and neuroimaging studies has revealed that the process of strategic retrieval relies on the prefrontal cortex and hippocampus (Davidson & Glisky, 2002; Nolde, Johnson, & D'Esposito, 1998). Despite impaired encoding and recall of novel information, older adults generally have intact recognition and cued recall when given a hint or asked specific questions about what they had previously learned, indicating impairments in recall (Rogers et al., 2007). Taken together with the normal cognitive aging process consisting of deficits in processing speed and memory, it appears that older adults do not have a rapid rate of forgetting but rather take longer to learn new information and struggle to retrieve this information after some time has passed once it is learned and stored.

Semantic memory. Episodic memory is commonly compared to semantic memory—the ability to recall learned, practical knowledge and facts (e.g., first U.S. president)—which appears to remain stable with age (Nilsson, 2003; Park, 2000). Therefore, many of the long-term memory deficits are largely due to inefficient encoding and retrieval rather than storage/retention over time (Haaland et al., 2003; Small, Stern, Tang, & Mayeux, 1999; Zec, 1995).

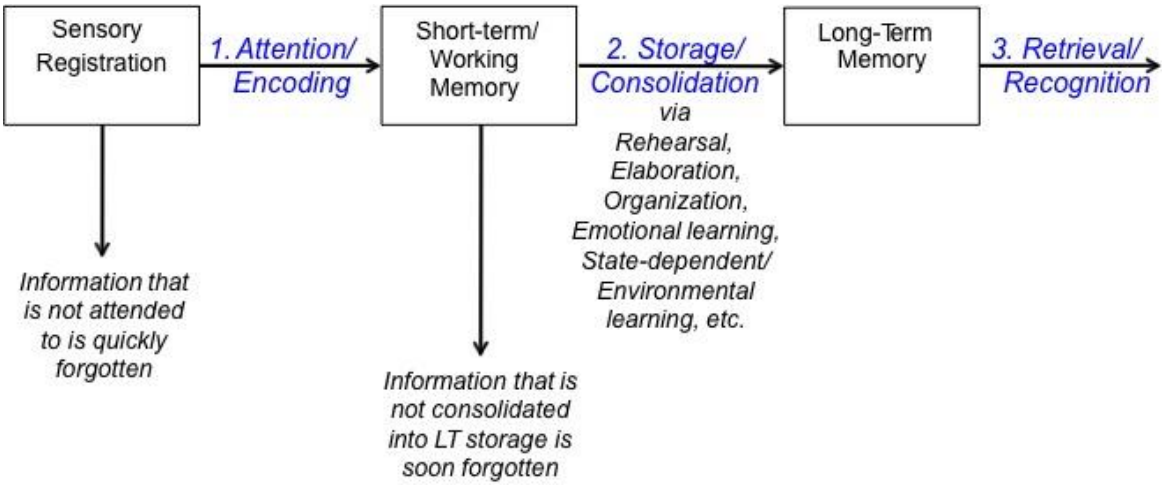

Figure 1. Stages of declarative (explicit) memory processing and formation. Adapted from Lee, G.J. (2016). Lecture on Neuropsychological Assessment: Memory. Personal Collection of Lee, G.J., Loma Linda University, Loma Linda CA.

Prospective memory. In addition to reduced aspects of declarative memory, older adults also commonly report increased difficulty in prospective memory, which is the ability to remember to engage in an activity in the future (Maylor, 1996; Salthouse, Berish, & Siedlecki, 2004; West & Bowry, 2005; Zimmermann & Meier, 2006). Prospective memory is necessary for performing instrumental activities of daily living (iADLs), particularly in older adulthood, such as remembering to pay the bills, take one's medications, return a library book, and attend upcoming appointments and events. Older adults often use various external aids, such as calendars and notepads, to remind themselves of these activities and have greater difficulty with tasks requiring self-initiation that do not have good cues for retrieval. Individuals with frontal lobe deficits often have similar difficulties with these tasks (Rogers et al., 2007), indicating that age-related deficits on tasks of daily living may also be due to declines in frontal lobe functioning (e.g., ability to plan, organize, initiate, inhibit, pay attention).

Remote and procedural memory. Conversely, non-declarative memory consists of the ability to remember implicit information or unconscious learning. Procedural ("knowing how") memory, which is referred to as the ability to remember ingrained motor and cognitive skills (e.g., riding a bike, swimming, reading a book), are found to be resilient to aging across the lifespan as they are acquired skills over time through extensive practice (Lezak, Howieson, & Loring, 2012). The higher the level of expertise, the longer it will take for performance to be affected by aging though some aspects of the skill may decline. For example, a pianist's fingers may be slower in movement with age. Still, overall ability to play a familiar song and even the speed in which he or she plays are maintained because other aspects of one's piano skills adjust (e.g., scanning the piano keys ahead; Müller et al., 2016). Procedural memory depends on several brain regions, such as the basal ganglia and cerebellum (Glisky, 2007).

Remote memory (e.g., memory for events and things that occurred many years prior) has also been found to be generally age-resistant alongside semantic and procedural memory. These preserved memories have a common thread in that they are more or less automatic and require minimal effort to recall, as they are deeply embedded in our unconscious or "body's" memories (Rogers et al., 2007). Despite select aspects of memory being preserved even with advancing age, many older adults may hone in on their memory problems and over-generalize or over-interpret these memory deficits, particularly older adults with higher education, as they are often keener to notice changes in cognition and experience symptoms of depression as a result (Rogers et al., 2007). Older adults with higher education typically engage in a comparative process in which they compare their current abilities to that of their younger selves, leading them to

become concerned with significant cognitive decline rather than chalking it up to normal expressions of cognitive aging.

Attention

Attention is a basic but complex cognitive process that generally refers to the ability to focus on a specific stimulus and has multiple subcomponents that specialize in different stages of attentional processing. Thus, deficits in attention can have a significant impact on one's ability to function in daily life. Aspects of attention are involved in all other cognitive domains, such as in memory and executive functioning, except when a task has become routine or automatic (Harada et al., 2013; Glisky, 2007). Attention consists of different levels of complexity, including simple attention, sustained attention, selective attention, and divided attention, with each aspect distinctive from one another in part or whole. Age-related effects are also shown to vary between them.

Simple attention. Simple attention is the most basic ability to attend to information when it is presented without distraction or other impediments. In contrast, sustained attention reflects an individual's ability to maintain focus and concentration on a task over an extended period. Simple attention span of older adults remains relatively stable throughout the aging process (Salthouse & Babcock, 1991; Sliwinski & Buschke, 1999). The average attentional capacity for adults ranges from 5 to 9 (7+/- 2) numbers (Miller, 1956). Although there may be a mild decline in attention with age, it typically remains within the normal limits of this 7+/- 2 span. For example, when individuals are asked to repeat numbers in correct order, the average 25-year-old is able to recall seven

numbers, whereas the average 80-year-old may recall five or six (Anstey & Low, 2004; Ryan, Lopez, & Paolo, 1996). This may be reflective of the experience of many older adults who report mild difficulty listening and paying attention to conversations or when performing simple tasks, although they may notice more difficulty with complex tasks involving higher executive skills.

Selective attention. Simple attention or the ability to focus on a specific task while inhibiting irrelevant information, and divided attention—the ability to maintain focus on dual-tasks and task-switching—are affected by normal aging, while tasks of sustained attention requiring simple attentional processes are found to remain stable with age until at least age 40 with subsequent normal decline (Anderson & Craik, 2017; Berardi, Parasuraman, & Haxby, 2001; Carlson, Hasher, Connelly, & Zacks, 1995; Carriere, Cheyne, Solman, & Smilek, 2010; Fortenbaugh et al., 2015; Lezak et al., 2012; Okonkwo, Crowe, Wadley, & Ball, 2008).

Divided attention. Performances in divided attention or attention switching have been found to significantly decline with age, particularly on tasks of greater complexity requiring the processing of two or more tasks and information sources simultaneously (McDowd & Craik, 1988; Glisky, 2007). Older adults perform more poorly than younger adults in dividing their attention and have more difficulty allocating attentional resources when instructed to vary task priority (Tsang, 1998). Additionally, older adults perform slower than their younger counterparts when asked to switch their attention from one task to another, as this requires a change of mental set (Verhaeghen & Cerella, 2002).

Executive Functioning

Executive functioning is mostly referred to as the "CEO" of the brain and consists of a set of cognitive processes that allow individuals to engage in self-monitoring, planning, goal-directed behavior, problem-solving, divided attention/set-switching, sequences of action, inhibition of irrelevant stimuli, mental control, reasoning, working memory, and mental flexibility— all of which constitute a higher-order construct and are used intentionally to regulate behavior (Corral et al., 2006; Gunstad et al., 2006). Some components of executive functioning are sensitive to aging effects, while others are not. For example, abstract interpretations of proverbs (Harada et al., 2013), abstract verbal reasoning and non-verbal problem-solving remain relatively stable with age, mainly if the task is complex and older adults are provided with opportunities for practice (Lezak et al., 2004; Royall, Palmer, Chiodo, & Polk, 2005). In contrast, research has shown that adults typically notice a decline in skills such as concept formation, abstraction, and mental flexibility, which gradually decline beginning at age 40 and especially after age 70, as older adults have been observed to think more concretely than younger adults (Lezak et al., 2012; Salthouse, 2010; Oosterman et al., 2010; Singh-Manoux et al., 2012; Wecker, Kramer, Hallam, & Delis, 2005). Craik (1977) also asserted that older adults have a harder time dividing their attention, or in other words, multitasking, "either between two input sources, input and holding, or holding and responding" except when the task is simple. Additionally, the process of shifting between two or more sets of information or instructions becomes increasingly difficult with age (Lezak et al., 2004), particularly when the information is presented in auditory versus visual form (Zec, 1995).

Researchers have found age-related decline in dual-task performance (Verhaeghen & Cerella, 2002).

Executive functioning consists of a wide range of cognitive abilities that heavily rely on the integrity of the prefrontal cortex, which itself is heterogeneous in structure and function with widespread connections throughout the cerebrum (see Drag & Bieliauskas, 2010 for a review). Failure to perform certain executive functioning tasks, such as planning or set-shifting, is associated with prefrontal structural volume and a loss in white matter integrity in older adults (Elderkin-Thompson, Ballmaier, Hellemann, Pham, & Kumar, 2008). In sharing vast connections with other brain regions, executive functioning is dependent on various cognitive domains, such as attention and memory. Reuter-Lorenz and Sylvester (2005) suggested that age-related deficits in working memory, a form of executive function, may be affected by an impairment in inhibitory control of attention, which may explain older adults' difficulties in driving. Treitz and colleagues (2007) demonstrated that executive functioning does not decline linearly throughout the life span but instead sharply declines after 60 years of age.

Due to the heavy involvement of the frontal regions in executive functioning and in other areas of cognition, the extent to which executive skills contribute to overall age-related cognitive decline has led researchers to theorize a frontal-aging hypothesis in neuropsychological aging (see Rogers et al., 2007 for a review). The frontal-aging hypothesis originated from findings that areas of cognitive decline most sensitive to aging are dependent on frontal and executive systems. For example, fluid intelligence alongside aspects of executive function (e.g., working memory, response inhibition, divided attention, learning, attention) are all affected by the normal aging process and associated

with the prefrontal cortex and associated frontal-subcortical pathways, including the frontal-striatal-thalamic circuit. Hence, these results suggest that the frontal lobes are more vulnerable to age-related cognitive decline than other cortical regions, whereas cognitive functions independent of frontal lobes are relatively preserved from the aging process (West, 2000). This theory also supports the "last in, first out" phenomenon, which suggests that frontal lobes, which are the last to become fully myelinated in adulthood, are also the first to functionally and structurally decline in older adulthood at a greater speed than other cortical regions (Bartzokis, 2004; Craik & Bialystok, 2006; Haug, Barmwater, Eggers, Fischer, Kuhl, & Sass, 1983; Haug & Eggers, 1991; Raz, 2005).

Since processing speed is also highly dependent on myelination and neutrally localized with prefrontal circuitry (Grady & Craik, 2000), the processing speed hypothesis is also subsumed within the frontal-aging hypothesis. However, whereas some cognitive functions can be localized to small-scale neural networks or areas—such as visual-spatial frequency and orientation processing (Mazer, Vinje, McDermott, Schiller, & Gallant, 2002)—other processes, such as executive control, may be dependent on the larger-level organization of distributed networks of brain areas (Braun et al., 2015). The complexity of both the neural and cognitive functions makes exact mapping between brain and behavior difficult (Glisky, 2007). Thus, a larger scale organizational approach may better capture the differentiation of the brain and its intricate response to aging, as it is especially relevant to understanding brain and cognitive reserve, which relies on complex psychological constructs that involve distributed circuits (Medaglia, Pasqualetti, Hamilton, Thompson-Schill, & Bassett, 2017).

Table 1. Summary of the normal aging neuropsychological profile (modified from Rogers, Kang, & Miller, 2007)

Domain	Stable into late adulthood	Declines in late adulthood
Global Intelligence	Crystallized intelligence Verbal knowledge	Fluid intelligence
Attention	Simple attention span (7+/- 2 span)	Sustained attention Selected attention
Language		Phonemic fluency
Processing Speed		Mental and psychomotor speed
Memory	Remote long-term memory Semantic memory Procedural memory Recognition	Working memory Recent long-term memory Episodic long-term memory Declarative memory (Encoding and delayed recall) Prospective memory
Executive Functioning	Set-shifting (visual information) Some abstract verbal reasoning Non-verbal/simple problem solving	Working memory Complex problem-solving Divided attention Inhibition Set-shifting (verbal information)

Pathological Cognitive Aging in Adulthood

Major neurocognitive impairment, or otherwise more universally known as dementia, is considered the third and final stage of abnormal cognitive decline (beyond what would be considered "normal" age-associated declines) and is conceptualized as an age-related disorder that typically occurs in late adulthood or over the age of 65 (Rogers et al., 2007). Although the prevalence of dementia has significantly declined (11.6% to 8.8%) between 2000 and 2012 (Langa et al. 2017), dementia was estimated to occur in 35.6 million individuals in the United States in 2010, with a number that is expected to reach 13.8 million people by 2050 (Plassman et al., 2007; Prince, Bryce, Albanese, Wimp, Ribeiro, & Ferri, 2013; Hebert, Weuve, Scherr, & Evans, 2013). The prevalence of dementia exponentially grows with increasing age (Jorm & Jolley, 1998), with the risk

steadily rising until age 85 or 90 and continuing to increase in the oldest old, although less rapidly. More specifically, dementia occurs in more than 5-10% of individuals age 65 and older and 30-37% of those 85 years and older, with the prevalence doubling every five years after age 65 (Jorm & Jolley, 1998; Plassman et al., 2007). Dementia is also greater among women than among men, mostly because women live approximately 4.5 years longer than men (Hugo & Ganguli, 2014; Riedel, Thompson, & Brinton, 2016).

As dementia is a complex and multifactorial disease, it may stem from a variety of etiologies, such as medical diseases, lifestyle and environmental factors, demographic factors, family history, and biological predispositions and alterations. Among neurodegenerative disorders that cause dementia, the most common form is Alzheimer's disease (AD). Our study will specifically be examining risk and protective factors related to AD below.

Alzheimer's Disease

According to the Alzheimer's Association published in 2018, AD occurs in approximately 5.7 million individuals in the United States, with an estimated 200,000 people under the age of 65 diagnosed with early-onset AD (Hyman et al., 2012) and one in ten (10%) Americans diagnosed with AD aged 65 and older (Hebert et al., 2013). The onset of AD typically occurs between the ages of 40 and 90, although most individuals are diagnosed after age 65 (Cummings, 2003). Although the specific pathogenic sequence of events leading to AD remain unknown, researchers have consistently identified the hallmark pathological characteristics of the disease as consisting of extracellular amyloid

plaques, intracellular tau neurofibrillary tangles, progressive synaptic loss and neuronal death that ultimately disrupt the process of neurotransmitter transmission.

Various genetic risk factors play a critical role in the clinical manifestation of AD, with many epidemiology studies demonstrating that a positive family history places individuals at a greater risk for AD, regardless of whether an individual carries the gene for AD (Heyman, Wilkinson, Stafford, Helms, Sigmon, & Weinberg, 1984; Mendez, Underwood, Zander, Mastri, Sung, & Frey, 1992; Donix et al., 2010). Specifically, individuals with a first-degree relative with dementia have a 10-30% increased risk for the disease (Van Duijn et al., 1991). Apart from the autosomal dominant mutations known to cause AD (which only account for approximately 5% of cases), the Apolipoprotein (ApoE) ε4 allele is the strongest AD genetic risk marker that has been found to date (Dumurgier & Tzourio, 2020). ApoE is a protein that transports cholesterol between cells in the brain, which plays a critical role in neuronal growth, neuronal maintenance and repair, and synaptic plasticity in the CNS (Liu, Kanekiyo, Xu, & Bu, 2013). The ApoE gene on chromosome 19 is significantly linked with late-onset AD and comes in three variants that encode proteins (ε2, ε3, and ε4; O'Brien & Wong, 2011; Strittmatter et al., 1993). The ApoE ε4 allele (ApoE-4) is the first gene identified for risk of AD. It remains the one with the most impact, as it is overrepresented in patients with AD relative to the general population, in approximately 10-30% of cases (Kaiser, Miller, Siddarth, Ercoli, & Small, 2013; Singh, Singh, & Mastana, 2006). ApoE-4 is strongly associated with poor efficiency at transporting brain cholesterol, which may lead to reduced long-term potentiation, delayed neuronal development, lower synaptic plasticity, and reduced clearance of amyloid-beta—all of which result in increased brain Aβ

deposition, which is the hallmark biomarker of AD (see O'Donoghue, Murphy, Zamboni, Nobre, & Mackay, 2018 for a detailed review). ApoE-4 carriers are at an increased risk for AD and have a lower average age of dementia onset (Corder et al., 1993; Van Gerven, Van Boxtel, Ausems, Bekers, & Jolles, 2012). In addition to older age (Brookmeyer, Gray, & Kawas, 1998; Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007; Hebert et al., 2013), individuals who inherit the ApoE-4 allele (Mayeux et al., 1993; Mahley, Weisgraber, & Huang, 2009; Liu et al., 2013) have the greatest risk for AD. In contrast, the ε3 allele of ApoE has been found to promote neurite growth and dendritic plasticity (Arendt, 2003). Thus, the effect of ApoE on AD risk may be entirely explained by its impact on Aβ deposition (O'Brien & Wong, 2011).

Inheritance of one or two ε4 alleles increases the likelihood of developing AD and makes its mean age of onset earlier than in individuals with the ε2 and or ε3 alleles (Corder et al., 1993; Saunders et al., 1993). Specifically, inheritance of a single copy of the ε4 allele may increase the likelihood of developing AD by three-fold, while the inheritance of two ε4 alleles from both parents may exponentially increase the risk by fifteen-fold (Singh et al., 2006). Thus, the ApoE-4 protein helps precipitate AD later in life, primarily in individuals' 60s and 70s. The greatest risk factors for individuals with late-onset AD are older age (Hebert et al., 2010; Hebert et al., 2013), a family history of AD (Green et al., 2002; Fratiglioni, Ahlbom, Viitanen, & Winblad, 1993; Lautenschlager et al., 1996; Mayeux, Sano, Chen, Tatemichi, & Stern, 1991), and being a carrier of the ApoE-4 gene (Farrer et al., 1997; Saunders et al., 1993). There is also evidence that inheritance of the ε2 allele may protect against the development of AD (Corder et al., 1994). It is important to note that although inheritance of ApoE-4 is considered a risk

factor, it is not a certainty or direct diagnostic marker of developing AD (Selkoe, 2001). Additionally, the effect of ApoE-4 on the risk of AD appears to wear off by the eighth decade of life, with some humans who are homozygous for the ε4 isoform showing no symptoms of AD even at age 90 or beyond. Many individuals who develop AD also do so without having ε4 alleles.

Mild Cognitive Impairment

Mild cognitive impairment (MCI) is considered a precursor to dementia, an intermediate state between normal cognition and dementia (Albert et al., 2011; Petersen et al., 2001), with essentially preserved functional abilities (Hugo & Ganguli, 2014). Although dementia is typically considered progressive and irreversible, results from conversion studies suggest that reversal effects can occur in the prodromal, MCI stage when the brain still has sufficient neuroplasticity and the trajectory of the disease is most modifiable. Many individuals with MCI can remain at the same level over a few years (~51%), while others (~35%) progress towards a form of dementia (Pandya, Lacritz, Weiner, Deschner, & Woon, 2017), particularly AD (Petersen et al., 1999). Annual progression rates of MCI to dementia are 10% to 15% of clinical samples and 6% to 10% of community samples, and the deficits associated with MCI typically remain relatively stable and plateau until three to six years prior to diagnosis of dementia (see Oltra-Cucarella et al., 2018 for review). However, some individuals have been found to improve and return to baseline cognitive functioning, although this has been found to vary with 3-24% rate of reversion at one-to-two years post-baseline in clinic-based and community-based studies (Canevelli et al., 2016; Malek-Ahmadi, 2016; Thomas et al.,

2019).

One possible explanation for varying rates of decline observed in MCI patients is that there may exist a reserve that protects the brain from cognitive damage. The concept of cognitive reserve posits that different aspects of innate individual and environmental factors may give an individual advantage that allow the individual to more effectively face physiological and anatomical brain changes as a consequence of normal aging, pathological aging, or brain injury. This additional reserve may in turn slow down, potentially stabilize, or improve declining trajectories of cognitive function, and counterweight elevated genetic risk (Stern, 2002).

Cognitive Reserve

As aforementioned, neurodegenerative disease processes may begin decades before a diagnosis of dementia, indicating that the preclinical stage may be the optimal window for prevention and disease-modifying pharmacological intervention; however, clinical presentation varies inter-individually, with some individuals demonstrating noticeable cognitive dysfunction while others their same-age with a similar degree of brain neuropathology show no clinical symptoms of disease (Mortimer, Snowdon, & Markesbery, 2003). The concept of cognitive reserve (CR) provides an explanatory framework for examining this heterogeneous effect of cognitive aging (Christensen, Anstey, Leach, & Mackinnon, 2008). It accounts for the repeated observation that approximately 25% of older adults who are cognitively normal during life have evidence of advanced AD pathology (amyloid plaques and neurofibrillary tangles) in their brains postmortem (see Scarmeas & Stern 2004 for a review). CR is an umbrella term that is

defined as an individual's ability to cope with or "resist" the deleterious effects of brain pathology, brain degeneration, and/or age-related expressions of cognition symptoms to maintain a stable level of functioning (Stern, 2002; 2009).

Neurophysiological mechanisms that drive the disjunction between the degree of brain damage and clinical manifestation of dementia have not been fully understood since the insurgence of the "reserve" phenomenon; however, two common models of reserve have been proposed that are said to operate in both cognitively healthy individuals and those with brain damage: passive ("brain reserve") and active ("cognitive reserve;" Stern, 2002; see Figure 2). The first model is coined the "passive model" (also referred to as the "brain reserve" model), where reserve is referred to the amount of brain damage a person can sustain before reaching a threshold for clinical manifestation (Stern, 2009). In other words, there is a proposed critical threshold of brain reserve capacity that individuals have, and when depleted, clinical and functional deficits appear. In this model, findings from neuroimaging or autopsy, such as whole brain (Coffey, Saxton, Ratcliff, Bryan, & Lucke, 2000; Stern, 2006), regional volume (Perneczky, Drzezga, Diehl-Schmid, Li, & Kurz, 2007), head circumference (Perneczky et al., 2010), lesion loads (Cader, Cifelli, Abu-Omar, Palace, & Matthrews, 2006), cerebral metabolism (Cohen et al., 2009), and synaptic count serve as measures of brain reserve, with more advanced network analysis measures of structural connectivity recently employed to accurately assess the relationship between brain damage and individual differences in cognitive functioning (Medaglia et al., 2017).

Passive Reserve Model

The passive model has been supported by many findings demonstrating a significant relationship between brain physiology and cognitive functioning in individuals with MCI and AD, such that patients with greater brain reserve (e.g., larger brain volume, head circumference, neurons, and more synaptic connections) have been shown to experience less cerebral atrophy, and slower and less severe cognitive and functional impairments compared to those with less brain reserve (Katzman et al., 1988; see Medaglia et al., 2017 for a thorough review). It is hypothesized that individuals with higher brain reserve can sustain more neuropathology or damage before symptoms become apparent than those with low brain reserve, as healthy brain tissue is able to accommodate for the lost neurons and synapses. However, the effects of the same brain injury may be readily noticeable in those with lower brain reserve due to the limited availability of resources and rapid expenditure of these neural resources (Desai, Grossberg, & Chibnall, 2010). Although many studies have independently examined the role of brain reserve in different disease processes, the brain reserve model has many limitations, with the largest being that it is too "passive" in accounting for individual variations in cognitive and functional aging and assumes that there is a fixed point at which damage will become apparent (Opdebeeck, Martyr, & Clare, 2016).

Active Reserve Model

To account for the individual differences, the active reserve model—commonly referred to as the "cognitive reserve model"—instead assumes that reserve is unfixed and can be accumulated through one's life experiences and activities. These life experiences—most commonly identified as education, occupational complexity, and cognitively stimulating leisure activities—are posited to be contributors to CR by helping to build more efficient processing mechanisms and optimize performance through the recruitment of alternative cortical networks. The use of alternative cognitive strategies involves active reorganization of brain networks in order to compensate for normal cognitive aging in healthy older adults or cognitive deficits in those with neurodegenerative diseases, such as dementia. This compensatory mechanism allows individuals to sustain more brain injury prior to the onset and worsening of clinical symptoms (Stern 2002; 2009). Hence, CR is not only important in the context of brain pathology and onset of dementia, but also to normal aging, as it may allow individuals to cope more effectively with typical age-related brain changes through the use of more flexible and efficient cognitive systems (Stern, 2009). It is important to emphasize that the concept of brain and cognitive reserve are not mutually exclusive (Stern, 2002); however, how both models of reserve interact remains unclear and has led to difficulty differentiating the two concepts.

Although the concept of CR has been extensively researched, it remains a latent and arbitrary construct that cannot be directly measured. As such, researchers have relied on proxy variables as measurements of CR (Clare et al., 2017), with the most common proxies related to innate intelligence—a fixed measure (Richards, Shipley, Fuhrer, &

Wadsworth, 2004), educational attainment (Garrett, Grady, & Hasher, 2010; Schmand, Smit, Geerlings, & Lindeboom, 1997), and/or life experiences (a variable measure), such as occupational activities (Andel, Kåreholt, Parker, Thorslund, & Gatz 2007) and engagement in cognitively stimulating activities (Akbaraly et al., 2009; Helzner, Scarmeas, Cosentino, Portet, & Stern, 2007; Scarmeas & Stern, 2004; Schooler & Mulatu, 2001; Wilson et al., 2011). Higher CR has been found to buffer individuals against multiple forms of neurologic insult, slow down the rate of age-related cognitive decline and delay the onset of MCI and dementia (see review by Opdebeeck et al., 2016). However, higher CR is also associated with faster rates of cognitive decline in memory (Hall, Derby, LeValley, Katz, Verghese, & Lipton, 2007; Stern, Albert, Tang, & Tsai, 1999), processing speed, and global cognition (Bruandet et al., 2008; Scarmeas, Albert, Manly, & Stern, 2006) in those diagnosed with AD. The "threshold effect" is a plausible explanation of the latter, and posits that CR initially masks or protects against early cognitive decline, but once brain pathology reaches a specific threshold (e.g., when clinical symptoms of dementia manifest), existing cognitive reserve depletes and rapid cognitive decline ensues (Carmelli, Swan, LaRue, & Eslinger, 1997; Meng & D'arcy, 2012; Mungas, Gavett, Fletcher, Farias, DeCarli, & Reed, 2018).

Researchers use either a single proxy of CR or a combination of CR factors to examine individual differences in brain pathology and cognitive functioning. However, there is still considerable debate as to how CR is best assessed, as variables are often categorized and grouped, often interchangeably, in the literature. Additionally, researchers have conceded that multiple proxies should be considered along with examination of the strength of the associations of CR with different cognitive domains in

healthy older people. The examination of CR is further important as much of the literature has taken a "risk or deficit approach" on identifying risk markers of dementia through neuroimaging, cognitive screening, and genetic testing. However, attention has increasingly turned towards a positive psychology framework, referring to actively exploring individuals' intact cognitive skills and the protective lifestyle factors that can prevent, maintain, or improve upon cognitive and functional status in addition to limiting effects of existing deficits—all of which align with the concept of cognitive reserve. Taking the traditional deficit approach may be too late within the disease process where remediation seems futile and may further reinforce patients to unknowingly participate in the self-fulfilling prophecy of ageism while using the "positive psychology framework" will encourage individuals to use what they already have and even expand upon it (Ahmed & Boisvert, 2013). This more novel concept has been used in therapeutic milieus with patients with psychiatric disorders, such as schizophrenia, to focus on areas of the brain that are intact but underutilized or underrecognized and can be generalized towards healthy individuals. In our study, each of the proxy variables of CR will be explored in detail along with its relationship to specific cognitive domains in order to capture active reserve within a positive psychological framework.

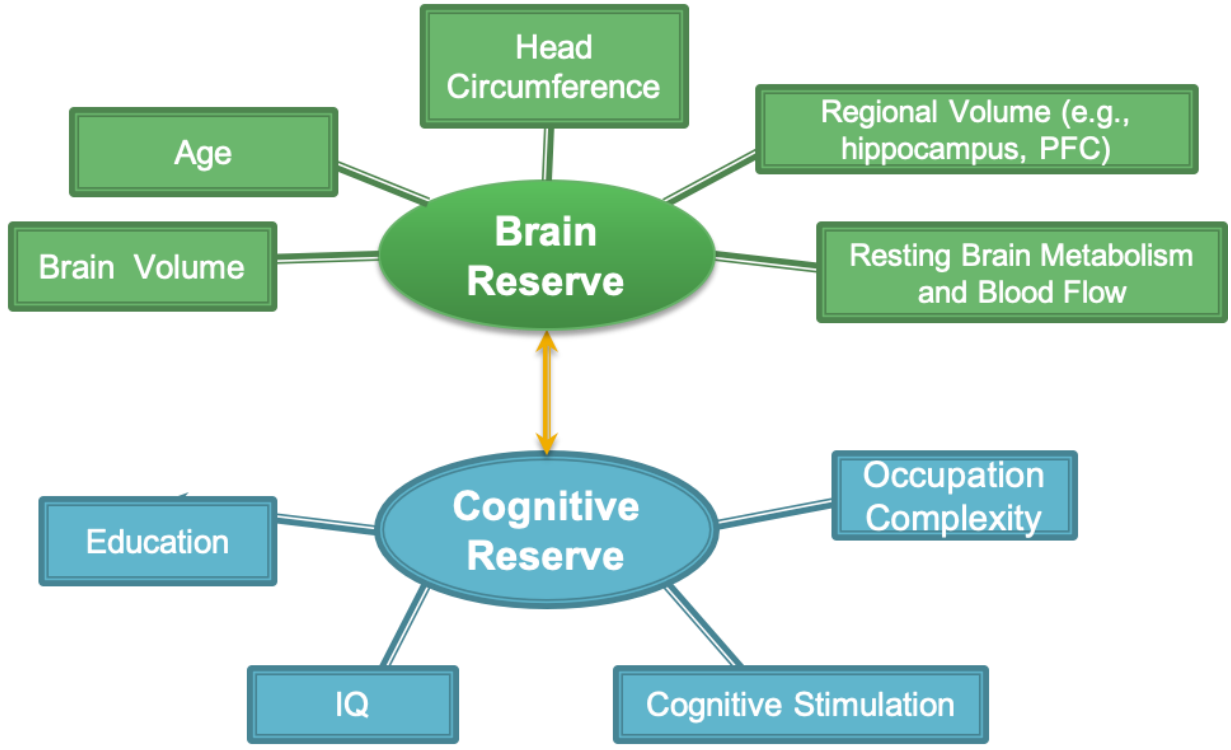

Figure 2. Active (cognitive) and passive (brain) reserve models.

Proxies of Cognitive Reserve

Education

Educational attainment is a critical experience that involves several decades of an individual's life, and its impact likely shapes an individual's later life experiences. Due to its ease of measurability, education has been consistently used as a proxy of CR to investigate the positive contribution of a complex and stimulating environment on age-related cognitive differences (found in cross-sectional studies) and rate of cognitive decline (found in longitudinal studies; Kramer, Bherer, Colcombe, Dong, & Greenough, 2004). The theoretical rationale for using formal education as a proxy measure of cognitive reserve is based on the assumption that it generates new cognitive strategies (Stern, 2002). Educational attainment has been assessed using various methods, with the

two most common being 1) years of formal education measured as a continuous variable (Albert & Teresi, 1999) and 2) levels of education. The latter either categorizes participants into different groups ranging from no formal education to greater than 12 years (Mathuranath, Cherian, Mathew, George, Alexander, & Sarma, 2007), dichotomizes participants into two groups of lower and higher levels of education (Amieva et al. 2014; Pillai et al., 2012; Roldán-Tapia, García, Cánovas, & León, 2012; Van Exel et al., 2001), or classifies people into different educational levels (Le Carret, Lafont, Letenneur, Dartigues, Mayo, & Fabrigoule, 2003; Meguro et al., 2001). Although education indices have varied within the literature, findings do not appear to rely on whether education was used as a categorical or continuous variable. For example, Christensen et al. (1997) found a significant association between education and cognitive change when education was assessed either as a continuous or categorical measure, and others concur (see Anstey & Christensen, 2000 for a review).

Education and Neuropsychological Correlates in Older Adults

A large body of literature investigating the relationship between educational attainment and aspects of cognitive function in older adults has yielded mixed results, suggesting that this relationship varies in accordance with the cognitive tasks assessed (Antsey & Christensen, 2000). In a well-cited meta-analysis, Anstey and Christensen (2000) identified that education is consistently predictive of crystallized abilities (i.e., verbal fluency, vocabulary, abstract reasoning) more so than fluid abilities (i.e., processing speed, executive functioning) (Christensen et al., 1997; Horn & Cattell, 1967; Lindenberger & Reischies, 1999; Lipnicki et al., 2017), with less educated older adults

(ages 70-79) scoring lower on the WAIS-IV vocabulary and similarities subtests than those with advanced education (Christensen et al., 1997).

Other studies have found educational effects for both crystallized and fluid abilities (Groot et al., 2018). There is now strong support of education's protective effects on fluid intelligence, such as visuospatial functioning (Vadikolias et al. 2012), processing speed (Jefferson et al., 2011; Proust-Lima, Amieva, Letenneur, Orgogozo, Jacqmin-Gadda, & Dartigues, 2008), and executive functioning **(**Andrejeva et al., 2016; Le Carret, Auriacombe, Letenneur, Bergua, Dartigues, & Fabrigoule, 2005; Wecker et al., 2005; Van Hooren, Valentijn, Bosma, Ponds, Van Boxtel, & Jolles, 2007). For example, Tun and Lachman (2008) demonstrated that older adults with higher education (i.e., college degree) had significantly faster reaction times on Stop and Go Switch task conditions of increasing complexity requiring greater executive skills (i.e., attention switching and inhibition) than those with lower levels of education. Similar results of education predicting performance on high-attention demanding tasks involving executive control processes and conceptualization (e.g., verbal memory, timed tasks, abstract reasoning) in samples of healthy older adults are consistently reported (Angel, Fay, Bouazzaoui, Baudouin, & Isingrini, 2010; Bherer, Belleville, & Peretz, 2001; Le Carret et al., 2003). Interestingly, the authors report that college-educated older adults perform on par with less educated individuals who were ten years younger, up to age 75; no benefit of education was found in the 75-85 age group. This suggests that having advanced education was protective in moderating age differences on complex executive tasks up to a certain age, after which age-related biological decline begins to dominate. In two studies, education was found to have protective effects throughout adulthood, rather than

just in old age. These protective effects were identified to begin at age 18 when cortical degeneration was minimal to non-existent (Farmer, Kittner, Rae, Bartko, & Regier, 1995; Lyketsos, Chen, & Anthony, 1999).

A cross-sectional study worth noting is one by Darby et al. (2017), in which the authors examined whether CR, measured as years of education, significantly predicted cognitive performances on tasks requiring low (e.g., Auditory Verbal Learning Test [AVLT] discriminability, digit span forward, Trails A, figure copying), moderate (e.g., AVLT delayed recall), and high (e.g., Logical Memory Test delayed recall, digit span backwards, Trails B, naming, semantic fluency) semantic and executive demands. The authors found that higher years of education was associated with superior performance on tasks with moderate-to-high executive and semantic demands in patients with mild MCI, while in AD patients, education influenced performance on tasks with semantic components only. In contrast, there were no education effects on memory tests with lower executive and semantic components. The significance of these results remained even after controlling for demographic variables and regional cortical atrophy in patients with mild MCI and AD. Overall, these findings suggest that there are broader effects of CR on task performance in patients with milder (MCI) versus severe cognitive impairments (AD) and that neural compensation, through the use of preserved executive and semantic functions, may be one mechanism in which CR acts to preserve cognitive performance differentially in patients with cognitive impairment. Additionally, this mechanism depends on the level of severity, as certain cognitive capacities (i.e., executive skills) are lost due to disease progression while others remain partially preserved (semantic). This is consistent with the idea that verbal memory is associated

with the mesial temporal lobe structures, while semantic properties of verbal memory are hypothesized to involve distributed network of brain regions, allowing for neural compensation (Saling, 2009). The majority of the abovementioned studies on education and executive functioning show that education is significantly related to frontal lobe measures in organizing and scheduling complex responses (Plumet, Gil, & Gaonac'h, 2005; Wecker et al., 2005). This finding is supported by Meguro et al. (2001) in that a significant effect of educational level on frontal lobe tasks related to working memory, verbal fluency, divided attention, and abstract reasoning was found, in addition to a positive association between frontal lobe atrophy and age that was only significant in participants with lower levels of education**.**

Other components of fluid intelligence, such as memory, have also been strongly associated with education (see review by Obdebeeck et al., 2016). However, there is evidence of minimal effects on recognition performance, indicating that education primarily affects memory performance in tasks with high strategic demands, such as encoding and spontaneous recall (Drag & Bieliauskas, 2010). A cross-sectional study by Capitani et al. (1996) comparing two extreme groups (illiterate participants versus those with > 10 years of education) across different cognitive domains found that age-related cognitive decline in verbal fluency and spatial memory tests ran the same course in both higher and less educated participants, but not in visual attention and verbal memory tests, which showed larger age-related decrements in the less educated group. A seminal study by Gregoire and Van der Linden (1997) showed that older adults who are highly educated performed similarly to their younger counterparts on digit forward and backwards tasks, indicating that higher education is associated with maintaining short-term memory

abilities despite age. From a cognitive perspective, education may help develop and enhance vocabulary abilities, high level of abstraction, and a broad repertoire of cognitive strategies and effective use of these strategies to assist performance in cognitive tasks, particularly within the domain of verbal memory.

It is important to highlight that existing discrepancies found in the literature between education and neuropsychological performance may be due to the fact that different cognitive domains have different age-related patterns of development and decline (Angel et al. 2010), such that some domains begin to decline in middle adulthood (e.g., processing speed, episodic memory, and working memory), while others do not decline until late-life (e.g., vocabulary, semantic knowledge, and short-term memory), with some even showing long-term stability (e.g., abstract reasoning, autobiographical memory) (Hedden & Gabrieli, 2004). Cognitive domains that remain stable through most of adulthood and begin to decline in late-life may only show benefit from the protective effects of education in study samples of older adults, whereas cognitive domains that gradually decline over the lifespan may only show significant associations with education in large samples that span various age ranges.

Education and Rate of Cognitive Decline in Normal Aging, MCI and AD

Education has repeatedly been shown to have robust protective effects against the development of MCI and dementia. That is, incidence rates and risk of dementia are lower (by approximately 47%) in highly educated individuals relative to their peers with less education (Valenzuela & Sachdev, 2006b), with delay in average age of onset (Amieva et al., 2014; Xu et al., 2015). The majority of studies on healthy individuals

have found non-significant differences in the rate of cognitive decline between individuals with higher and lower education within the domains of attention, processing speed, visuospatial ability, executive functioning (abstract reasoning and inhibition), and visual and verbal memory (see Lenehan, Summers, Saunders, Summers, & Vickers, 2015 for a review). In contrast, other studies have found rapid age-related cognitive decline on tasks of processing speed and verbal memory in those with lower education relative to those with higher education (Cullum et al., 2000).

Surprisingly, Nishita et al. (2013) found the opposite, such that those with higher educational level (high school degree or greater) showed greater decline in processing speed than their less educated counterparts over a 10-year span, although they yielded higher scores at every time point measured throughout the study. This leads the authors to several explanatory conclusions. First, it is possible that highly educated adults might use their high crystallized ability to compensate for declining fluid ability (Alley, Suthers, & Crimmins, 2007). However, when highly educated older adults reach age 65, they gradually lose their crystallized abilities, a phenomenon that is consistent with the compensation hypothesis, in which intact domains compensate for declines in other cognitive abilities until they, too, begin to deteriorate, leading to more rapid decline (Alley et al., 2007; Reuter-Lorenz & Mikels, 2006; Zahodne et al., 2011). Second, those with lower education may possibly demonstrate a larger and faster rate of decline in cognitive performance prior to age 65 (at baseline). In contrast, the highly educated may have had minimal decline in processing speed earlier in life (before age 65 years), but their greatest rate of decline was observable after baseline. Thus, Nishita et al. (2013)'s findings may reflect a difference in the "onset of degeneration" (Alley et al., 2007) in

processing speed between higher- and lower-educated older adults. The discrepancy in findings between longitudinal studies are said to involve different populations and cohort effects and use of different measurement methods that do not support the association between education and rate of late-life cognitive decline (Early et al., 2013; Gross et al., 2015). Also, with the increase in the average level of education in more advanced and industrialized societies, it is possible that the potential benefits of higher education are no longer noticeable in populations as the average educational levels go beyond the 8-year threshold that is said to distinguish high- versus low- education reported by Lyketsos et al. (1999).

More recent studies have investigated the rates of cognitive decline pre-and post-clinical manifestation of MCI and AD through longitudinal studies. Research on individuals with MCI and AD demonstrates support for both reserve models. A large multisite study in Korea found that cognitive decline was slower in higher educated patients with early-stage MCI in global cognition (MMSE) and sum scores on the Clinical Dementia Rating (CDR; Ye et al., 2013). However, in late-stage MCI patients, higher levels of education (>8 years) were associated with more rapid cognitive decline in the domains of language, memory, and CDR scores, along with increased risk for AD conversion near the 1.5-year mark relative to those with lower education. These results suggest education's protective effect against cognitive decline is present in early-stage MCI but may dissipate in the later stages of the disease process (Ye et al., 2013). These findings are consistent with the Stern et al. (1999) seminal study and have been replicated in a body of literature that has examined education and cognition in patients with AD, as many have demonstrated that higher education is associated with slower decline

preceding the clinical manifestation of AD (Zahodne et al., 2011), but faster cognitive decline after the diagnosis of AD (Alley et al., 2007; Amieva et al., 2014; Scarmeas et al., 2006). Lyketsos et al. (1999) also interestingly found that while those with eight years of education had slower rates of decline relative to those with <8 years, subjects who had ≥9 years of education garnered no additional benefits. Findings from these studies indicate that education promotes brain resilience and buffers against changes associated with the development of dementia, therefore, delaying the onset of clinical sequelae. However, there seems to be a "threshold effect" to which the higher education initially masks or protects against early cognitive decline, but once brain pathology reaches a specific threshold, educational reserve depletes, and rapid cognitive decline ensues (Carmelli et al., 1997; Meng & D'arcy, 2012; Mungas et al., 2018). Individuals with greater educational attainment, in this case, continue to perform at a higher level than similarly aged individuals with less education but decline rapidly after reaching a fixed point (Stern, 2002).

Extant research overall supports education's contributions to CR via the active and reserve models. It is important to acknowledge that formal education may causally influence cognitive abilities during childhood development (Ceci's, 1996), with these accumulated benefits appearing to persist until late adulthood in the maintenance of cognitive function in the face of age-related brain and cognitive changes, which is in line with active reserve (Deary, Whalley, Lemmon, Crawford, & Starr, 2000). Hence, higher educated individuals begin adulthood with higher levels of cognitive functioning and take longer to reach clinically significant levels of cognitive decline and functioning, but once past this point, the benefits of education disappear and well-educated individuals exhibit

similar degrees of age-related cognitive dysfunction compared to their less-educated peers, which is in line with the passive reserve model (Tucker-Drob, Johnson, & Jones, 2009).

Although education has proven to be a moderately robust measure of CR, some studies have not found an effect of education on the rate of cognitive decline (Carmelli et al. 1997; Hultsch, Hertzog, Small, & Dixon, 1999). For example, Lyketsos et al. (1999) did not find any association between education and the rate of cognitive decline in individuals with more than eight years of education. Significant differences in rates of decline in global cognition in older people as a function of education have also not been found (Christensen, Hofer, Mackinnon, Korten, Jorm, & Henderson, 2001; Seeman, Huang, Bretsky, Crimmins, Launer, & Guralnik, 2005; Van Dijk, Van Gerven, Van Boxtel, Van der Elst, & Jolles, 2008). However, with regard to those individuals with the apolipoprotein ε4 allele, a nonsignificant trend for a faster decline in global cognitive performance was found in individuals with greater educational attainment (> 9 years) (Seeman et al., 2005).

Education and Neuroanatomical Correlates

Literature supports the notion that higher education can modulate the relationship between markers of brain pathology and neuropsychological performance. Higher levels of education have been associated with increased cortical thickness, including the medial-frontal, temporal, and parietal lobes (Cox et al., 2016). A study by Rentz and colleagues (2010) found that in both healthy subjects and those with AD, proxies of CR (years of education and AMNART IQ) individually modified the relationship between amyloid

deposition and cognitive performance, such that participants with less CR (lower education and premorbid IQ) demonstrated lower performance on tests of memory, working memory, semantic fluency, language, and visuospatial perception and had greater amyloid deposition. These results suggest that proxies of CR may be protective against amyloid-related cognitive decline. Additionally, individuals with higher education (>18 years) performed better on the MMSE, language, and memory despite reduced cortical thickness (Pillai et al., 2012).

In regard to the relationship between structural integrity and education, advanced education has been associated with greater grey and white matter bilaterally in the temporo-parietal lobes and orbitofrontal lobes (Amieva et al., 2014). Individuals who exhibited greater cortical atrophy had less education than those with less atrophy (Mungas et al., 2018), indicating that protective educational effects are depleted as brain degeneration progresses. A study by Foubert-Samier (2012) of healthy older adults demonstrated that education, occupational attainment, and engagement in leisure activities differentially contributed to the reserve capacity, such that higher education, participation in more leisure activities (in midlife and currently), and working in a stimulating work environment all led to higher scores on a semantic fluency task, but that only education was significantly associated with gray and white matter (cerebral volume). Differences in gray matter were explicitly found in the left temporoparietal lobe—representing linguistic and memory abilities—and bilateral orbitofrontal lobes—reflecting decision-making abilities—between those with high versus low education. Individuals with more severe white matter lesions and less education (<8 years) are also at greater risk for progression from normal aging to MCI and AD during a 7-year period

(Mortamais et al., 2014), highlighting that education can protect against negative effects of white matter lesions, but cannot prevent its development.

Additionally, studies have shown the influence of education on brain activation during memory tasks. For example, Springer et al. (2005) used fMRI during an episodic recognition memory task in young and healthy older adults. They demonstrated that in young adults, education was correlated to medial-temporal activity more so than frontal regions, but education was positively correlated only with prefrontal activity in older adults. Angel et al. (2010) similarly found that older adults with less education (mean of 9 years) had significantly less frontal lobe activation and poorer performance on the recall task relative to higher educated older adults. Greater activations in the frontal lobe reflect strategic aspects of episodic memory recall (Becker & Lim, 2003) and executive functions (Baudic, Barba, Thibaudet, Smagghe, Remy, & Traykov, 2006) in healthy elderly patients, with frontal activations demonstrated by healthy older adults related to CR proxies tending to decay in older adults with amnestic MCI and AD (Colangeli, Boccia, Verde, Guariglia, Bianchini, & Piccardi, 2016). As such, these authors suggest that engagement of the prefrontal cortex by older adults, particularly those who are highly educated, is a compensatory mechanism utilizing alternative networks to aid cognitive function. However, the ability to compensate shows marked diminishment once an individual reaches the tipping point of MCI. These two studies suggest that age differences in the pattern of cerebral activation during episodic memory tasks differ as a function of education and neurodegenerative disease severity.

In sum, while there is incongruence in the observed relationship between education and cognition in the literature, the majority of empirical findings suggest that

the association is moderate, with some disparity in results due to the utilization of different cut-off levels to differentiate between high and low education (Opdebeeck et al., 2016). It seems unrealistic that there is a specific universal cut-off at which education exerts beneficial effects, but rather, it is probable that any additional formal education aids in maintaining cognitive function, as the majority of evidence has suggested that in general, individuals with higher educational level have better cognitive functioning. Furthermore, most neuroimaging and autopsy studies that use educational level as the CR proxy measure support the CR theory, indicating that educational level continues to stand as a prominent proxy measure of CR (Bennet et al., 2003).

While formal education is vastly used in the literature and is important in potentially influencing the propensity for greater physical and mental stimulation throughout the life course, it is important to acknowledge that it is limited as a stand-alone measure of CR because education is relatively fixed and acquired early in life (Meng & D'arcy, 2012). Another primary difficulty is that the nature, intensity, and content of education differ across nationalities and social groups. Indeed, it has been suggested that literacy, reading ability, or crystallized intelligence may be better measures of educational attainment (Albert & Teresi, 1999; Fyffe, Mukherjee, Barnes, Manly, Bennett, & Crane, 2011; Manly, Schupf, Tang, & Stern, 2005; Manly, Touradji, Tang, & Stern, 2003). As such, measures of estimated premorbid intellectual functioning are commonly used as CR proxies, and it is suggested that verbal IQ might be a better marker for CR than education (Alexander et al., 1997; Manly et al., 2005) with many studies using a combination of education and estimated premorbid intelligence for proxies of CR (Barulli, Rakitin, Lemaire, & Stern, 2013; Giogkaraki, Michaelides, &

Constantinudou, 2013).

Estimated Premorbid Intelligence Quotient (IQ)

Due to variability in the quality of education, premorbid intellectual ability is often used either as a substitute for or in tandem with education as a proxy of CR. Premorbid IQ is typically measured using a single-word reading test and has generally been found to provide more accurate estimations than sociodemographic information (e.g., educational and occupational achievement; Bright, Jaldow, & Kopelman, 2002; Franzen, Burgess, & Smith-Seemiller, 1997). Since reading ability is highly correlated with general intelligence and also robust to age-related and early AD-related declines, it can be used to estimate a person's IQ preceding neural damage or deterioration (Caffo et al., 2016). The underlying assumption is that reading ability is stable, offers a general sketch of an individual's lifetime intellectual achievement, and mainly depends on cognitive function at time of acquiring correct pronunciation rather than at time of reading. Similar to vocabulary and fund of information, reading ability is supposedly retained across time despite deterioration in other cognitive domains. This makes reading ability relatively resistant to brain injury and other disorders affecting cognitive function and a good estimator of premorbid cognitive function (Franzen et al., 1997; Ravdin & Katzen, 2013).

Together with age, premorbid intelligence is a major predictor of cognitive functioning in healthy individuals and those with dementia across a wide range of severity (Folstein et al., 1975; Starr & Lonie, 2007) as well as progression and regression in patients with MCI (Osone, Arai, Hakamada, & Shimoda, 2016). It is also said that

unlike education, which is static and unlikely to change after early adulthood, literacy or premorbid IQ may be a better reflection of reserve (Manly et al., 2003; 2005), as both literacy and vocabulary may change over time, thereby making them more sensitive CR proxies. For example, in a study of Japanese patients diagnosed with MCI, higher premorbid IQ, and not years of education, was found to be protective against cognitive decline, while brain volume was the strongest predictor of reversion and conversion. Specifically, patients who demonstrated reversion to normal cognitive baseline had higher premorbid IQ and atrophy ratio (hippocampal volume/whole brain volume) at baseline and better cognitive performance over 12 months compared to those who progressed to dementia.

Premorbid IQ and Neuropsychological Correlates in Older Adults

Some studies that explore the relationship between premorbid IQ as a measure of CR and neuropsychological functioning in healthy older adults have shown that individuals with low premorbid IQ were six times more likely to obtain impaired scores (≤1.5 SD below the mean) in attention, memory, and global functioning relative to their higher premorbid IQ counterparts, suggesting that premorbid IQ acts as a protective factor against the expression of cognitive decline related to age in healthy individuals (Corral et al., 2006). Jefferson et al. (2011) is consistent with these findings, such that premorbid IQ, followed by education, was a robust predictor of working memory and secondarily to episodic memory and global cognition. Past studies have demonstrated that longitudinal studies examining the predictive strength of premorbid IQ on cognitive decline over time have found performance on the National Adult Reading Test (NART)

in English and Dutch languages at baseline predicted MMSE performance 9-12 years later (Cervilla, Prince, Joels, Lovestone, & Mann, 2000) onset of dementia over a four-year period (Schmand et al. 1997), and change in episodic memory scores and working memory over a 7-year period better than educational attainment (Lowe & Rogers, 2011; Taylor et al., 1996).

Premorbid intelligence can also be estimated by the use of visual tests. In a unique study that followed a group of healthy older adults from age 70 until death, Thorvaldsson et al. (2017) found that individuals with higher IQ (as measured using the Raven's Coloured Progressive Matrices) exhibited a later onset of accelerated terminal decline (defined as cognitive decline prior to death). More specifically, one standard deviation on the IQ scale was associated with a delay in onset of terminal decline by 1.87 years on speed tasks and 1.96 years on verbal comprehension ability, and 0.88 years on visuospatial ability. However, once the phase of terminal decline began, those with higher premorbid IQ showed a steeper decline trajectory than those with lower IQ. Surprisingly, education was not found to be associated with the rate of terminal decline. A study investigating patients with AD similarly revealed that those with greater pre-morbid intelligence had a more rapid decline after diagnosis, at least in terms of life expectancy (Starr & Lonie, 2008; Stern, 2006). Similar to longitudinal findings of education's effect on the rate of cognitive decline, there is support for the buffering effects of premorbid IQ on cognition, in that older adults with higher IQ tended to have larger and more efficient neuronal networks, which allowed for the use of effective cognitive strategies to delay the onset of cognitive decline, but that once a threshold is reached, neuropathology may accumulate at a faster rate for those with higher

intelligence in old age. These results suggest that cognitive reserve continues to have a limited influence on cognition after onset of AD, and thus, indirectly, has an impact on ADLs (Starr & Lonie, 2008).

Premorbid IQ and Neuroanatomical Correlates

In the past decade, greater attention has been given to not only education and premorbid IQ but the role that genetics (ApoE-4 allele) plays in altering the clinical manifestation and progression of dementia. Some studies have found a significant interaction between AMNART scores and amyloid deposition in association with cognitive performance in individuals with no cognitive impairment (Rentz et al., 2010) and those with mild AD (Bracco et al., 2007). For example, Bracco and colleagues (2007) found an association between higher premorbid IQ and better baseline cognitive performance on measures of executive functioning and memory in patients with mild AD, with higher premorbid IQ even reducing the negative effects of ApoE-4 on memory performance. In line with many other studies, higher premorbid IQ, but not the presence of ApoE-4, was related to faster memory decline (Bracco et al., 2007). Additionally, a recent cross-sectional study by Rentz et al. (2017) of clinically normal, MCI, and AD older-aged subjects found that within the whole sample, subjects who had higher AMNART scores and elevated tau had better MMSE scores than those with low AMNART scores and similar levels of tau pathology.

Additionally, premorbid IQ has been associated with reversion in patients with MCI during a one-year period, while years of education did not yield predictive significance (Osone et al., 2016). Furthermore, the relation between estimated premorbid

intellectual function and cerebral glucose metabolism has been linked to neuropsychological performance in patients with AD. Higher levels of premorbid IQ has been associated with greater cerebral dysfunction (hypometabolism), reflecting decreased synaptic activity associated with loss or dysfunction of brain synapses in areas typically affected in AD (prefrontal, premotor, and left superior parietal association areas) among patients of similar dementia severity levels (Alexander et al., 1997). The authors of this study highlight that premorbid IQ, particularly as measured by the Wide Range Achievement Test-III reading subtest, is sensitive to the neurophysiological effects of AD.

Overall, findings from these studies suggest that premorbid experience may directly influence brain function at the neuronal level, with higher premorbid IQ potentially protecting against early AD processes and allowing some individuals to remain cognitively stable despite increased cortical atrophy, elevated tau or beta amyloid burden (Alexander et al., 1997).

Occupational Complexity

A complex and challenging occupation is thought to provide an additive and independent contribution to CR throughout a person's lifetime (Stern, 2006). The benefits of occupational complexity on cognitive functioning are of special interest. Most individuals spend a substantial amount of time at work, with several job properties having been suggested to preserve or improve cognitive abilities (Sörman, Hansson, Pritschke, & Ljungberg, 2019). Schooler and colleagues' concept of "environmental complexity" posits that exposure to complex environments at work or during leisure enables the

continued practice of cognitive skills and facilitates cognitive functioning (Schooler, Mulatu, & Oates, 2004). The exploration of occupational complexity on cognitive aging has been more recent within the past decade; however, findings have been mixed. Several studies have supported the environmental complexity hypothesis with respect to the work environment and cognitive function. Using data from the Maastricht Aging Study based in the Netherlands, Bosma et al. (2003) found that higher mental work demands were associated with lower risk of cognitive impairment. Using almost 4,000 older male twins from the same study, Potter and colleagues (2006) reported that greater general intellectual demands at work were associated with more stable cognitive performance in older adulthood when assessed over approximately seven years of follow-up. Finally, using a U.S.-based nationally representative sample of older men, Wight, Aneshensel, and Seeman (2002) found a positive association between post-educational training on the job or elsewhere and cognitive function in older adulthood, again highlighting that complexity of environment at work may play a role in maintaining cognitive function in older adulthood. A meta-analysis by Valenzuela and Sachdev (2006b) showed that the majority of studies found higher occupational complexity or status to be protective in lowering the risk for dementia by 44%. However, three out of the 12 studies did not show any protective effects and found no associations between occupation and changes in cognition (Valenzuela & Sachdev, 2006b; Helmer et al., 2001). A recent review emphasized that the relationship between occupational complexity as a proxy measure of CR and cognitive function in later life have yielded findings of a strong association between occupation and the screening measures of global cognitive function, but weak correlations with memory and visuospatial skills (Finkel, Andel, Gatz, & Pedersen, 2009;

Fritsch, McClendon, Smyth, Lerner, Friedland, & Larsen, 2007; Leung et al., 2010) to a moderate correlation with executive function (Foubert-Samier et al., 2012).

Studies that have found support for the protective role of occupation emphasize that older adults exposed to complex work environments and demanding roles in work or recreational activities are able to continue exercising their mental abilities, which help them preserve them for a longer period (Schooler et al., 2004). Individuals who have worked in cognitively stimulating environments have been found to demonstrate higher scores on immediate and delayed memory as well as processing speed (Ansiau, Marquié, Soubelet, & Ramos, 2005), with older adults in less prestigious occupations demonstrating lower scores on measures of immediate and delayed memory, attention, and orientation (Scherr et al., 1988). Individuals who work in forestry, fishing, and craftwork have shown an elevated risk for cognitive impairment compared to former legislators, business executives, and managers, as indicated by lower scores in the Short Portable Mental Status Questionnaire (Li, Wu, & Sung, 2002). A large study indicated that higher lifetime occupational attainment (manager business/government, professional/technical) as opposed to lower attainment (unskilled/semiskilled, skilled trade or craft, clerical/office worker) was associated with decreased risk for incident dementia (Stern, Gurland, Tatemichi, Tang, Wilder, & Mayeux, 1994). Other researchers have supported these findings (Bickel & Cooper, 1994; Dartigues et al., 1992; Kroger, Andel, Lindsay, Benounissa, Verreault, & Laurin, 2008).

A commonly used measure of occupational complexity stems from the Dictionary of Occupational Titles (DOT; U.S. Department of Labor, 1977), which categorizes occupations into three complexity dimensions: complexity of data, people, and things.

Using the DOT classification, a study of Swedish twins by Andel et al. (2005) found that greater complexity while working with people and data was associated with reduced risk of AD, above and beyond age, gender, and level of education. Higher levels of occupational complexity working with people (Smart, Gow, & Deary, 2014) and with data (Andel et al., 2007; Correa Ribeiro, Lopes, & Lourenço, 2013; Smart et al., 2014) have also been found to be related to improved performance on global measures of cognitive functioning (e.g., MMSE). Moreover, work with data and people was associated with cognitive function above and beyond age, sex, and childhood socioeconomic status. The results were sustained when either education or adult socioeconomic status was added into the regression models (Andel et al., 2007). In contrast, in a sample of older Puerto Rican adults, although work complexity was related to lower risk of cognitive impairment on the MMSE, most of the associations became nonsignificant after controlling for education (Andel, Dávila-Roman, Grotz, Small, Markides, & Crowe, 2019).

Other studies have indicated that after controlling for age, sex, IQ, and years of education, both complexity with people and data were related to higher general cognitive ability scores (Smart et al., 2014). Complexity with data was also related to better performance processing speed, whereas complexity with people was associated with higher memory scores. Other studies have found that higher work complexity with data was associated with both better memory and processing speed, while higher complexity with things was associated with slower speed and poorer MMSE scores in older adults (Lane, Windsor, Andel, & Luszcz, 2017). In a cross-sectional study on participants aged 50-75 (Sörman et al., 2019), occupations with higher levels of complexity with both

people and data were associated with performance on aspects of executive functioning, such as errors made on tasks requiring task-switching and updating (monitor and relevance screening of incoming information to revise the information used in one's working memory). In a study that examined occupational complexity on postretirement cognitive outcomes, high work complexity with people was found to be related to better executive functioning and overall cognition during working life and slower decline after retirement across a span of nine years (Vélez-Coto, Andel, Pérez-García, & Caracuel, 2021).

Studies with clinically defined MCI and dementia support the notion that occupational complexity may also relate to cognitive status. Specifically, subjects who work with data performed better on measures consisting of higher attentional demands (Feldberg, Hermida, Maria Florencia, Stefani, Somale, & Allegri, 2016), processing speed, and working memory (Carolina, Hermida, Tartaglini, Dorina, Veronica, & Allegri, 2016). Participants who worked more with people performed better on verbal abilities and reasoning measures, while those who work with things performed best on tasks requiring visuospatial skills (Carolina et al., 2016). Stern et al. (1994) found that high interpersonal demands of primary lifetime occupation delayed the onset of Alzheimer's disease independent of age and education. Participants with jobs characterized by lower mental and higher physical occupational demands are also more likely to be diagnosed with Alzheimer's disease after controlling for race, gender, year of birth, and education (Smyth et al., 2004).

Similarly, Kroger et al. (2008) reported that higher complexity of work with people and things might reduce the risk of incident dementia or Alzheimer's disease.

Individuals with low education and blue-collar occupations, compared to white-collar occupations, have an increased risk of Alzheimer's disease and dementia (Karp et al., 2004). Among those with dementia, older adults who attained high education levels or high complexity level occupation have been found to be 4.6 to 7.1 times more likely to have better global cognitive function than those who attained lower education or occupational complexity, respectively (Darwish, Farran, Assaad, & Chaaya, 2018). It is said that more demanding occupational roles that provide mental exercise and motivate individuals to continue to develop intellectual capacities are protective against dementia (Kroger et al., 2008).

In contrast, other studies have not supported these findings in patients with MCI (Andrejeva et al., 2016) and have not found that occupational complexity predicts incident dementia (Paykel et al., 1994). One study even found that the protective effect of higher occupational attainment seemed to be partly mediated by educational status (Evans et al., 1997). This is in contrast to other studies showing that occupation appears to provide additional benefit for cognitive function independently of that provided by education (Andel et al., 2007; Correa Ribeiro et al., 2013).

Researchers have found that higher education and occupational complexity in combination led to poorer cognitive outcomes (e.g., global cognition, inductive reasoning, verbal memory, verbal fluency) in late adulthood except on vocabulary (Singh-Manoux, Marmot, Glymour, Sabia, Kivimaki, & Dugavot, 2011). This implies that some of the initial gains may be lost with aging, which is in line with the cognitive reserve model such that individuals who are high in reserve must experience substantial cognitive deterioration before they reach any threshold of impairment. In a study of the

oldest-old (age 90+) individuals, cognitive and functional decline was not influenced by work complexity nor work duration (Hakiki et al., 2020). Gow et al. (2014) investigated the influence of occupational characteristics (e.g., intellectual vs. manual) on cognitive aging in persons born in 1914 until they reached 80 years of age and found that individuals with more intellectually challenging occupations had higher cognitive ability relative to those who worked in more physically hazardous occupations. However, there was no association after accounting for cognitive ability at age 50 and after demographic factors were adjusted. None of the occupational characteristics were associated with cognitive change between age 60 and 80.

Given that occupational complexity has been associated with reduced cognitive decline in late-life, recent studies have begun to examine occupational complexity in middle adulthood in association with brain structure and AD neuropathology. Recent studies found that individuals who had cognitively complex occupations earlier in adulthood performed better on measures of processing speed, executive function, and visuospatial skills but not memory in mid-life (Kaup et al., 2018; Jonaitis, La Rue, Mueller, Koscik, Hermann, & Sager, 2013). This, in turn, was associated with better white matter integrity in mid-life but not with gray matter volume. The authors posit that occupational complexity may preserve axon tract structure against age-related deterioration, consistent with the concept of "brain maintenance" (Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012), with certain lifestyle variables aiding individuals to avoid age-related brain changes. Alternatively, occupational complexity may help promote neural plasticity or myelination to strengthen or increase white matter connections (Chanraud, Zahr, Sullivan, & Pfefferbaum, 2010).

Furthermore, among middle-aged participants at risk of AD, complex occupation (based on three main lifetime occupations) with "people" was associated with increased brain atrophy and decreased hippocampal volume when participants were matched for cognitive function (Boots et al., 2015). Thus, it seems that individuals with a history of complex work with people are more able to cope with AD pathology since they have equal cognitive ability, but worse AD pathology compared to those with an occupational history that has lower complexity relating to working with people. Previous findings suggest that occupational complexity effects on cognitive functioning are in support of the cognitive reserve hypothesis (Stern, 2002), which posits that environmental enrichment may provide resources to better cope with dementia pathology.

Overall, discrepancies in findings may be due to the fact that occupation has been measured in a variety of different categories. For example, low occupation was described as house duties, farmers, domestic, blue-collar in one study (Helmer et al. 2001), while another described it as unskilled, semiskilled, housewife (Bickel & Cooper, 1994). Additionally, Forstmeier and colleagues (2012) classified occupational complexity into motivational and cognitive abilities, while Dekhtyar and colleagues (2015) coded occupations according to their complexity with data, people, and things. Across most reviews of occupation, different terms were used in the definition, such as work complexity, occupational attainment, occupation, etcetera. For our study, we will be using the term occupational complexity.

Physical Function on Cognitive Aging

Physical function is defined as the ability to move one's body through space and carry out physical activities important for daily living, including walking, standing up, reaching, turning, and climbing stairs (Painter, Stewart, & Carey, 1999). The literature uses the term physical function interchangeably with other terms representing the same concept, such as "physical fitness, physical performance, physical abilities, motor abilities, mobility, and functional status" within the literature. Of note, this study will use the terms "physical function" and "physical abilities" interchangeably.

Physical and cognitive function are both indicators of biological aging (Clouston et al., 2013). Cognitive dysfunction and poor physical function are two of the most prevalent age-related conditions that place individuals at greater risk for a variety of adverse outcomes, including incident disability and functional decline in instrumental and basic activities of daily living, hospitalization, need for personal care and home nursing care, and death in older adults (Barberger-Gateau & Fabrigoule, 1997; Binder, Storandt, & Birge, 1999; Cesari et al., 2009; Guralnik et al., 1994; Aud & Rantz, 2005; Wolinksy, Callahan, Fitzgerald, & Johnson, 1993; Vaarst et al., 2021). Age-related declines in physical function are observed in the absence of disease from midlife and onward due to changes in the musculoskeletal and other body systems (Cooper et al., 2011). Participating in physical activity has been shown to improve various aspects of physical fitness and functioning. Hence, it is of no surprise that researchers have also found a significant relationship between measures of physical function and cognitive function in healthy older people within and outside the U.S. (Voelcker-Rehage, Godde, & Staudinger, 2010; Won et al., 2014; Dansereau, Hunter, Gomez, Guralnik, DePaul, &

Auais, 2020), with remarkable individual differences in rates of age-related decline and in the age at which these declines begin to accelerate (Clouston et al., 2013). In fact, older adults who have faster gait speed (Fitzpatrick, Buchanan, Nahin, DeKosky, Atkinson, Carlson, & Williamson, 2007), better balance (Sattler, Erickson, Toro, & Schröder, 2011), muscle strength (Annweiler et al., 2011), and functional mobility (Huh, Yang, Lee, Lim, Kim, & Paik, 2011) have better cognitive functions. A high level of physical fitness in certain domains, such as balance and strength, may also reduce the risk for dementia in later life (Wang, Larson, Bowen, & van Belle, 2006).

Cross-sectional studies have shown an association between cognition and physical performance (Ble et al., 2005; Carlson, Fried, Xue, Bandeen-Roche, Zeger, & Brandt, 1999; Malmstrom, Wolinsky, Andresen, Philip Miller, & Miller, 2005; Raji, Ostir, Markides, & Goodwin, 2002; Rosano et al., 2005). Specifically, slower gait speed alone may serve as an indicator of the onset of age-related cognitive decline and sign of MCI (Buracchio, Dodge, Howieson, Wasserman, & Kaye, 2010) and early dementia (Holtzer, Verghese, Xue, & Lipton, 2006; Verghese, Lipton, Hall, Kuslansky, Katz, & Buschke, 2002; Waite, Grayson, Piguet, Creasey, Bennett, & Broe, 2005; Wang et al., 2006), especially in older adults with significant executive dysfunction (Liu-Ambrose, Ashe, Graf, Beattie, & Khan, 2008; Persad, Jones, Ashton-Miller, Alexander, & Giordani, 2008). Notably, in a recent review, poor gait performance was found to be present between 3 and 9 years before the diagnosis of dementia, which provides evidence for a close relationship between gait and cognitive dysfunctions and its directionality (Beauchet et al., 2016).

Gait Speed Effects Cognition

A large volume of literature has investigated gait speed and cognitive performance, as gait is the most common measure to include in representing physical decline due to the fact that gait speed commonly slows down with age and is associated with increased risk of adverse outcomes, including but not limited to cardiovascular disease, disability and mortality (Studenski et al., 2011; Verghese, Wang, & Holtzer, 2011). Reductions in measures of gait speed have been associated with impairment in global cognition in healthy older adults (Peel, Alapatt, Jones, & Hubbard, 2019). Additionally, gait speed has been found to be significantly associated with global cognitive function, memory, and executive function (Toots, Taylor, Lord, & Close, 2019; Mielke et al., 2013), with cognitive scores and gait speed declining over time (Mielke et al., 2013). Furthermore, the authors indicated that executive function demonstrated the strongest association and remained significantly associated with gait speed after adjusting for attention, memory, language, and visuospatial ability in the regression models.

One study showed that participants who scored in the slowest quartile of a rapid-paced walking task were at twice the risk of performing poorly on cognitive tasks than those who were deemed the fastest walkers (Fitzpatrick et al., 2007). The association between usual-paced walking speed and cognition was of borderline significance, while there was no relationship found with self-reported physical functioning measures. Results from this study demonstrated that fast gait speed used in rapid-paced walking tasks was a more sensitive measure than self-paced walking speed in differentiating levels of cognition (higher cognition defined as 3MSE score of >90 and lower cognition as 80–85) in older healthy adults. One probable explanation of these findings is that in

cognitively and physically high functioning older adults, differences that may distinguish individuals at extremes of functionality may only be detectable on more challenging tasks (e.g., fast-paced walking) that provide greater variability compared to basic physical tasks (e.g., usual/self-paced walking). Thus, walking at a faster pace allowed for the distinction between individuals with higher and lower levels of physical fitness to emerge, as walking faster may not have been as physically and cognitive taxing for participants with higher physiologic reserve, but may be taxing for those with less physiologic reserve, as fast walking requires executive abilities and additional concentration and effort (Coppin et al., 2006; Puente, Lindbergh, & Miller, 2015). Another study showed that when paired with memory concerns, gait speed is a strong predictor of cognitive decline (Verghese, Wang, Lipton, & Holtzer, 2013).

Results of the above study also demonstrated the greater utility of objective performance-based measures in investigating relationships between physical and cognitive function. The use of objective performance-based physical function measures has been supported by other studies that have found it predictive of physical decline without noticeable cognitive symptoms, further highlighting that physical changes may precede neurological symptoms of dementia (Atkinson et al., 2005). However, per the cognitive reserve hypothesis, it may also be the case that those individuals with a faster walking speed are more likely to have preserved cognitive functions. Additionally, it is possible that rather than a direct causal relationship, physical and cognitive function may be interrelated or linked by common pathophysiologic mechanisms (Fitzpatrick et al., 2007).

Physical Function Measures and Cognition

Outside of the use of gait speed, some studies have used a more comprehensive approach in assessing multiple domains of physical function or otherwise termed in the literature as physical ability, mobility, or performance. Assessing multiple domains of physical function allows researchers to examine a range of complexity in tasks requiring the integration of motor, sensory, and cerebellar activities (Wang et al., 2006). Unidirectional longitudinal studies also suggest that poorer mobility is associated with worse performance on measures of global cognitive function (Narazaki, Matsuo, Honda, Nofuji, Yonemoto, & Kumagai, 2014) and executive function in healthy community-dwelling adults (Demnitz et al., 2016), and risk of cognitive impairment, such as MCI (Liu et al., 2021) and dementia (Sattler, Erickson, Toro, & Schröder, 2011; Doi et al., 2019). Poorer cognitive function, particularly global and executive function, also predicted greater decline in mobility (Beauchet et al., 2016). Deterioration of specific motor functions, such as hand dexterity and handgrip strength, has also been associated with global cognition cross-sectionally and longitudinally (Kobayashi-Cuya, Sakurai, Suzuki, Ogawa, Takebayashi, & Fujiwara, 2018). Findings from a review by Demnitz et al. (2016) suggest that healthy older adults with better physical mobility perform better on measures of global cognition, processing speed, executive function, and memory. However, not all measures of mobility were equally associated with cognitive function. There were significant, although small, effect sizes revealing a positive association between performance on mobility measures (e.g., gait and lower-extremity function) and cognitive assessments. In contrast, most studies examining balance and cognition measures yielded no significant results.

Longitudinal studies have shown declines in cognitive performances of healthy participants aged 70 to 79 over a seven-year span were associated with decline on both novel/attentional demanding physical tasks (e.g., balancing, standing on a single leg, standing and walking with tandem foot placement, tapping one's feet, and walking at a fast pace) and routine physical tasks (e.g., completing five repeated chair stands, turning in a circle, signing one's name, walking at a normal pace, and gripping an object with one's hand). These results suggest that cognition plays an integral role in the execution of most physical tasks (Tabbarah, Crimmins, & Seeman, 2002). A review by Clouston et al. (2013) examining relations between rates of change in physical and cognitive functioning in older cohorts found that baseline physical and cognitive functioning were correlated with poorer cognitive and physical functioning at follow-up, respectively. Not all measures of physical and cognitive functioning were equally associated, such that the degree of change depended on the particular measures of physical and cognitive functioning. Specifically, grip strength was associated with changes in mental status examination, while walking speed was correlated with changes in fluid cognition. The authors posit that walking speed is regulated by the cerebellum, as it requires motor coordination and balance (Baillieux, De Smet, Paquier, De Deyn, & Mariën, 2008). The cerebellum connects to cortical associative areas supporting higher mental function, including the prefrontal cortex, which regulates several aspects of fluid cognitive skills. White matter integrity is also associated with information processing speed (Penke et al., 2010), balance, and gait speed (Starr et al., 2003). These possible mechanisms may explain variations in the results.

Among several physical abilities tests, the Physical Performance Test (PPT) and

Timed Up and Go (TUG) Test are physical function assessments commonly used in clinical practice and research to assess geriatric populations. Studies using the PPT as gait and balance measures have shown that the PPT is moderately correlated to MMSE scores and processing speed tasks, such as Stroop Color (Balci, Yener, & Angin, 2011). The TUG test is also a valuable tool for gait, balance, and risk of falls assessment (Alexandre, Meira, Rico, & Mizuta, 2012). Differences in TUG test subtask scores and total score performances have significantly differentiated individuals with normal cognition from those with AD (Gillain et al., 2009).

In a cross-sectional study, older individuals with AD performed worse on all TUG subtasks than those who were cognitively intact, except for the sit-to-stand subtask. Interestingly, the walking forward subtask of the TUG test differentiated people with normal cognition and MCI, while the walking back, turn, and turn-to-sit subtasks distinguished people with MCI from those with AD. The authors noted that the more complex act of turning may explain the subtask's robustness in differentiating cognitively impaired groups, as it requires frontal lobe functions, such as attention, executive skills, visual processing, and orientation to the environment. These results suggest that each TUG subtasks is unique in identifying early motor changes associated with specific cognitive decline. Each TUG subtask seems to require different cortical areas (Herman, Giladi, & Hausdorff, 2011), and some of these areas are compromised in people with AD, such as the frontal cortex and temporal areas (Sheridan & Hausdorff, 2007). The results of this work improve understanding of the motor control of TUG test. In a study that used the TUG test to measure mobility, visuospatial attention was the most robust predictor of mobility of community-dwelling older adults (Giannouli, Bock, & Zijlstra, 2018). Other

studies showed significant relationships between attention and several aspects of mobility, such as motor performance (Inzitari et al., 2007; Owsley & McGwin, 2004) and stair descent performance (Telonio, Blanchet, Maganaris, Baltzopoulos, Villeneuve, & McFadyen, 2014).

In a recent study by Gatto and colleagues (2020), higher performance-based physical abilities (as measured by faster time on the TUG test and higher scores on PPT test) were associated with better neuropsychological performance on tasks of cognitive processing speed, with participants showing faster completion times on Trail-Making Test A, faster reaction times on the Cogstate Identification task, and higher scores on Stroop Word. The PPT test was also individually associated with phonemic fluency (FAS) and verbal memory (RAVLT-IR), but the relationships were no longer significant after adjusting for ApoE genotype, suggesting that ApoE status may contribute to the physical ability-cognition relationship. Self-reported physical activity was not associated with performance on any of the cognitive domains. Previous studies have also found the association between the TUG test and processing speed in middle-aged and older adults (Chen & Tang, 2016) and executive function in older adults who are healthy (Muir-Hunter et al., 2014), with memory impairment and mild cognitive impairment (McGough et al., 2011). These authors concluded that a poorer performance in the TUG test was associated with inferior executive function performance. In contrast to these findings, Ramnath et al. (2018) did not find any significant associations between performance on the TUG test and cognitive performance in independent-living South African participants.

Pathways to age-related functional deficits are complex and not fully elucidated

(Buchman, Boyle, Leurgans, Barnes, & Bennett, 2011). Proposed mechanisms range from specific age-related brain changes to a more global deterioration of brain integrity (Clouston et al., 2013). Studies examining directionality of the association between physical function and cognitive function have yielded conflicting results, with some studies showing that cognitive functioning decrements may precede (Best, Davis, & Liu-Ambrose, 2015; Mielke et al., 2013) or co-occur with (Atkinson et al., 2010; Callisaya, Blizzard, Wood, Thrift, Wardill, & Srikanth, 2015; Tabbarah et al., 2002) physical declines, and others indicate bidirectional longitudinal associations (Gale, Allerhand, Sayer, Cooper, & Deary, 2014; Mielke et al., 2013). However, some studies have not found support of physical declines preceding and predicting cognitive decline (Best et al., 2015). These mixed results may be due to differences in sample, the timing of follow-up, and types of measures of physical function and cognition.

A large longitudinal study of older adults ranging from normal cognition to dementia by Tolea and colleagues (2015) examined the directionality of association between physical and cognitive decline and found that cognitive impairment across various cognitive domains at baseline was a better predictor of physical decline involving upper and lower extremity-related tasks on the PPT test than baseline physical impairment was of predicting the rate of cognitive decline. Additionally, participants who were cognitively impaired at baseline had a steeper rate of physical decline, but this pattern was not seen for those who were physically impaired at baseline; hence, baseline impaired physical performance does not drive cognitive decline. In contrast, Tian et al. (2016) found a bidirectional relationship overtime between slower usual gait speed and poorer executive functioning, while a directional relationship of physical function to

cognitive decline was revealed when examining fast gait speed, with slower-fast paced endurance predicting both executive function and memory scores; the reverse relationship was not found. Based on neuroimaging evidence, poorer physical and cognitive functioning are associated with cortical volume loss and white matter lesions (Holtzer, Epstein, Mahoney, Izzetoglu, & Blumen, 2014). Second, researchers have proposed that the increasing cellular senescence (a phenomenon in which cells stop dividing) during the aging process, in combination with the secretion of pro-inflammatory cytokines, growth factors and proteases, may explain findings of a bidirectional relationship (Campisi & Fagagna, 2007). Third, having multiple chronic conditions and poor lifestyle factors may contribute to the worsening of both physical and cognitive health and functions (Fabbri et al., 2016). Taken together, these results suggest not only that cognitive and physical functioning are interrelated but also that cognitive processes may be part of a causal pathway to, or share a common mechanism with, physical functioning outcomes.

Physical Function and Cognitive Reserve Influence Cognition

Due to the above findings that a relationship between physical function and cognition may exist prior to the onset of dementia, studies assessing healthy samples of older adults are important to understand further this relationship alongside other lifestyle or innate factors (e.g., proxies of cognitive reserve) that may influence this relationship. For example, cognitive reserve (i.e., premorbid verbal IQ) has been shown to significantly moderate associations between cognitive function and decline in gait speed in non-demented older adults, with individuals who have a higher CR possibly using brain systems related to executive function more effectively to protect against decline in gait speed compared to those with lower CR (Holtzer et al., 2014); however, when higher

CR individuals began to decline, they showed a faster rate of decline in follow-up periods. This counterintuitive finding is consistent with the brain reserve theory and previous research showing that higher CR is associated with more rapid cognitive decline. This may be possibly due to regression to the mean, as higher CR was linked to faster gait speed at baseline (Singh-Manoux et al., 2011).

A recent study by Ihle et al. (2017) found that more education, engagement in higher cognitive level jobs, and greater grip strength were significantly related to higher MMSE scores. Additionally, the relationship between cognitive reserve (education, occupational cognitive complexity, cognitive leisure activity engagement) and MMSE scores was moderated by degree of grip strength, with those with greater grip strength performing better in global cognitive functioning. In a follow-up study by Ihle and colleagues (2018) of healthy community-dwelling Brazilian older adults, the authors once again examined the relation of education and cognitive leisure activity as proxies of cognitive reserve to MMSE scores, with functional fitness (e.g., lower and upper body strength and flexibility, agility and balance, aerobic endurance) as the moderator. The authors noted that better performance on functional fitness tests and higher education and engagement in cognitive leisure activity were significantly related to higher MMSE scores. Additionally, the relationship of education and cognitive leisure activity to MMSE scores was significantly larger in individuals with low, compared to those with high functional fitness status in moderation analyses. This suggests that cognitive functioning in old age may more strongly depend on accumulated cognitive reserve during the life course in individuals with low, compared to those with high functional fitness status.

Findings that the relation between cognitive reserve and cognitive functioning in older adults may be more pronounced for those who are physically weaker may be explained by Spini et al. (2017)'s "vulnerability framework" and Baltes and Baltes (1989) "Selective Optimization with Compensation (SOC)" model. The vulnerability framework postulates that vulnerability is due to a lack of resources that make it difficult for individuals to cope with health problems in old age, while the SOC model recognizes that aging often leads to losses and limitations in one or more health domains and the allowance for conditions to manifest. "Successful aging" is then viewed as the ability to adapt to these limitations and optimize one's remaining capacities through a cross-domain compensatory mechanism that occurs between domains in the presence of depleted resources. Activation of "cross-domain compensation" works in buffering against lack of physical resources, which supports the cognitive reserve hypothesis. Thus, perhaps participants with lower physiologic reserve are more vulnerable and depend on their high cognitive reserve for compensating effects more so than those who are less vulnerable (Arenaza-Urquijo, Wirth, & Chetelat, 2015; Ihle et al. 2017). This "cross-compensation" mechanism may allow more vulnerable people to compensate for low physical function abilities by tapping into their cognitive reserve as a buffering resource. Therefore, the need for physical compensation in terms of cognitive reserve would be disproportionately higher in vulnerable (compared to less vulnerable) individuals. This corroborates models of cognitive reserve with regard to the notion that physical vulnerability in old age (e.g., low physical function status) may also initiate cognitive reserve effects. This explanation may—at least partly—account for the large variability in cognitive reserve–cognition relations debated in the literature (Ihle et al., 2017).

Physical Functioning and Brain Health

In addition, growing evidence suggests that structural changes of the brain in older people are related to physical fitness, such as gait dysfunction, postural instability (Whitman, Tang, Lin, & Baloh, 2001), and lack of cardiorespiratory fitness (Burns et al., 2008), suggesting that brain function is associated with physical function abilities. For example, a multi-study analysis (Colcombe, Kramer, McAuley, Erickson, & Scalf, 2004) demonstrated that older, physically fit adults had significantly greater activation in frontal, temporal, and parietal cortical regions representing executive control than their unfit counterparts. Other studies reported that lower brain volume in the prefrontal areas was associated with slower gait in high functioning or cognitively normal older adults (Rosano, Brach, Studenski, Longstreth, & Newman, 2007; Rosano, Studenski, Aizenstein, Boudreau, Longstreth, & Newman, 2011). Neuroimaging studies have revealed that the act of walking requires complex visuo-sensorimotor coordination and is associated with activation of the sensory and motor areas of the medial frontoparietal region (Fukuyama et al., 1997).

Overall, the majority of cross-sectional studies have used self-reported measures of physical activity and physical functioning, which may be problematic due to its subjectivity and low specificity (Rubenstein, Schairer, Wiland, & Kane, 1984). For those studies that have examined physical functioning, it is becoming clear that some measures of performance-based physical function may be better markers than others of early cognitive decline. The use of performance-based measures has been noted to provide more objectivity in measurement and allow for variability in effort needed for different tasks (Guralnik, Branch, Cummings, & Curb, 1989). The literature suggests that

maintenance of functional ability later in life may benefit an individual's functional capacity and play a role in attenuating cognitive decline (Ramnath et al., 2018). Together, these findings of possible preventative interventions suggest that physical activity and/or fitness may have an essential role as a non-pharmacologic means to combat MCI and perhaps dementia in older people. As many preventative interventions are now working based on a multi-domain framework, it is thus important to examine the influence of multiple factors, whether fixed or fluid throughout life, on cognitive aging (Richard et al., 2009; Vellas et al., 2014).

Apolipoprotein E (ApoE) Gene on Cognitive Aging

ApoE and Cognition

The ε4 allele of the ApoE gene (ApoE-4) is the strongest genetic risk for sporadic late-onset AD (Dumurgier & Tzourio, 2020) and the single most replicated finding in AD genetics research. It is known to be associated with cognitive performance in cognitively healthy and pathological samples. Generally, the ApoE-4 allele has been found to have a significant, though relatively small negative effect on global cognitive function and specific cognitive domains, such as processing speed, episodic memory, and executive function in cross-sectional studies of healthy older adults (Ferencz et al., 2014; Small, Rosnick, Fratiglioni, & Backman, 2004; López et al., 2017). In contrast, ApoE-4 does not appear to affect attention, visuospatial skill, and language (Wisdom, Callahan, and Hawkins, 2011). In a review by Wisdom et al. (2011), the authors indicated that with increasing age, there were significantly larger differences between ApoE-4 carriers and non-carriers on tests of memory and global cognitive function, with ApoE-4 carriers

demonstrating worse scores on the two domains. Faster declines among ApoE-4 carriers occurred within the domains of memory, executive functioning and language over a four-year period among healthy individuals (Salmon et al. 2013). Cognitive impairment, particularly in memory, is also identifiable years before a dementia diagnosis.

According to the "prodromal AD hypothesis" (Smith et al., 1998), cognitive impairments demonstrated by healthy older adults age 60 and over who are ε4 carriers are indirectly due to prodromal AD pathology. Findings from neuroimaging studies have supported this hypothesis, showing that healthy ApoE-4 carriers have reduced white matter integrity before symptom onset and smaller bilateral hippocampal and amygdala structures (O'Donoghue et al., 2018). Although the studies mentioned have found significant associations between ApoE-4 and cognition in healthy individuals, other studies have reported null findings in cognitively normal adults but have found significant adverse effects of ApoE-4 on cognitive performance among cognitively impaired subjects (Small, Basun, & Bäckman, 1998). The consensus in most meta-analyses (Small et al., 2004; Wisdom et al., 2011) is that ApoE-4 exerts general adverse effects on a range of cognitive functions in cognitively healthy adults. However, given the small effects revealed in the healthy aging literature, it is noteworthy that some very large population studies (Jorm, Mather, Butterworth, Anstey, Christensen, & Easteal, 2007) did not yield an effect of ApoE genotype at all. Thus, in contrast to the clear association between AD and ApoE-4, the impact of ApoE-4 on normal cognitive aging is less well understood (see the review by Anstey & Christensen, 2000).

Fewer longitudinal studies have investigated cognitive change as a function of ApoE genotype. Several longitudinal studies have found more rapid cognitive decline in

ApoE-4 carriers relative to non-carriers, especially in the memory domain (Mayeux, Small, Tang, Tycko, & Stern, 2001; Riley, Snowdon, Saunders, Roses, Mortimer, & Nanayakkara, 2000; Tupler et al., 2007). For example, in a large study of healthy elderly assessed over seven years, participants significantly declined on a composite score of memory but not for global cognitive functioning, language, or visuospatial abilities (Mayeux et al., 2001). A faster rate of decline on the memory scores was associated with ApoE-4 even after age, education, and ethnicity were taken into account; this discrepancy increased with age, indicating an interaction between age and genotype. Many other studies examining adults age 70 or older have found similar findings (Jonker, Schmand, Lindeboom, Havekes, & Launer, 1998; O'Hara, Yesavage, Kraemer, Mauricio, Friedman, & Murphy, 1998); however, there is evidence that rate of memory decline in association with ApoE-4 occurs as early as age 50-to-60-years-old (Caselli et al., 2009). Studies of early or preclinical AD have also demonstrated that being an ApoE-4 carrier increases the rate of beta amyloid-related cognitive decline over a period of 54 months in healthy adults, which placed them at greater risk for AD. This was most evident in the verbal and visual memory domains, as amyloid beta levels did not increase the rate of memory decline until ApoE-4 carrier status was added to predictive models (Doraiswamy et al., 2012; Lim et al., 2012; Roe et al., 2013). As such, it seems likely that amyloidosis is related to cognitive decline in healthy older adults, and this decline is increased among ApoE-4 carriers.

Overall, there remain large discrepancies in the cross-sectional and longitudinal literature concerning ApoE-4's relation to cognitive decline in healthy and pathologically aging individuals. One reason for this discrepancy is that some studies may not have

controlled for age. This is a necessary control because it has been suggested that the role of ApoE-4, as a risk factor for developing late-onset AD, may function differentially according to age (O'Donoghue et al., 2018). Due to these inconsistencies, ApoE-4 sensitivity and specificity are considered low when used as a single marker (López et al., 2016). Mixed findings across studies may also be related to unaccounted confounding factors that may modify ApoE effects on cognition, such as education, physical activity, or functional status (Reas, Laughlin, Bergstrom, Kritz-Silverstein, Barrett-Connor, & McEvoy, 2019). Thus, we will explore the literature on the relationships between ApoE and these other factors, as ApoE-4 is believed to be a vulnerability gene that enhances an individual's susceptibility to environmental influences (Sachs-Ericsson, Sawyer, Corsentino, Collins, & Blazer, 2010).

ApoE and Proxies of Cognitive Reserve

As mentioned earlier, evidence suggests that life experience factors and environmental enrichment may act to directly or indirectly prevent or slow the accumulation of AD pathology. Existing heterogeneous research findings on CR and cognition have informed researchers that high CR does not necessarily guarantee that an individual will remain free from a cognitive disorder, as many contributing factors, such as genetics, may interplay in altering one's risk for cognitive impairment. Thus, a less investigated but potentially more fruitful approach to unraveling the specific role of ApoE genotype in normal or pathological cognitive aging might be to investigate its interaction with other potential determinants of cognitive aging. ApoE-4 carriers have been found to be at potential risk for pronounced cognitive decline, whereas educational

attainment, for example, has been shown to be a risk or protective factor. Thus, education may strengthen or weaken the negative effect of having the ApoE-4 genotype (or vice versa).

A number of researchers have examined the relationship between ApoE genotype and proxies of CR on cognition. Bracco et al. (2007) investigated premorbid intelligence and the ApoE genotype and found that higher premorbid intelligence was associated with better baseline cognitive performance but faster memory decline. Additionally, a significant interaction between premorbid intelligence and ApoE- ε4/ ε4 was discovered, with the homozygous ApoE-4 genotype strengthening the role of cognitive reserve in shaping the disease's clinical expression. In a longitudinal study of lifestyle activities and cognitive performance, participation in challenging activities was associated with higher baseline scores on word and fact recall, vocabulary, and verbal fluency (Runge, Small, McFall, & Dixon, 2014). ApoE-4 genotype significantly moderated cognitively-stimulating lifestyle activities that require less and more cognitive effort with baseline verbal fluency and fact recall scores. ApoE-4 non-carriers' baseline performance were more likely to be moderated by participation in cognitively-stimulating lifestyle activities relative to ApoE-4 carriers, suggesting that ApoE may be a "plasticity" gene that makes individuals more or less amenable to the influence of protective factors such as cognitively-stimulating lifestyle activities and other life experience factors.

Similarly, Mazzeo et al. (2019) found an interaction between CR (estimated premorbid intelligence) and ApoE-4 in progression from subjective cognitive decline to MCI, with higher CR serving as a protective factor. However, higher CR was a risk factor for progression from MCI to AD, such that conversion time from MCI to AD was shorter

by three years in ApoE-4 carriers with high CR relative to non-carriers with high CR or ApoE-4 carriers with low CR. Again, this is in line with Stern's (2002) CR model suggesting that a faster decline is evident in higher functioning and genetically vulnerable individuals when cognitive reserve is overcome.

In terms of ApoE-4's relationship with education, healthy older adults with less education carrying the ApoE-4 genotype showed significantly lower scores (global cognitive functioning, episodic memory, verbal fluency, and naming) than non-carriers, while no differences were found between carriers and non-carriers in the higher education group (López et al., 2017). In a study examining the combined effect of ApoE genotype and education on cognitive change over a 27-year span, ApoE-2 carriers showed slower executive function decline with age compared to ApoE-3 homozygotes, whereas ApoE-4 carriers showed a faster decline, even after exclusion of individuals with evidence of cognitive impairment. Education moderated the negative effects of ApoE-4 on age-related decline, such that ApoE-4 carriers with lower education exhibited accelerated declines in executive functioning (Reas et al., 2019). Van Gerven et al. (2012) found similar results, but with only small evidence that older high-educated ApoE-4 carriers showed a more pronounced decline in executive abilities (mental set-shifting) than younger, low-educated carriers and non-carriers over a 12-year span, with no protective effects of higher education found on any of the other neuropsychological tests. In contrast, Kalmijn and colleagues (1997) found no association between educational attainment and rate of cognitive decline in ApoE-4 carriers, whereas there was evidence for accelerated cognitive decline in low-educated male non-carriers. Seeman et al. (2005) showed that higher educated ApoE-4 carriers showed a more pronounced cognitive

decline (e.g., memory, language, and total cognitive performance) than education-matched non-carriers; this difference was not observed among lower educated participants. These findings suggest that the combination of ApoE-4 allele and high educational attainment may be a risk factor for accelerated cognitive decline in older age, but only to a very limited extent. If anything, high-educated ε4 carriers seem to be less protected against cognitive decline than low-educated ε4 carriers and non-carriers. This may be due to their higher baseline performance; that is, they simply may have more to lose in terms of their cognitive abilities. The outcomes of these studies are partially puzzling in light of the cognitive reserve framework, as Kalmijn et al. (1997) has found some support for cognitive reserve, while Seeman et al. (2005) and Van Gerven et al. (2012) may have revealed its protective limits.

Although previous studies have shown that low education—a form of lack of mental demands in early lifetime—increase dementia risk in ApoE-4 carriers, few studies have examined whether the association between occupational complexity and cognitive decline in old age differs in ApoE-4 carriers and non-carriers. In a longitudinal study of patients aged 75 years and older by Rodriguez et al. (2021) utilizing the occupational titles O*Net database, the authors found that older adult patients who worked in jobs with higher levels of mental work demands, particularly those that required the use of language, knowledge, pattern detection abilities, complex information processing, and service-orientation were associated with a slower cognitive decline in old age in both ApoE-4 carriers and non-carriers. ApoE-4 carriers tend to have a faster cognitive decline but seem to experience a greater benefit from having a medium compared to low level of mental work demands than non-carriers. These results are supported by other studies who

found a cognitive gain for ApoE-4 carriers through intellectual lifestyle activities. For instance, a lower amount of Alzheimer's pathology was observed in ApoE-4 carriers if they had higher lifetime cognitive activity (Wirth, Villeneuve, La Joie, Marks, & Jagust, 2014; Arenaza-Urquijo et al., 2015a). A study by Jonaitis and colleagues (2013) examined baseline risk of AD (based on ApoE-4 genotype and a positive family history of AD) as a moderator of the relationship between complexity of work with data and cognitive performance in a middle-aged cognitively healthy population. The authors found a significant main effect on visuospatial function, with lower performance in the ApoE-4 carriers and a marginal interaction between ApoE-4 status and complexity of work with data on verbal ability, suggesting a possibly stronger effect of job complexity in ApoE-4 carriers than in non-carriers. The presence of at least one ApoE-4 allele has also been found to reduce the protective effects of education for those with at least a ninth-grade education or more, resulting in steeper cognitive declines with age (Seeman et al., 2005).

Other studies have found no differences in the protective effects of cognitive reserve between ApoE-4 carriers and non-carriers. No interaction effects were observed between ApoE-4 status and occupational complexity in predicting late-life cognitive change or AD risk (Potter Helms, Burke, Steffens, & Plassman, 2007; Green et al., 2013; Dekhtyar et al., 2019). Similarly, no difference was observed between ApoE-4 carriers and non-carriers in the protective effect of occupational attainment on cognitive performance and brain metabolism (Garibotto, Borroni, Sorbi, Cappa, Padovani, & Perani, 2012). Overall, these results suggest that cognitively stimulating occupations seem to build up a cognitive reserve equally in ApoE-4 allele carriers and non-carriers.

ApoE-4 carriers and non-carriers equally profited from specific high mental demands across their lifetime, and there was no protective effect of mental demands in offsetting the genetic risk (Rodriguez et al., 2021).

Both ApoE status and proxies of CR have been found to independently modify dementia onset (Ferrari et al., 2013; Ngandu et al., 2007); however, it is unknown to which degree CR alters the effect of ApoE status on the risk of progressing from normal cognition to onset of clinical symptoms in MCI or AD. In a longitudinal study, cognitive reserve (a combination of premorbid IQ and years of education) was found to be equally protective in both ApoE-4 carriers and non-carriers (Pettigrew et al., 2013). These results are consistent with previous longitudinal studies of cognitively healthy individuals (Ferrari et al., 2013; Hsiung, Sadovnick, & Feldman, 2004; Ngandu et al., 2007) and imply that the independent effects of CR and ApoE-4 status on clinical progression are evident during both the preclinical and symptomatic phases of disease. Although the mechanism by which CR protects against the effect of ApoE-4 on risk of cognitive decline remains unknown, past studies indicate that ApoE-4 enhances AD risk by increasing cortical amyloid deposition (Kim, Basak, & Holtzman, 2009), whereas CR may reduce the clinical onset of amyloid pathology (Yaffe et al., 2011). This is consistent with Soldan et al. (2013)'s findings that normal aging adults with higher CR have a higher tolerance for greater levels of AD pathology (amyloid beta and tau) and support theoretical perspectives proposing that high levels of CR allow one to better cope with brain pathology (Stern, 2009), even when brain pathology results from a genetic predisposition.

Interestingly, ApoE status has not been shown to modify the effect of CR on cognitive decline over time (Soldan et al., 2017); however, this may be due to the past observations that ApoE-4 carriers have greater amyloid accumulation at an earlier age, which in turn, leads to earlier onset, with less influence on the rate of cognitive impairment among those who develop symptoms of MCI (Albert et al., 2014). Thus, the ApoE-4 genotype may have a different role in regulating the effect of education on cognition depending on the level of impairment and/or underlying pathology. For example, one study found that ApoE-4 status did not modify the positive effect of education on cognition in the healthy control group but did weaken the positive effect of education on cognition in ApoE-4 carriers with subjective cognitive decline. Moreover, in the cognitively impaired group, ApoE-4 carriers exhibited a negative effect of education on cognition that was not observed in the non-carriers (Chen, Yang, & Han, 2020).

Limitations of Current Literature

Notably, there is extensive research on the association of cognitive reserve proxies to cognition in cross-sectional and longitudinal studies. Similarly, physical activity and function have been widely explored in association with cognition in the literature. However, findings across studies on cognitive reserve and cognition have been largely variable, with fewer studies on performance-based physical functioning in association with cognitive aging. Studies of physical functioning are extremely important in healthy older adults prior to any onset of dementia, as with aging comes physical and functional limitations, such as reduced muscular strength, muscle mass, gait difficulties,

and issues with balance, which are associated with increased frailty, risk of falls, and difficulty performing self-care functional tasks (Daley & Spinks, 2000). Additionally, older adults with both physical and cognitive impairment are at higher risk for dementia and disability (Grigsby, Kaye, Baxter, Shetterly, & Hamman, 1998).

Although IADLs and ADLs have been largely researched and found to be useful markers of functional decrements and decline in individuals with dementia, research on more subtle decrements of physical function in individuals with age-related or subclinical cognitive impairment before the loss of functional abilities remains limited. Most studies investigating the relationship between cognition and physical function have measured overall cognitive functioning using screening tools for gross cognitive impairment, such as the MMSE (Crowe, Andel, Wadley, Okonkwo, Sawyer, & Allman, 2008), mental status examination (Baillieux et al., 2008, and/or single measures of physical ability, such as gait speed (Holtzer et al. 2006; Inzitari et al. 2007). However, gait speed is only one aspect of lower extremity function, and limited research has examined the association between cognition and other physical function measures. It is important to use more comprehensive physical function measures and sensitive cognitive tests that assess specific cognitive domains. It is also important to examine multiple domains of physical function rather than a single measure in order to better capture the construct along with real-life mobility, as mobility consists of a series of complex activities requiring complex cognitive contributions (Giannouli et al. 2018).

Moreover, there have been no studies to date that have evaluated a composite score of physical function measures with a focus on distinct cognitive domains. To our

knowledge, two cross-sectional studies by Ihle and colleagues (2017; 2018) are the only ones to explore the relation of cognitive reserve on cognition and its interplay with physical fitness. However, the authors used a global cognitive score (MMSE) as the outcome on both studies, which does not parse out the unique effect of proxies of cognitive reserve on specific cognitive domains as a function of physical fitness. Additionally, while many studies have examined cognition in relation to self-reports of physical activity (Gagliardi, Papa, Postacchini, & Giuli, 2016; Howard et al., 2016; Lam et al., 2015; Lerche et al., 2018), few have utilized objective measures of physical function.

Many longitudinal studies have also found evidence that suggest genetic factors (e.g., ApoE-4) and cognitive reserve factors (e.g., education, estimated premorbid intelligence, cognitively leisure activities, occupational complexity factors) could interplay to affect cognitive decline in normal aging (Van Gerven et al., 2012; Seeman et al. 2005; López et al. 2017; Winnock et al. 2002; Brewster et al., 2014; Chen et al., 2020; Rodriguez et al., 2021; Dekhtyar et al., 2019) as well as progression to MCI or AD (Mazzeo et al., 2019). However, no previous study has examined interaction effects of the ApoE-4 genotype and multiple factors of cognitive reserve in normal aging older adults. While both ApoE and CR modify risk for dementia, little is known about the degree to which ApoE-4 (genetic susceptibility for AD) alters the effect of CR, such as education, occupation, and premorbid intelligence, on cognitive performance among cognitively normal individuals.

Overall, a consensus among research on CR is that the best models explaining inter-individual differences in cognitive functioning in old age are those that incorporate

multiple risk factors across different variable categories (e.g., demographic, cognition, physical abilities, and health) (Tang et al., 2015). ApoE-4, physical functioning, and cognitive reserve, when considered in isolation, provide limited prognostic information regarding prospective cognitive decline. Hence, it is important to understand the extent to which these various factors are associated in combination with late-life cognition.

Aims and Hypotheses

To date, the relative contributions of various proxies of CR on cognitive functioning in old age remain unclear. Furthermore, the roles of physical function and ApoE genotype in potentially modifying the effects of CR on cognition is unknown. Therefore, the present study aims to extend the current body of literature by investigating whether each key marker of cognitive reserve (i.e., premorbid verbal intelligence, years of education, occupational complexity) add predictive value to cognitive performance (i.e., global cognitive functioning, attention, processing speed, language, memory, executive functioning) in a population of cognitively intact elderly adults who are in relative in good health. Additionally, we will examine whether physical ability and ApoE status separately moderate the relationship between cognitive reserve and cognitive function. Understanding the association between physical function, ApoE genotype, and cognition in combination with specific cognitive reserve variables in healthy adults is warranted, as it can increase our understanding of the mechanisms by which ApoE-4 and physical ability increase dementia risk, particularly as strategies for primary prevention are developed (Salmon et al., 2013). It is our hope that this study will inform prospective

interventions to delay the onset of cognitive decline and maintain and/or improve cognitive functions in older adults.

To our knowledge, this is the first study to systematically evaluate the added value of using three proxies of cognitive reserve on cognitive performance, and physical performance measures as well as ApoE-4 status as moderators in the prediction of cognitive performance in a healthy community-dwelling older adult population. In line with the literature on the complex relationship between cognitive reserve, physical functioning, genetics, and cognition outlined above, we hypothesized the following:

Aim 1: Investigate the cross-sectional relationships between individual markers of cognitive reserve (CR) and performance in various cognitive domains.

Hypothesis 1: Five predictor variables that represent cognitive reserve (i.e., years of education, premorbid verbal intelligence, and occupational complexity with data, people, things) will be investigated independently. This study predicts that individuals with more years of education and higher estimated verbal intelligence will perform significantly better on measures of language, psychomotor speed, verbal memory, executive functioning, and global cognition. Additionally, individuals with occupations characterized by higher complexity of work with data and people will significantly perform better on global cognitive functioning and executive function. In contrast, individuals with higher complexity working with things will significantly perform poorer on measures of psychomotor speed and global cognitive functioning.

Aim 2: Examine the role of physical function in moderating the relationship between cognitive reserve and cognitive function.

Hypothesis 2**:** Physical functioning will significantly moderate the relationships between cognitive reserve markers and cognitive function that were found in Aim 1 above. Specifically, in line with the "vulnerability framework" described previously, higher years of education, estimated verbal intelligence, and occupational complexity will have a stronger protective effect on cognition in individuals with low, compared to high physical functioning.

Aim 3: Examine the role of ApoE genotype in moderating the relationship between cognitive reserve and cognitive function.

Hypothesis 3: ApoE genotype (ε4-; ε4+) will significantly moderate the relationship between cognitive reserve markers and cognitive functioning. Specifically, the potential protective effects of cognitive reserve proxies on cognitive functioning in old age may be reduced in individuals who are ApoE-4 carriers.

CHAPTER TWO

METHODS

Participants

Participants are 130 healthy older adults (43.1% males, 56.9% females, 60 to 96 years of age), who were originally recruited for a longstanding prospective cohort study, the Adventist Health Study-2 (AHS-2). During 2002-2007, the cohort reported excellent health, with 45% of cohort participants following vegetarian diets (Rizzo, Jaceldo-Siegl, Sabate, & Fraser, 2013); additionally, 1.1% of individuals endorsed being a current smoker and 6.6% currently consumed alcohol (Butler et al., 2008). In 2016, the AHS-2 Cognitive and Neuroimaging (AHS2-CAN) substudy identified 2,685 participants who were 60 years or older, community-dwelling, and living within 75 miles of Loma Linda University (Gatto et al., 2020). From 2016 to 2018, 199 participants were invited to participate in the study by telephone. Exclusion criteria included: a diagnosed neurological condition, such as Parkinson's disease, epilepsy, multiple sclerosis, etc.; history of diabetes, brain tumor, stroke, or other focal brain injury; and any current acute medical conditions such as infections, nutritional deficiencies, or adverse drug reactions that could adversely impact cognitive function. Of those, 168 (84%) agreed to participate and were screened for eligibility. Two did not meet inclusion criteria for being proficient in writing, speaking, and understanding English. Twelve withdrew, one could not be scheduled, twelve were unreachable, and five postponed. One hundred and thirty-six otherwise healthy adults were enrolled in the study and attended an in-person visit at our study clinic. Four were later excluded for having a medical condition that could adversely impact cognitive function, and two had incomplete data. Thus, 130 participants who had

complete data on cognitive and physical abilities were included in the analyses. In the present study, participants identified themselves as Caucasian (80.0%), Black or African American (8.5%), Hispanic (4.6%), Asian (5.4%), and Native Hawaiian or other Pacific Islander (1.5%). Each subject gave informed written consent, and all procedures were approved by the Loma Linda University Institutional Review Board.

Procedure

At the in-person visit, a brief interview was conducted to gather information regarding participants' demographic information (e.g., age, sex, ethnicity, handedness, years of education, marital status), significant physical or medical concerns, and basic psychiatric, social and family history. Participants were then administered a 2-hour comprehensive neuropsychological battery and approximately 30-minutes of physical function assessment by trained psychometrists. A phlebotomist obtained a sample of whole blood from participants, which was then analyzed for ApoE genotype at the LLU Center for Genomics; the protocol for bloody and DNA analysis has been previously described (Gatto et al., 2020).

Neuropsychological Assessment

Cognitive function was assessed utilizing a battery of neuropsychological tests designed to assess a broad range of cognitive abilities in specific domains. The selected cognitive battery emphasizes tasks used to detect age-associated changes in elderly populations, particularly episodic memory, attention, processing speed, and executive function. Specifically, the battery included the following tests:

Estimated premorbid intelligence

American National Adult Reading Test (AMNART). The AMNART error score (Lo et al., 2013) was used as a measure of estimated premorbid verbal intelligence (IQ). AMNART error scores were reverse scored as a continuous variable, such that more errors indicated lower premorbid verbal intelligence. The error score for the AMNART was used in analyses rather than the total VIQ score, as the VIQ equation consists of years of education, which may produce problems with multicollinearity since education was used as a separate variable representing cognitive reserve.

Global cognitive functioning

Mini-Mental State Examination (MMSE). The MMSE was administered as a descriptive measure of gross cognitive impairment. The MMSE consists of five subsections covering orientation (0–10 points), immediate and delayed free recall (0–3 points each), working memory (0–5 points), and language (0–9 points). A total score can be derived by adding the five subsection scores (0–30 points).

A global cognition composite score was computed as a combination of 14 neuropsychological test scores across four cognitive domains (processing speed, language, verbal memory, and executive function), which are described in the following paragraphs. All test scores were transformed into z-scores and then averaged. Of note, z-scores reflect the standardized difference of an individual's performance level compared to the study sample's mean and standard deviation.

Psychomotor/processing speed

Wechsler Adult Intelligence Scale - 4th edition (WAIS-IV) Coding subtest. The Coding subtest is a visual, paper and pencil task that requires individuals to match numbers with symbols based on a "key" at the top of the page by drawing the correct symbol in the boxes provided. Coding measures visual processing speed, short-term visual memory, and the ability to shift the eyes efficiently back and forth between the "key" and the responses. This task also assesses the ability to sustain focus and effort for two minutes.

Trail-making Test (Part A). The Trail-making Test - Part A (TMT-A) is a measure of psychomotor speed wherein the participant must draw a line to connect consecutive numbers, from 1 to 25.

Stroop Test (Word and Color Naming). The Stroop Color Naming and Word Reading tasks are measures of verbal processing speed, requiring the rapid naming of colors and rapid reading of words, respectively.

For our analyses, we transformed TMT-A, Stroop Word, Stroop Color, and the WAIS-IV Coding subtest into z-scores based on the tests' sample means and standard deviations and then averaged in order to create a psychomotor speed composite score.

Language

Boston Naming Test (BNT). The BNT is a 60-item test that requires participants to name simple black and white pictures that are presented. If the participant fails to give the correct response, the examiner may give the participant a semantic (e.g., for broccoli "it is a vegetable") or phonemic cue (e.g., it begins with "br"), with the latter consisting

of an initial sound of the target word after a 20-second period. For our analyses, we used the "correct with semantic cue" scores, as this score most likely simulates everyday life naming.

Controlled Oral Word Association Test (COWAT) Animals. The Animals subtest of the COWAT was used to assess participants' ability to generate words belonging to a semantic category (e.g., animals) in one minute.

For our analyses, we transformed BNT and Animals to z-scores based on the sample means and standard deviations and then averaged in order to create a language composite score.

Verbal learning and memory

Rey Auditory Verbal Learning Test (RAVLT). This task measures learning of a list of 15 words (List A) over five trials with immediate free-recalls after each trial. Subjects then learn a distractor list, followed by immediate free-recall, after which they must recall the first list again (recall after interference). A delayed recall (episodic memory measure) of the first list is then required after 30 min, followed by a recognition test. The score is the number of words recalled over the five immediate recall trials, delayed recall and recognition tests.

WMS-IV Logical Memory (LM). Immediate (LM I) and delayed (LM II: after 30 min) recall (measure of episodic memory) of prose were assessed. The score used was the number of the idea units recalled. We transformed the RAVLT Immediate Recall and Delayed Recall raw scores and LM I and LM II raw scores to z-scores based on both

tests' sample means and standard deviations and then averaged in order to create a verbal memory composite score.

Executive Function

WAIS-IV Digit Span Forward subtest. Participants are required to repeat series of numbers in order (Forward), in reverse order (Backward), and from lowest to highest (Sequencing). The task measures how long a participant can pay attention to what they hear and "hold" the information in short-term memory long enough to immediately recite the information back or perform a simple operation with the information (such as re-ordering the numbers).

Trail-Making Test Part B. The Trail-Making Test Part B (TMT-B) is a measure of mental flexibility and set-shifting. The participant is asked to connect numbers and letters in an alternating progressive sequence, 1 to A, A to 2, 2 to B, and so on.

Stroop C. This test measures an individual's ability to inhibit an over-learned verbal response (reading a word) in order to generate a conflicting response (saying the color of the print ink). It is primarily a measure of inhibition or impulse control. Inhibition requires the client to inhibit verbal impulses (to read the word) and instead to name the color of the ink.

COWAT Phonemic Fluency Task (FAS). FAS is a measure of phonemic fluency to assess participants' ability to generate words beginning with a specific letter (e.g., FAS) in a time limit of one minute per letter.

For our analyses, we transformed TMT-B, Stroop C, FAS, and the WAIS-IV Digit Span subtest total score to z-scores based on each tests' sample mean and standard deviation and then averaged in order to create an executive function composite score.

Physical Function Assessment

Current level of physical functioning and mobility were measured during the clinic visit using two performance-based measures (e.g., Physical Performance Test (PPT) & Timed Up and Go (TUG) Test). Performance-based measures were used to assess physical functioning rather than self-reported measures, as the former provides more objectivity in measurement, is not biased to participant under- or over-reporting, and allows for variability in effort needed for different tasks (Fitzpatrick et al. 2007). Participants were given a maximum of two chances to complete each item within each task when necessary. Assistive devices were permitted for tasks involving body rotation, walking, and stair climbs. On timed tasks, trained examiners asked participants to engage in the activity in a rapid pace. For example, participants were asked to engage in rapid-paced walking, as fast gait speed has been found to be a more sensitive measure than self-paced walking speed in differentiating levels of cognition in older healthy adults (Fitzpatrick et al., 2007). The following physical functioning measures were used:

Physical Performance Test (PPT)

The PPT is a clinical assessment tool used to monitor and describe through several performance tasks the multiple domains of physical function in frail and well community-dwelling older adults (Reuben & Siu, 1990). Specifically, the PPT consists of

nine timed activities, including sentence writing, simulated eating, ability to lift a book and place it on a shelf, simulating dressing, picking up a penny from the floor, 360 degrees turning right and left, walking 50 feet, and climbing 1 flight of stairs, and climbing several flights of stairs (a maximum of 4). Each of the nine tasks was scored on a 5-point scale (0 = lowest through 4 = highest performance). Participants were asked to perform a task as fast as they can and are scored based on the time taken to achieve task completion. The total PPT score was computed by summing up these items (ranging from 0–36) with lower scores indicating poor functionality. The score of 36 is the highest score, which reflects optimal performance. The test administration and scoring adhere to the protocol published by Reuben and Siu (1990). The PPT has demonstrated concurrent validity with high correlation with basic daily activities and the Tinetti Performance Oriented Mobility Assessment test, which measures balance and gait (Soubra, Chkeir, & Novella, 2019).

Timed Up and Go (TUG) Test

The TUG test (Podsiadlo & Richardson, 1991) is a clinical assessment task commonly used to assess balance and walking ability in older adult populations (Bohannon & Scaubert, 2005; Mathias, Nayak, & Isaacs, 1986). Participants are observed and timed in seconds, while they rise from an armed chair seated position of approximately 46 cm seat height and 65 cm arm height, walk at their fast pace a distance of 9.8 feet meters towards a line marked on the floor, turn 180 degrees, walk back to the chair, and sit down—all which is asked to do at their fastest speed ensuring safety. Participants are also asked to wear their regular footwear and use their walking assistance

devices if necessary. A faster time (in seconds) indicates better performance. Although it is a simple task, the TUG test is highly recommended since it includes the basic everyday movements and daily life tasks (standing, walking, and turning) and contains valuable components (Herman et al., 2011; Nordin, Rosendahl, & Lundin-Olsson, 2006). Moreover, it correlates well with other tests of mobility, such as balance and transfer ability test called the Berg Balance Scale ($r = -0.81$), gait speed ($r = -0.61$), and the Barthel Index ($r = -0.78$), which measures neuromuscular and musculoskeletal disorders (Podsiadlo & Richardson, 1991).

A composite score of both the PPT and TUG reflect physical function ability. The TUG time (recorded as 00:seconds:hundredths of a second) was converted by splitting the variable into three pieces at the colons. Seconds and hundredths of a second were retained as separate variables. The latter variable was then multiplied by 100 and added to the seconds to comprise the total TUG time. Mean scores on the PPT and TUG within this study have been found to be comparable with published values for populations of other community-dwelling adults (Gatto et al., 2020; Papadakis et al., 1995; Steffen, Hacker, & Mollinger, 2002; Steffen & Mollinger, 2005).

Occupational Complexity Assessment

Occupational data were gathered from participants in the baseline AHS-2 questionnaires. Participants were asked to report up to three main occupations held in their adult life and the number of years spent on each job. Following the example of most other studies that have used the job complexity rating system, each reported occupation was then matched with the best fitting category and coded using 2019 O*NET-SOC according to the 1970 U.S. Census Dictionary of Occupational Titles (DOT; United States Employment Service, 1991). The DOT classifies occupations based on a 9-digit code (i.e., 092.227-010, primary school teacher). The fourth, fifth, and sixth digits represent occupational complexity with data, people, and things, respectively (Roos & Treiman, 1980), with values ranging from 0 (most complex) to 6 (least complex) for complexity of work with *data*, 0 to 8 for complexity of work with *people*, and 0 to 7 for complexity of work with *things*. This process for coding and categorization of work activities has been used (see e.g., Smart et al., 2014; Boots et al., 2015; Feldberg et al., 2016; Sörman et al., 2019) and validated in previous studies (Kohn and Schooler, 1983; Petersen et al., 2001). Similar to Krohn and Schooler (1983), occupational complexity scores for data, people, and things were then reverse coded so that higher scores reflect greater job complexity. Complexity classifications of occupations are summarized in Table 2. See Table 3 for raw means (SDs) for each occupation complexity category in our sample.

Table 2. Dimensions used in the rating of occupations into complexity of working with data, people, and things.

Data	People	Things
6 Synthesizing	8 Mentoring	7 Setting Up
5 Coordinating	7 Negotiating	6 Precision Working
4 Analyzing	6 Instructing	5 Operating-Controlling
3 Compiling	5 Supervising	4 Driving-Operating
2 Computing	4 Diverting	3 Manipulating
1 Copying	3 Persuading	2 Tending
0 Comparing	2 Speaking-Signaling	1 Feeding-Offbearing
	1 Serving	0 Handling
	0 Taking Instructions-Helping	

Note: Reference from the Dictionary of Occupational Titles (DOT). Rating Scales have been reversed for the current study, so a higher score reflects greater complexity.

ApoE Genotype Lab Analysis

A phlebotomist obtained a sample of whole blood from participants using standard venipuncture procedures and BD Vacutainer® Mononuclear Cell Preparation Tubes (CPT) with sodium citrate. CPTs were processed within 2 hours of the blood draw following the manufacturer's protocol. White blood cells (WBCs) were collected and stored in -80°C freezers at the Center for Genomics at LLU. Genomic DNA was extracted using the Qiagen All prep DNA/RNA/miRNA Universal kit from frozen human WBCs. DNA was quantified using Qubit 3.0 assay. Genotyping was carried out in 96-well plates using TaqMan Genotyping Master Mix by Applied Biosystem. PCR was performed on the Applied Biosystems QuantStudio 7 Real Time PCR System according to manufacturer's specifications and data analyzed with the SDS2.4 software. Genotyping for two single nucleotide polymorphisms (rs429358 and rs7412) was used to determine the apolipoprotein E genotype (2,3; 3,3; 3,4; 4,4). For analyses, ApoE genotype was collapsed into two categories (ε2/3 and ε3/3 = ε4-; ε3/4 and ε4/4 = ε4+).

CHAPTER THREE

RESULTS

Data were analyzed for 130 healthy older adults and sample demographics are in Table 3. There were more females than males, more Whites, and the average age was 75.16 years. The sample was highly educated indicating a possible restriction of range. The majority of the sample (75%) were ApoE-4 non-carriers.

Table 3. Characteristics of study participants

Gender, *n (%)*	
Male	56 (43.1%)
Female	74 (56.9%)
Race, *n (%)*	
Caucasian	104 (80.0%)
Black or African American	11 (8.5%)
Hispanic	6 (4.6%)
Asian	7 (5.4%)
Native Hawaiian or other Pacific Islander	2 (1.5%)
ApoE genotype, *n (%)*	
ε4-	81 (75.0%)
ε4+	27 (25.0%)
Age (years), M (SD), *range*	75.16 (8.14), *60-96*
Education (years), M (SD), *range*	16.69 (2.54), *11-20*
AMNART *n* of errors, M (SD), *range*	11.39 (7.40), *0-38*
Occupational Complexity (reverse coded), M (SD), *range*	10.59 (4.19), *0-19*
Complexity of data, M (SD), *range*	4.08 (1.18), *0-6*
Complexity of people, M (SD), *range*	4.06 (2.73), *0-8*
Complexity of things, M (SD), *range*	2.45 (2.49), *0-6*
Physical Performance Test total, M (SD), *range*	26.58 (4.45), *13-34*
Timed Up and Go (seconds), M (SD), *range*	10.44 (2.78), *5.34-22.44*

Prior to creating composite scores to represent the dependent variables, z-scores were formed for the components of each composite. The z-scores for Trails A and B and TUG completion times were reversed by subtracting them from zero, since higher raw

scores on these measures indicated poorer performance. Four cognitive composite scores were computed as the means of the *z*-scores for the appropriate subtests as detailed in Table 4. A fifth composite score was formed to represent global cognition, using the mean of the z-scores of all 14 subtests included in the domain-specific composites. One additional composite score was created to represent the covariate, physical functioning, as detailed in Table 4. Missing subtests within a composite were estimated using mean substitution if at least 75% of the subtests were present. For example, if only one of four subtests was missing, its value was estimated using the mean of the remaining three tests. The estimation of missing subtests was successful for one respondent missing a subtest for the psychomotor speed composite, one respondent missing a subtest for the verbal memory composite, two respondents missing a subtest for the executive function composite, and three respondents missing subtests for the global cognition composite.

Table 4 also provides summary statistics for age and gender, which were used as covariates during hypothesis testing, and the independent variables, years of education, AMNART score and the three levels of occupational complexity (OCC Data, OCC People, and OCC Things). The normality assumption was assessed for these measures and for the composite scores using *z*-scores formed by dividing skewness by the standard error of skewness. A *z*-score within ± 3.29 is indicative of a normal distribution (West, Finch, & Curran, 1995). Four variables, AMNART, physical function, language, and OCC Data exhibited substantial skewness. (Note that non-normality was not addressed for the components of the composite scores). Normalizing transformations were applied according to recommendations provided by Tabachnick and Fidell (2013). All four scales were skewed to the high ends of their respective distributions, so these scores were

reflected (subtracting each from the maximum value plus 1), prior to normalization. The distributions of AMNART, physical function, and language were normalized using square roots. The distribution of OCC Data was normalized using a logarithm transformation. Since the reflected scores reversed the original direction of the scores, making higher values represent poorer performance, the normalized scores were again reflected, by subtracting the square roots or logarithm from the highest value within each square root or logarithm distribution plus 1. The resulting normalized scores were appropriately higher for respondents with better performance. The normalized scores were used in all subsequent analyses. Prior to conducting the analyses to test Hypotheses 2 and 3, the predictors were converted to z-scores to aid in the interpretation of results and to avoid issues of multicollinearity.

The distributions of all continuous variables were examined for the presence of extreme outliers, using the benchmark of > 3*IQR. After normalization, the distribution of the language composite score had one extreme outlier. This value was set to missing.

Table 4. Summary statistics for age, independent measures, composite scores and their components

Variables	*N*	*Mean*	*SD*	*Skewness*	*SE*	*z*
Age	130	75.16	8.14	0.12	0.21	0.56
Years of Education	130	16.69	2.54	-0.30	0.21	-1.41
AMNART - errors	130	11.39	7.40	1.03	0.21	-4.86
Occupational Complexity						
OCC Data	126	0.96	0.37	-0.31	0.22	-1.44
OCC People	126	4.06	2.73	0.24	0.22	1.09
OCC Things	126	2.45	2.49	0.29	0.22	1.32
Physical Function Composite	126	0.01	0.95	-1.11	0.22	-5.12
Physical Performance Test - Total	127	26.58	4.45	-0.89	0.22	-4.16
Timed Up and Go - completion time (secs)	126	10.44	2.78	1.24	0.22	5.76
Psychomotor Speed Composite	129	0.00	0.80	-0.20	0.21	-0.93
Trails A - completion time (secs)	129	36.85	14.64	2.01	0.21	9.44
WAIS-IV Coding - Total	129	53.05	13.50	0.31	0.21	1.45

Stroop Color - Total correct	128	61.10	11.45	0.22	0.21	1.03
Stroop Word - Total correct	130	90.83	13.65	0.11	0.21	0.53
Language Composite	130	0.00	0.85	-0.90	0.21	-4.26
BNT - Total correct w/ stimulus cues	130	54.65	5.74	-1.92	0.21	-9.04
Animals - Total words	130	17.42	4.89	0.17	0.21	0.78
Verbal Memory Composite	130	0.00	0.83	0.09	0.21	0.42
RAVLT - Total recall Trials 1-5	130	38.71	9.74	0.05	0.21	0.23
RAVLT - List A, long-delay recall	130	7.56	3.55	0.03	0.21	0.14
Logical Memory I - Total Recall	129	30.87	7.23	-0.02	0.21	-0.10
Logical Memory II - Total Recall	130	17.62	7.14	0.01	0.21	0.06
Executive Function Composite	130	0.00	0.72	-0.43	0.21	-2.01
FAS - Total	130	36.08	10.75	0.31	0.21	1.47
Trails B - completion time (secs)	129	108.98	61.53	2.15	0.21	10.08
Digit Span - Total	130	24.76	5.06	0.30	0.21	1.42
Stroop Color-Word - Total correct	128	31.77	9.33	0.12	0.21	0.54
Global Cognition Composite	130	0.00	0.61	-0.35	0.21	-1.64

Pearson intercorrelations were computed between the *z*-scores for subtests within each composite (see Table 5). Of note, the significance level for this study is set to 0.05. All intercorrelations were significant ($p < .001$), with the exception of the correlation between FAS and TMTB, which was significant at $p = 0.012$, and FAS with Stroop Color/Word ($p = .004$).

Table 5. Intercorrelations between subtest z-scores within each cognitive composite

Physical Function Composite (n = 126)	
	TUG time
PPT total	0.83

Psychomotor Speed Composite (n = 128-9)			
	Coding	Stroop Color	Stroop Word
TMTA	0.58	0.37	0.31
Coding		0.62	0.52
Stroop Color			0.67

Language Composite (n = 130)	
	Animals
BNTsc	0.43

Verbal Memory Composite (n = 129-130)			
	RAVLTLD	LMI	LMII
RAVLTIR	0.76**	0.48**	0.53**
RAVLTLD		0.38**	0.52**
LMI			0.82**

Executive Function Composite (n = 129-130)			
	TMTB	DS Total	Stroop Color/Word
FAS	0.22*	0.43**	0.25*
TMTB		0.44**	0.46**
DS Total			0.37**

Note: All correlations were significant at $p < .001$ except FAS with TMBT ($p = .012$) and FAS with Stroop Color/Word ($p = .004$). *. $p < .05$; ** $p < .001$.

Pearson intercorrelations between the dependent variables are shown in Table 6. All relationships were significant at the .001 level, except between Psychomotor Speed and Verbal Memory ($p = .009$).

Table 6. Intercorrelations between dependent variables

		2	3	4	5
1	Global Cognition	0.76**	0.71**	0.73**	0.86**
2	Psychomotor Speed		0.37**	0.23*	0.66**
3	Language			0.53**	0.49**
4	Verbal Memory				0.44**
5	Executive Function				

Note. Psychomotor Speed and Language $n = 129$, otherwise $n = 130$; *$p < .01$, ** $p < .001$.

The Pearson intercorrelations between independent variables, covariates, and moderators are presented in Table 7. Several univariate relationships will be addressed in the context of hypothesis testing.

Table 7. Intercorrelations between independent variables, covariates and moderators

		2	3	4	5	6	7	8	9
	Independent Variables								
1	AMNART	0.19 *	0.32 ***	0.06	0.43 ***	-0.04	-0.02	0.25 **	-0.11
2	OCC Data		0.58 ***	-0.11	0.41 ***	-0.22 *	0.05	0.21 *	-0.03
3	OCC People			-0.06	0.63 ***	-0.24 **	0.02	0.11	-0.08
4	OCC Things				0.09	-0.26 **	-0.07	0.11	-0.10
	Covariates								
5	Years of Education					-0.19 *	-0.03	0.24 **	-0.04
6	Female Gender						-0.03	-0.22 *	0.04
7	Age							-0.45 ***	-0.18
	Moderators								
8	Physical Function								-0.01
9	ApoE genotype								

Note. Occupational Complexity (OCC Data, OCC People, OCC Things) $n = 126$; Physical Function $n = 126$; ApoE genotype $n = 108$; otherwise $n = 130$; * $p < .05$, ** $p < .01$, *** $p < .001$.

A final set of Pearson correlations was conducted between the dependent variables and the independent variables, covariates and moderators (see Table 8). The significant univariate relationships will be addressed in the context of the multivariate analyses to test the hypotheses.

Table 8. Correlations between the dependent variables and the independent variables, covariates, and moderators

	Dependent Variables				
	Global Cognition	Psychomotor Speed	Language	Verbal Memory	Executive Function
Independent Variables					
AMNART	0.45 ***	0.19 *	0.45 ***	0.33 ***	0.47 ***
OCC Data	0.16	0.09	0.10	0.07	0.24 **
OCC People	0.20 *	0.02	0.19 *	0.23*	0.20 *
OCC Things	-0.04	0.01	-0.01	-0.06	-0.04
Years of Education	0.29 ***	0.12	0.17 *	0.26 **	0.33 ***
Covariates					
Female Gender	0.11	0.09	-0.05	0.23 **	0.01
Age	-0.51 ***	-0.50 ***	-0.31 ***	-0.29 ***	-0.43 ***
Moderators					
Physical Function	0.39 ***	0.41 ***	0.25 **	0.18 *	0.33 ***
ApoE genotype	-0.13	-0.09	-0.07	-0.09	-0.13

Note. Occupational Complexity (OCC Data, OCC People, OCC Things), Physical Function, and Language n =126; ApoE genotype n = 108; otherwise n = 130; * $p < .05$, ** $p < .01$, *** $p < .001$

Hypothesis Testing

All three hypotheses were tested using hierarchical linear regression. In addition to testing the underlying assumption of normality as part of the preliminary analyses, the underlying assumptions of homoscedasticity and multicollinearity were also tested. Scatterplots between the predicted values and residuals for the regressions were conducted to test Hypothesis 1, and indicate that for each regression, the assumption of homoscedasticity was met, meaning that random disturbance in the relationships between the independent variables and the dependent variable were similar across all values of the independent variables. The assumption of lack of multicollinearity was assessed using variance inflation factors, which are displayed in all regression tables and indicate that multicollinearity was not evident in any of the regressions (VIF ≥ 1.0 and < 3.0).

Hypothesis 1

Individuals with more years of education and higher estimated verbal intelligence will perform significantly better on measures of language, psychomotor speed, verbal memory, executive functioning, and global cognition. Additionally, individuals in occupations characterized by higher complexity of work with data and people will significantly perform better on global cognitive functioning and executive function while individuals with higher complexity working with things will significantly perform poorer on measures of psychomotor speed and global cognitive functioning.

This hypothesis was tested using hierarchical linear regressions on the five dependent variables. Years of age and gender were entered in the first step, followed by the five independent variables (AMNART, occupational complexity levels [work with data, people, things], and years of education) in the second step. The results are presented in Tables 9 through 13.

As shown in Table 9, gender and age explained a significant 27% of the variance in global cognition (F (2,123) = 23.16, $p < .001$). The cognitive reserve variables (AMNART, occupational complexity with people, data, and things, and years of education) explained an additional 23% of the variance (F (5,118) = 10.71, $p < .001$). However, in the final model, estimated premorbid verbal intelligence (AMNART score) was the only CR variable which contributed significantly to the prediction of global cognition ($\beta = 0.38$, $p < .001$).

Table 9. Hierarchical regression on Global Cognition using AMNART score, Occupational Complexity Levels, and years of education as predictors and controlling for age and gender

Step	Variables Entered	R^2	R^2 Change	F	df	p	β	p	VIF
1	Female Gender	0.27	0.27	23.16	2,123	< .001	0.14	0.053	1.18
	Age						-0.51	< .001	1.01
2	AMNART	0.50	0.23	10.71	5,118	< .001	0.38	< .001	1.25
	OCC Data						0.10	0.239	1.55
	OCC People						-0.02	0.819	2.13
	OCC Things						-0.07	0.342	1.14
	Years of Education						0.13	0.136	1.89

As shown in Table 10, age was the only significant predictor of psychomotor speed (β = -0.51, p < .001). The cognitive reserve variables did not add significantly to the prediction. (F (5,117) = 1.62, p = .160).

Table 10. Hierarchical regression on Psychomotor Speed using AMNART score, Occupational Complexity Levels, and years of education as predictors and controlling for age and gender

Step	Variables Entered	R^2	R^2 Change	F	df	p	β	p	VIF
1	Female Gender	0.27	0.27	22.71	2,122	< .001	0.09	0.287	1.20
	Age						-0.51	< .001	1.01
2	AMNART	0.32	0.05	1.62	5,117	0.160	0.15	0.082	1.25
	OCC Data						0.14	0.133	1.55
	OCC People						-0.13	0.248	2.13
	OCC Things						-0.01	0.914	1.16
	Years of Education						0.08	0.443	1.89

In terms of language, after controlling for age and gender, the cognitive reserve variables added significantly to the prediction, explaining an additional 21% of the variance (F (5,117) = 7.03, p < .001). AMNART score was the only significant predictor of language (β = 0.46, p < .001); occupational complexity and years of education did not contribute significantly to the prediction of language scores (Table 11).

Table 11. Hierarchical regression on Language using AMNART score, Occupational Complexity Levels, and years of education as predictors and controlling for age and gender

Step	Variables Entered	R^2	R^2 Change	F	df	p	β	p	VIF
1	Female Gender	0.10	0.10	6.80	2,122	0.002	-0.05	0.555	1.18
	Age						-0.31	< .001	1.01
2	AMNART	0.31	0.21	7.03	5,117	< .001	0.46	< .001	1.25
	OCC Data						0.00	0.983	1.55
	OCC People						0.10	0.354	2.12
	OCC Things						-0.06	0.472	1.14
	Years of Education						-0.11	0.294	1.89

The cognitive reserve variables were significantly predictive of executive function and explained an additional 27% of the variance (F (5,118) = 11.75, p < .001) after controlling for age and gender. Specifically, AMNART score (β = 0.40, p < .001), OCC Data (β = 0.20, p = .021), and years of education (β = 0.19, p = 0.048) contributed significantly to the prediction of executive function scores (see Table 12).

Table 12. Hierarchical regression on Executive Function using AMNART score, Occupational Complexity Levels, and years of education as predictors and controlling for age and gender

Step	Variables Entered	R^2	R^2 Change	F	df	p	β	p	VIF
1	Female Gender	0.19	0.19	14.65	2,123	< .001	0.04	0.608	1.18
	Age						-0.44	< .001	1.01
2	AMNART	0.46	0.27	11.75	5,118	< .001	0.40	< .001	1.25
	OCC Data						0.20	0.021	1.55
	OCC People						-0.15	0.134	2.13
	OCC Things						-0.08	0.256	1.14
	Years of Education						0.19	0.048	1.89

Performance on verbal memory tasks was significantly predicted by the AMNART score (β = 0.24, p = .005). Years of education and occupational complexity did not add significantly to the prediction (Table 13).

Table 13. Hierarchical regression on Verbal Memory using AMNART score, Occupational Complexity Levels, and years of education as predictors and controlling for age and gender

Step	Variables Entered	R^2	R^2 *Change*	*F*	*df*	*p*	*β*	*p*	*VIF*
1	Female Gender	0.14	0.14	9.70	2,123	< .001	0.28	0.001	1.18
	Age						-0.28	< .001	1.01
2	AMNART	0.31	0.17	5.94	5,118	< .001	0.24	0.005	1.25
	OCC Data						-0.06	0.525	1.55
	OCC People						0.15	0.169	2.13
	OCC Things						-0.03	0.712	1.14
	Years of Education						0.16	0.124	1.89

In conclusion, the results of the first set of analyses partially supported Hypothesis 1. After controlling for age and gender, estimated verbal intelligence (AMNART score) significantly predicted global cognition, language, executive function, and verbal memory, but not psychomotor speed. Occupational complexity with data and years of education significantly contributed only to the prediction of executive function. Complexity of work with people and things did not add significantly to the predictions of any of the cognitive outcomes.

Hypothesis 2

Physical functioning will significantly moderate the relationships between cognitive reserve (e.g., education, estimated verbal intelligence, and occupational complexity levels) and cognitive function, such that higher cognitive reserve will have a more protective effect in individuals with low, compared to high physical functioning supporting the "vulnerability framework."

This hypothesis was tested using hierarchical linear regressions on the five dependent variables. Participant gender and years of age were entered in the first step. In the second step, the five independent variables, AMNART, OCC Data, People and Things, and years of education were entered, in addition to the moderator variable, the physical function composite. In the third step, the interactions of physical function and the five independent variables were entered. The results are presented in Tables 14 through 18.

The results presented in Table 14 indicate that neither physical function nor its cross-products with the CR variables added significantly to the prediction of global cognition beyond the effects of age and estimated verbal intelligence.

Table 14. Hierarchical regression on Global Cognition using AMNART score, Occupational Complexity Levels, and years of education as predictors, physical function as a moderator, controlling for age and gender

Step	Variables Entered	R^2	R^2 *Change*	*F*	*df*	*p*	*β*	*p*	*VIF*
1	Female Gender	0.26	0.26	20.89	2,119	< .001	0.18	0.029	1.38
	Age						-0.45	< .001	1.53
2	AMNART	0.49	0.23	8.28	6,113	< .001	0.36	< .001	1.40
	OCC Data						0.04	0.641	1.82
	OCC People						0.05	0.671	2.59
	OCC Things						-0.06	0.431	1.25
	Years of Education						0.11	0.268	2.01

	Physical Function						0.05	0.552	1.75
3	AMNART x Physical Function	0.50	0.01	0.53	5,108	0.750	0.07	0.378	1.28
	OCC Data x Physical Function						0.02	0.829	1.97
	OCC People x Physical Function						-0.14	0.213	2.82
	OCC Things x Physical Function						0.06	0.450	1.25
	Years of Education x Physical Function						0.05	0.672	2.50

In terms of Psychomotor Speed (Table 15), age was the only significant predictor (β = -0.41, p < .001). No interaction effects were observed, indicating that physical function did not modify the effects CR on psychomotor speed.

Table 15. Hierarchical regression on Psychomotor Speed using AMNART score, Occupational Complexity Levels, and years of education as predictors, physical function as a moderator, controlling for age and gender

Step	Variables Entered	R^2	R^2 *Change*	*F*	*df*	*p*	β	*p*	*VIF*
1	Female Gender	0.28	0.28	22.46	2,118	< .001	0.17	0.074	1.41
	Age						-0.41	< .001	1.53
2	AMNART	0.34	0.07	1.93	6,112	0.083	0.08	0.404	1.41
	OCC Data						0.09	0.378	1.83
	OCC People						-0.09	0.453	2.60
	OCC Things						0.01	0.920	1.28
	Years of Education						0.09	0.444	2.01
	Physical Function						0.19	0.068	1.75
3	AMNART x Physical Function	0.35	0.01	0.30	5,107	0.910	-0.02	0.853	1.28
	OCC Data x Physical Function						-0.03	0.800	1.97
	OCC People x Physical Function						-0.02	0.868	2.82
	OCC Things x Physical Function						0.07	0.456	1.25
	Years of Education x Physical Function						0.09	0.481	2.50

Consistent with results from the first aim, age (β = -0.27, p = .006) and AMNART score (β = 0.48, p < .001) were significant predictors of language (see Table 16). Although physical function did not have a significant main effect on language, the interaction between AMNART score and physical function did contribute significantly to the prediction (β = 0.19, p = .034). Of note, both AMNART score and physical function were significant positive predictors of Language (see Tables 7 and 8 for correlations). The interaction effect is illustrated in Figure 3. In separate regressions for cases above and below the median of physical function (i.e., high vs. low), the prediction of language by AMNART was stronger for cases above the median, showing that the relationship between AMNART and language is stronger when physical function is higher.

Table 16. Hierarchical regression on Language using AMNART score, Occupational Complexity Levels, and years of education as predictors, physical function as a moderator, controlling for age and gender

Step	Variables Entered	R^2	R^2 Change	F	df	p	β	p	VIF
1	Female Gender	0.09	0.09	5.67	2,118	0.004	-0.02	0.810	1.38
	Age						-0.27	0.006	1.53
2	AMNART	0.31	0.22	5.85	6,112	< .001	0.48	< .001	1.39
	OCC Data						-0.01	0.933	1.82
	OCC People						0.16	0.202	2.58
	OCC Things						-0.03	0.759	1.24
	Years of Education						-0.14	0.223	2.01
	Physical Function						0.00	0.990	1.74
3	AMNART x Physical Function	0.34	0.03	1.04	5,107	0.399	0.19	0.034	1.28
	OCC Data x Physical Function						-0.02	0.829	1.96
	OCC People x Physical Function						-0.04	0.787	2.81
	OCC Things x Physical Function						-0.01	0.957	1.25
	Years of Education x Physical Function						-0.09	0.457	2.50

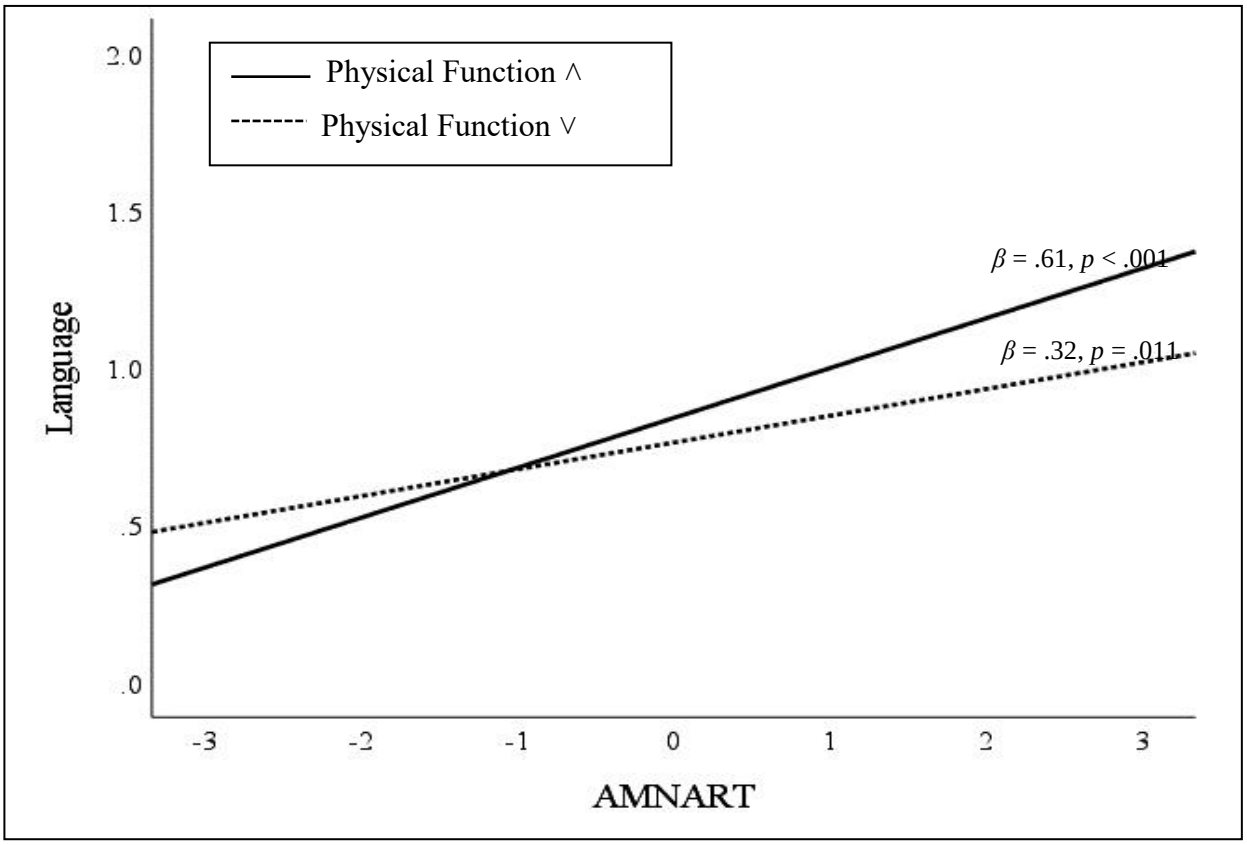

Figure 3. Separate regressions of AMNART on Language for Physical Function above (∧) and below (∨) the median.

In terms of executive function, neither physical function nor its cross-products added significantly to the prediction. In the final model, only age and AMNART score contributed significantly to the prediction of executive function (Table 17).

Table 17. Hierarchical regression on Executive Function using AMNART score, Occupational Complexity Levels, and years of education as predictors, physical function as a moderator, controlling for age and gender

Step	Variables Entered	R^2	R^2 Change	F	df	p	β	p	VIF
1	Female Gender	0.17	0.17	12.46	2,119	< .001	0.07	0.420	1.38
	Age						-0.43	< .001	1.53
2	AMNART	0.44	0.27	9.07	6,113	< .001	0.40	< .001	1.40
	OCC Data						0.14	0.142	1.82
	OCC People						-0.08	0.494	2.59
	OCC Things						-0.09	0.273	1.25
	Years of Education						0.16	0.108	2.01
	Physical Function						-0.05	0.622	1.75
3	AMNART x Physical Function	0.46	0.02	0.94	5,108	0.459	0.03	0.683	1.28
	OCC Data x Physical Function						0.08	0.444	1.97
	OCC People x Physical Function						-0.21	0.086	2.82
	OCC Things x Physical Function						0.11	0.167	1.25
	Years of Education x Physical Function						0.04	0.733	2.50

Similarly, neither physical function nor its cross-products added significantly to the prediction of Verbal Memory (Table 18).

Table 18. Hierarchical regression on Verbal Memory using AMNART score, Occupational Complexity Levels, and years of education as predictors, physical function as a moderator, controlling for age and gender

Step	Variables Entered	R^2	R^2 Change	F	df	p	β	p	VIF
1	Female Gender	0.12	0.12	8.27	2,119	< .001	0.26	0.006	1.38
	Age						-0.27	0.008	1.53
2	AMNART	0.30	0.18	4.70	6,113	< .001	0.26	0.007	1.40
	OC Data						-0.09	0.415	1.82
	OC People						0.21	0.112	2.59
	OC Things						-0.04	0.655	1.25
	Years of Education						0.12	0.277	2.01
	Physical Function						-0.02	0.888	1.75
3	AMNART x Physical Function	0.31	0.02	0.50	5,108	0.779	0.08	0.370	1.28

OC Data x Physical Function	0.02	0.880	1.97
OC People x Physical Function	-0.16	0.226	2.82
OC Things x Physical Function	-0.01	0.950	1.25
Years of Education x Physical Function	0.04	0.745	2.50

In summary, physical function had a moderating effect on language ability, strengthening the protective effect of estimated verbal intelligence on this aspect of cognitive function. However, physical function did not have a moderating effect on any of the other cognitive domains.

Hypothesis 3

ApoE genotype will significantly moderate the relationship between cognitive reserve and cognitive functioning. Specifically, the potential protective effects of cognitive reserve proxies on cognitive functioning in old age may be reduced in individuals who are ApoE-4 carriers.

This hypothesis was tested using hierarchical linear regressions on the five dependent variables. Participant gender and years of age were entered in the first step. In the second step, the five independent variables, AMNART score, OCC Data, People and Things, and years of education were entered, in addition to the moderator variable, the ApoE genotype, dichotomized to represent the presence/absence of at least one ε4 allele. In the third step, the cross-products of the ApoE genotype and the five independent variables were entered. The results are shown in Tables 19 through 23.

The results presented in Table 19 indicate that, along with age and AMNART score, the ApoE genotype was a significant negative contributor to the prediction of global cognition (β = -0.14, p = 0.050). In the second step, OCC Things was negatively related to global cognition, although it's contribution to the prediction was not significant

(β = -0.15, p = 0.072). However, in the final model, the crossproduct of OCC Things and the ApoE-4 genotype added significantly to the prediction of global cognition (β = 0.25, p = 0.006). The positive beta weight for the crossproduct indicates that individuals who are ApoE-4 carriers who exhibited higher occupational complexity with regard to things had significantly higher global cognition scores. Thus, the ApoE-4 genotype actually changed the direction of the effect of OCC Things, revealing a hidden protective effect of this proxy of cognitive reserve on global cognition. So, in contrast to the hypothesized effect, the potential protective effect of this CR proxy is enhanced in individuals who are ApoE-4 carriers. This result is further illustrated by the crossed regression lines in Figure 4. In separate regressions for ApoE-4 carriers and non-carriers, the prediction of global cognition by OCC Things was positive in the ApoE-4 carriers and negative in the non-carriers.

Table 19. Hierarchical regression on Global Cognition using AMNART score, Occupational Complexity Levels, and years of education as predictors, ApoE genotype as a moderator, controlling for age and gender

Step	Variables Entered	R^2	R^2 *Change*	*F*	*df*	*p*	β	*p*	*VIF*
1	Female Gender	0.31	0.31	22.60	2,101	< .001	0.12	0.138	1.26
	Age						-0.55	< .001	1.07
2	AMNART	0.52	0.21	6.70	6,95	< .001	0.27	0.004	1.80
	OCC Data						0.08	0.398	2.05
	OCC People						0.09	0.444	2.67
	OCC Things						-0.15	0.072	1.49
	Years of Education						0.09	0.419	2.74
	ApoE genotype ε4+						-0.14	0.050	1.11
3	AMNART x ApoE genotype	0.58	0.07	2.81	5,90	0.021	0.10	0.257	1.66
	OCC Data x ApoE genotype						0.13	0.213	2.40
	OCC People x ApoE genotype						-0.23	0.060	2.99
	OCC Things x ApoE genotype						0.25	0.006	1.65
	Years of Education x ApoE genotype						0.04	0.712	2.42

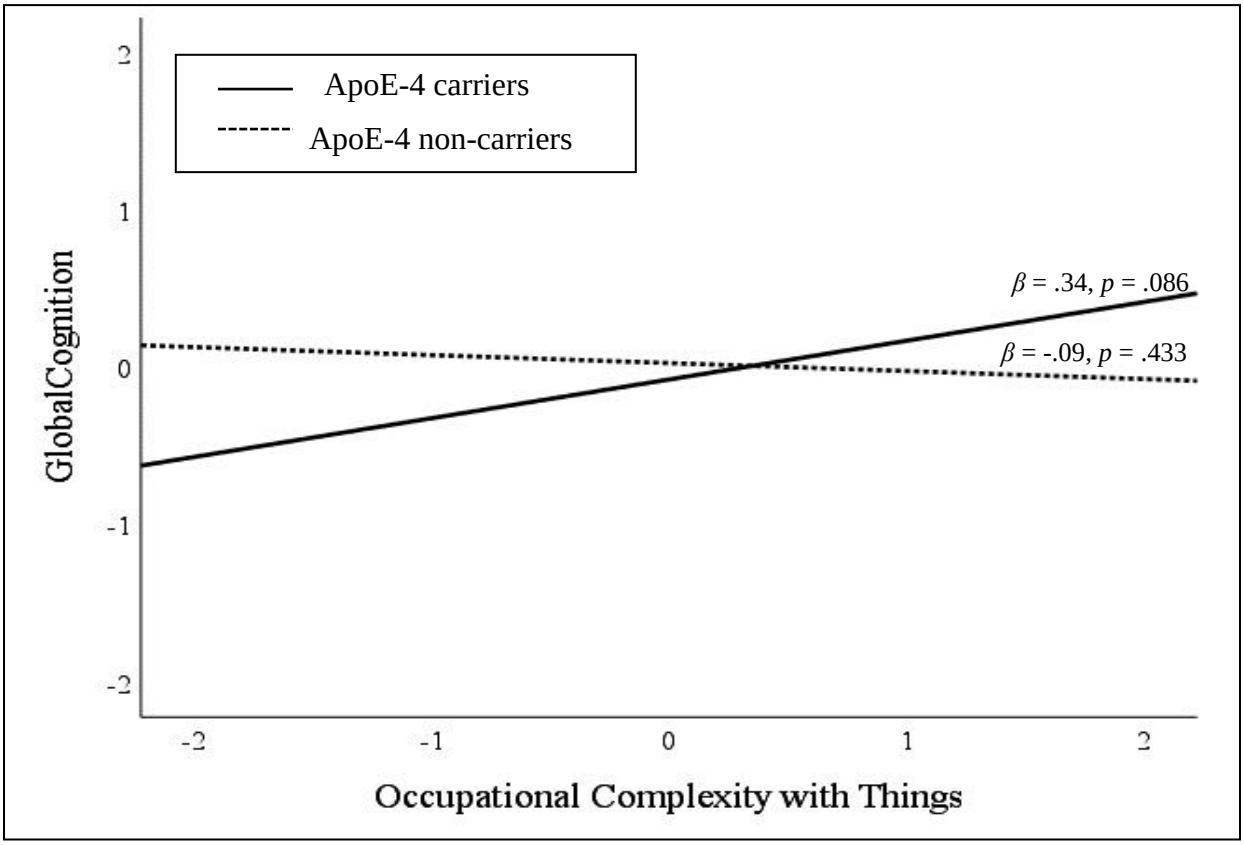

Figure 4. Separate regressions of OCC Things on Global Cognition for ApoE-4 carriers and non-carriers.

None of the CR variables, nor ApoE genotype had a significant main effect on psychomotor speed (β = -0.15, p = .073); however, the interaction between OCC People and ApoE-4 status added significantly to the prediction (β = -0.39, p = .005). In contrast to the finding for global cognition shown it Table 19, here the relationship between the crossproduct and psychomotor speed was negative, indicating that higher OCC People was associated with lower psychomotor speed in ApoE-4 carriers. The interaction effect is illustrated in Figure 5. In separate regressions for ApoE-4 carriers and non-carriers, the prediction of psychomotor speed by OCC People was negative in the ApoE-4 carriers and positive in the non-carriers. This indicates that psychomotor speed is reduced in those

with higher occupational complexity with regard to people, but only within ApoE-4 carriers.

Table 20. Hierarchical regression on Psychomotor Speed using AMNART score, Occupational Complexity Levels, and years of education as predictors, ApoE genotype as a moderator, controlling for age and gender

Step	Variables Entered	R^2	R^2 *Change*	*F*	*df*	*p*	*β*	*p*	*VIF*
1	Female Gender	0.29	0.29	20.05	2,100	< .001	0.09	0.298	1.29
	Age						-0.54	< .001	1.08
2	AMNART	0.36	0.08	1.92	6,94	0.085	0.07	0.487	1.81
	OCC Data						0.19	0.105	2.07
	OCC People						0.01	0.918	2.68
	OCC Things						-0.03	0.747	1.52
	Years of Education						-0.04	0.784	2.75
	ApoE genotype ε4+						-0.15	0.073	1.11
3	AMNART x ApoE genotype	0.45	0.09	2.91	5,89	0.018	0.11	0.269	1.66
	OCC Data x ApoE genotype						0.10	0.407	2.40
	OCC People x ApoE genotype						-0.39	0.005	2.99
	OCC Things x ApoE genotype						0.16	0.108	1.66
	Years of Education x ApoE genotype						0.12	0.311	2.42

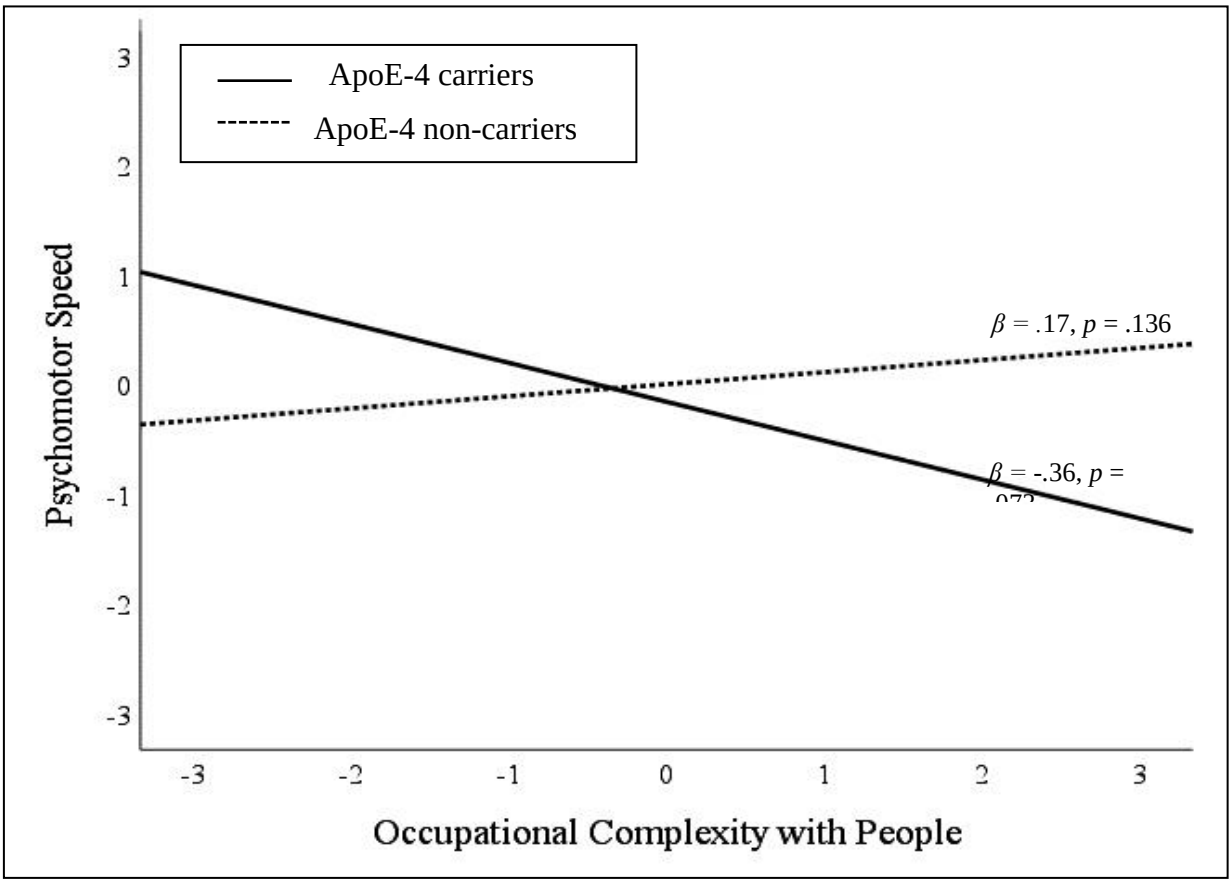

Figure 5. Separate regressions of OCC People on Psychomotor Speed for ApoE-4 carriers and non-carriers.

With respect to language (see Table 21), neither the ApoE-4 genotype nor any of the occupational complexity levels contributed significantly to the prediction. However, the crossproduct of ApoE-4 genotype and OCC Things was a significant contributor to the prediction (β = 0.21, p = .049). The positive beta weight indicates that higher occupational complexity with Things was associated with higher language performance in ApoE-4 carriers. So, in contrast to the hypothesized effect, the potential protective effect of this cognitive reserve proxy appears to be only in ApoE-4 carriers. This result is further illustrated in Figure 6. In separate regressions for ApoE-4 carriers and non-

carriers, the prediction of language by occupational complexity with things was positive in the ApoE-4 carriers and negative in the non-carriers.

Table 21. Hierarchical regression on Language using AMNART score, Occupational Complexity Levels, and years of education as predictors, ApoE genotype as a moderator, controlling for age and gender

Step	Variables Entered	R^2	R^2 *Change*	*F*	*df*	*p*	*β*	*p*	*VIF*
1	Female Gender	0.15	0.15	9.05	2,101	< .001	-0.05	0.563	1.26
	Age						-0.38	< .001	1.07
2	AMNART	0.35	0.20	4.94	6,95	< .001	0.42	< .001	1.80
	OCC Data						-0.05	0.671	2.05
	OCC People						0.14	0.292	2.67
	OCC Things						-0.15	0.127	1.49
	Years of Education						-0.16	0.251	2.74
	ApoE genotype ε4+						-0.06	0.486	1.11
3	AMNART x ApoE genotype	0.40	0.04	1.24	5,90	0.298	0.02	0.887	1.66
	OCC Data x ApoE genotype						0.16	0.199	2.40
	OCC People x ApoE genotype						-0.05	0.723	2.99
	OCC Things x ApoE genotype						0.21	0.049	1.65
	Years of Education x ApoE genotype						0.08	0.523	2.42

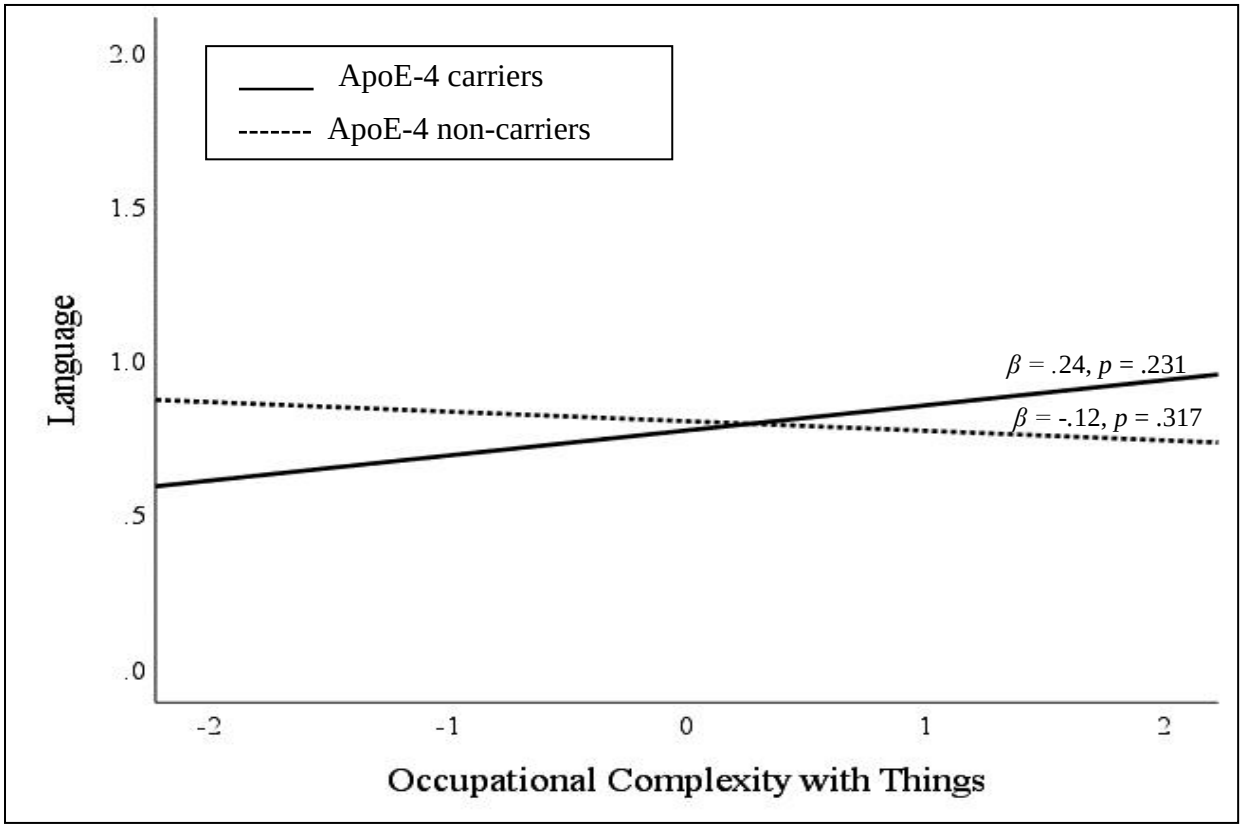

Figure 6. Separate regressions of OCC Things on Language for ApoE-4 carriers and non-carriers.

Similarly, while neither the occupational complexity scores nor ApoE genotype had significant main effects on executive function, their crossproduct contributed significantly to the overall prediction (β = 0.19, p = .046, Table 22). Again, the positive beta weight indicates that higher occupational complexity with things was associated with better executive function in ApoE-4 carriers. This result is the opposite of the moderating effect hypothesized, since the potential protective effect of this CR proxy appears to have been enhanced rather than reduced in individuals who are ApoE-4 carriers. This effect is further illustrated in Figure 7. In separate regressions for ApoE-4

carriers and non-carriers, the prediction of language by OCC Things was positive in the ApoE-4 carriers and negative in the non-carriers.

Table 22. Hierarchical regression on Executive Function using AMNART score, Occupational Complexity, and years of education predictors, ApoE as a moderator, controlling for age and gender

Step	Variables Entered	R^2	R^2 *Change*	*F*	*df*	*p*	*β*	*p*	*VIF*
1	Female Gender	0.23	0.23	15.01	2,101	< .001	-0.01	0.914	1.26
	Age						-0.47	< .001	1.07
2	AMNART	0.49	0.26	8.00	6,95	< .001	0.34	0.001	1.80
	OCC Data						0.18	0.086	2.05
	OCC People						-0.05	0.677	2.67
	OCC Things						-0.15	0.085	1.49
	Years of Education						0.15	0.220	2.74
	ApoE genotype ε4+						-0.13	0.082	1.11
3	AMNART x ApoE genotype	0.54	0.05	1.81	5,90	0.119	0.08	0.421	1.66
	OCC Data x ApoE genotype						0.19	0.098	2.40
	OCC People x ApoE genotype						-0.23	0.068	2.99
	OCC Things x ApoE genotype						0.19	0.046	1.65
	Years of Education x ApoE genotype						-0.03	0.814	2.42

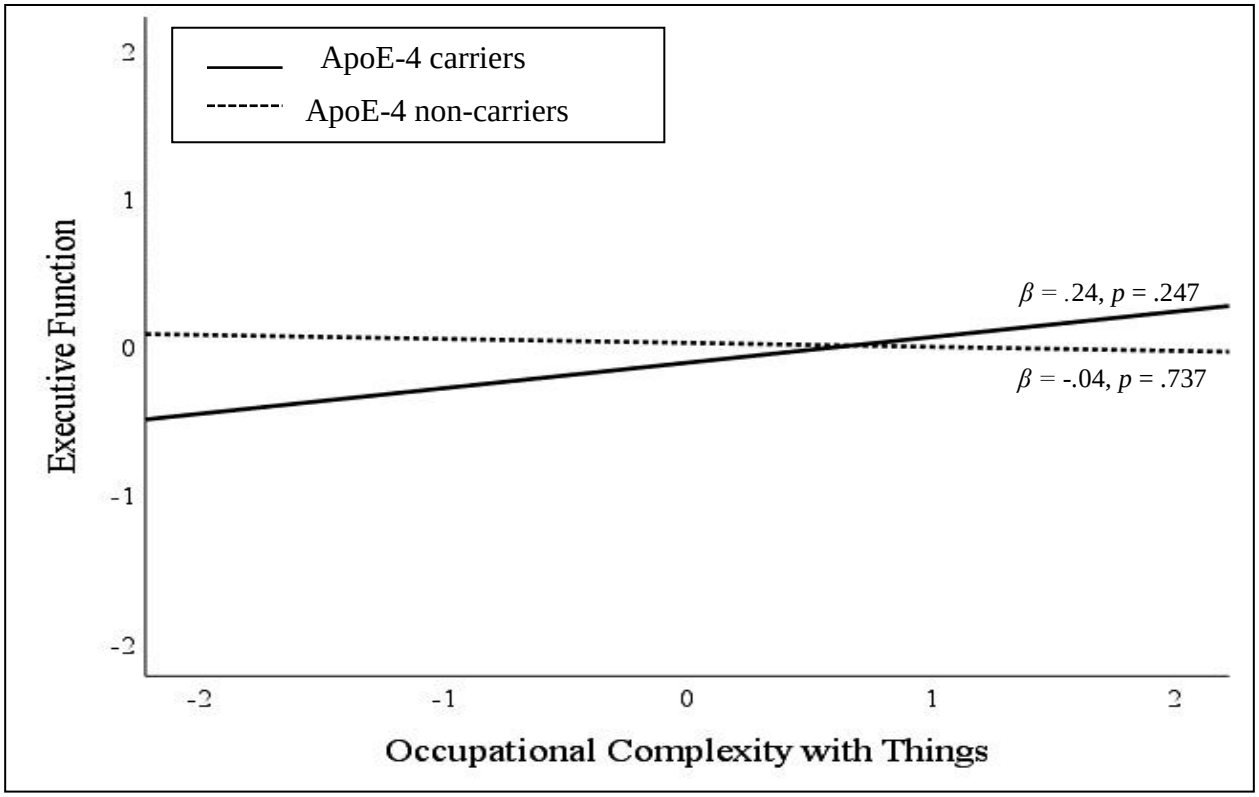

Figure 7. Separate regressions of OCC Things on Executive Function for ApoE-4 carriers and non-carriers.

A final regression on Verbal Memory did not reveal any significant contributions of the CR variable, the ApoE genotype or their cross-products after controlling for gender and age (see Table 23).

Table 23. Hierarchical regression on Verbal Memory using AMNART score, Occupational Complexity Levels, and years of education as predictors, ApoE genotype as a moderator, controlling for age and gender

Step	Variables Entered	R^2	R^2 *Change*	*F*	*df*	*p*	*β*	*p*	*VIF*
1	Female Gender	0.13	0.13	7.85	2,101	0.001	0.27	0.008	1.26
	Age						-0.32	0.001	1.07
2	AMNART	0.29	0.15	3.41	6,95	0.004	0.11	0.339	1.80
	OCC Data						-0.07	0.592	2.05
	OCC People						0.20	0.171	2.67
	OCC Things						-0.11	0.283	1.49
	Years of Education						0.20	0.160	2.74

	ApoE genotype ε4+						-0.08	0.374	1.11
3	AMNART x ApoE genotype	0.32	0.04	0.97	5,90	0.443	0.07	0.518	1.66
	OCC Data x ApoE genotype						-0.01	0.952	2.40
	OCC People x ApoE genotype						-0.01	0.951	2.99
	OCC Things x ApoE genotype						0.20	0.074	1.65
	Years of Education x ApoE genotype						-0.02	0.912	2.42

In summary, ApoE-4 genotype had a negative modifying effect on the relationship between OCC People and psychomotor speed. In contrast, analyses revealed a protective effect of OCC Things on global cognition, language, and executive function in ApoE-4 carriers but not in non-carriers. It should be noted that only 27 (25%) of the individuals included in the regressions to test Hypothesis 3 were ApoE-4 genotype carriers.

CHAPTER FOUR

DISCUSSION

The majority of researchers have only examined 1 to 3 proxy variables of CR. A more complete account of CR would have to integrate these complex interactions between modifiable life factors, life experiences, and genetic predispositions on CR and the ability to actively compensate for the effects of dormant pathology. Existing heterogeneous research findings on CR and cognition have informed researchers that high CR does not necessarily guarantee that an individual will remain free from a cognitive disorder, as many contributing factors, such as genetics and physical function, may interplay in altering one's risk for cognitive impairment. Thus, a less typical but potentially more fruitful approach to unraveling the specific role of CR in normal cognitive aging might be to investigate its interaction with other potential determinants of cognitive aging, including genetic risk and physical function. ApoE-4 carriers and individuals with poor physical abilities have been found to be at potential risk for pronounced cognitive decline, whereas educational attainment, premorbid verbal intelligence, and occupational complexities have been shown to be protective factors. Thus, the current study aims to explore whether ApoE-4 genotype and physical function may strengthen or weaken the protective effects of cognitive reserve.

Findings of Current Study

To our knowledge, this is the first reported study to investigate the relation of key markers of cognitive reserve to cognitive performance and its interplay with physical function and ApoE-4 genotype in a community-dwelling sample of older adults. This study first examined the association between cognitive performance (global cognition, verbal memory, language, psychomotor speed, and executive function) and three commonly used measures of CR: estimated premorbid verbal intelligence, occupational complexity factors (work with data, people, things), and years of education. Regarding our first hypothesis, the results of this study demonstrate that select proxies of CR influenced cognitive functioning independently and differentially within different cognitive domains, with some measures of cognitive reserve standing out over the others.

Hypothesis 1

Two measures of cognitive reserve stood out over the others. *First*, estimated premorbid verbal intelligence was significantly predictive of global cognition, language, executive function, and verbal memory, suggesting that individuals with higher estimated premorbid verbal intelligence demonstrated better performance on these investigated cognitive performance measures. These results are consistent with previous studies that have found premorbid verbal intelligence to be protective of cognitive aging, specifically in global functioning and memory (Corral et al., 2006; Jefferson et al., 2011). Older adults with higher premorbid intelligence may have larger and more efficient neuronal networks, which allowed for the use of effective cognitive strategies that lead to better cognitive performance.

Secondly, years of education significantly contributed to the prediction of executive function. Our results corroborate studies that reported effects of education on other tests of executive functioning (Christensen et al., 1997; Horn & Cattell, 1967; Lindenberger & Reischies, 1999; Lipnicki et al., 2017; Angel et al., 2010; Bherer et al., 2001; Le Carret et al., 2003; Wecker et al., 2005), suggesting that education may be associated with a general benefit in organizing and scheduling complex responses (Plumet et al., 2005; Wecker et al., 2005). Divided attention and switching processes may be modifiable by educational experience, perhaps due to greater cognitive reserve or processing efficiency (Stern et al., 2005). Or, education may afford selective protection to different aspects of executive function, such that some processes benefit while other executive processes (e.g., psychomotor speed) may benefit less with higher education. Unlike other studies (see review by Obdebeeck et al., 2016; Capitani et al., 1996; Darby et al., 2017), education was not found to be predictive of verbal memory. Cognitive aging literature has consistently found that older adults yield weaker scores on learning and memory tests compared to younger adults and generally have more difficulty remembering newly presented information, such as a word list, details of events, or the context in which something occurred. Findings from the current study suggest that highly educated older adults might use their high crystallized ability to compensate for specific age-related declining fluid abilities, such as executive functioning, more so than other fluid abilities (Alley et al., 2007). Specifically, attaining more years of education may help develop and enhance vocabulary abilities and a broad repertoire of cognitive strategies, with more educated individuals more likely to implement effective and meaningful cognitive strategies to assist performance on cognitive tasks requiring

executive skills relative to their less-educated counterparts.

Additionally, it is possible that individuals with higher educational attainment may have less frontal lobe atrophy in association with executive systems, an area most sensitive to aging, relative to their less-educated peers. However, longitudinal studies have found that education may only mask or exert protection against early cognitive decline up to a certain age (e.g., 65; Nishita et al., 2013), but that once brain pathology reaches a specific threshold (e.g., when clinical symptoms of dementia manifest), educational reserve depletes and rapid cognitive decline ensues (Carmelli et al., 1997; Meng & D'arcy, 2012; Mungas et al., 2018).

Inconsistent with previous studies, education and estimated premorbid intelligence was not found to be predictive of psychomotor speed (Jefferson et al., 2011; Proust et al., 2008; Tun & Lachman, 2008; Thorvaldsson et al., 2017). However, our findings do parallel previous studies that have found that NART performance and education was not strongly associated with perceptual speed (Jefferson et al., 2011) and observed no significant benefit of higher education after age 75 (Tun & Lachman, 2008), which is in contrast to educational advantages on processing speed seen in younger adults. Findings from extant literature suggest that education may compensate for age differences in psychomotor speed up to a point in the aging process, at which point the benefits of having higher education may diminish (Hultsch et al., 1999). The discrepancy in findings, particularly with education, may involve different populations and cohort effects and the use of different measurement methods that do not support the association between education and late-life cognitive performance (Early et al., 2013; Gross et al., 2015). Also, with the increase in the average level of education in more advanced and

industrialized societies, such as the one our sample was collected, it is possible that the potential benefits of higher education on specific cognitive domains (e.g., processing speed and verbal memory) are no longer noticeable in highly industrialized populations. A study by Lyketsos et al. (1999) showed that as the average years of education go beyond the 8-year threshold, individuals with nine or more years of education evidenced no additional benefits, and cognitive performance was no longer distinguishable between those with high- versus low- education. This may at least partly explain why no relationship was observed our study, as the relatively high level of education in our AHS-2 sample consisted of older adults with an average mean of 16 years of education (and minimum of 11 years).

Third, complexity of work with data—a factor of occupational complexity—significantly predicted executive function but did not add any predictive value to global cognition or the other three cognitive domains. Occupations that contain synthesizing, for example, the highest-level factor of complexity working with data, is to a great extent related to aspects of executive functioning (Sörman et al., 2019). According to DOT classification (see https://occupationalinfo.org/appendxb_1.html), synthesizing reflects: "integrating analyses of data to discover facts and/or develop knowledge concepts or interpretations." It is reasonable that occupations involving analytical thinking and integration of data for knowledge development, can be related to the ability to constantly monitor and evaluate incoming information for task relevance and revise information in working memory based on this, which is an important aspect of "updating ability" (Morris and Jones, 1990; Miyake et al., 2000). This finding generally supports studies that have found that occupation appears to provide additional benefit for cognitive

function independently of that provided by education (Andel et al., 2007; Correa Ribeiro et al., 2013). For example, findings from studies examining older adults found that occupations with higher level of complexity with both people and data were associated to performance on aspects of executive functioning (Sörman et al., 2019; Andel et al., 2021) above and beyond age, sex, and childhood socioeconomic status, and the results were sustained when either education or adult socioeconomic status was added into the regression models (Andel et al., 2007).

The current study did not find any predictive effects between work with people and things, and any of the cognitive domains, however. Studies that have found relations in regard to occupational complexity working with people have either examined specific sub-components of executive functioning, such as inhibition, updating, and switching (Sörman et al., 2019), rather than utilizing a composite score of executive functioning such as in this study or investigated this relationship in older adults who are retired (Finkel et al., 2009; Fisher, Stachowski, Infurna, Faul, Grosch, J., & Tetrick, 2014). This difference in domain measurement and population sample may explain the non-significant findings between complexity of work with people and executive functioning. Higher complexity with things was also not associated with slower speed and poorer global cognitive functioning; however, this may be due to the author using a different occupational reference (the 1971 Australian Classification and Classified List of Occupations) than the one used in the current study (2019 O*NET-SOC according to the 1970 U.S. Census Dictionary of Occupational Titles). Findings from this study also did not reveal significant relationships between any occupational complexity factors and global cognition. Studies that have found this relationship used the MMSE (Lane et al.,

2017; Andel et al., 2019) to measure global cognitive functioning while we measured global cognition using a composite score of all neuropsychological tests.

Overall, our findings for the first hypothesis are in support of estimated premorbid verbal intelligence as being the most prominent proxy of CR (Bennet et al., 2003) in association with cognitive functioning. Education and occupational complexity with data only exhibited predictive value to executive functioning. Due to variability in the quality of education, premorbid intellectual ability may serve as a more reliable proxy of CR than years of education or any occupational complexity factors. This study provides support for the utility of the AMNART (particularly the error score) as a proxy measure of cognitive reserve, such that the AMNART reflects an accumulation of experience as one must have come in contact with test items to recognize their irregular sound-to-spelling association. It has been suggested that measures of reading ability may more accurately reflect native ability than years of education because vocabulary and reading ability—measures of premorbid intelligence—may change over time (unlike education which is unlikely to change after early adulthood), thereby making it a more sensitive CR proxy (Manly et al., 2003; 2005). These findings also corroborate the idea that exposure to a more enriching environment or accumulated benefits that have persisted from childhood until adulthood, as found in formal education and premorbid verbal intelligence, may promote that learning, socialization, and neuroplasticity and lead to higher cognitive performance (Kobayashi et al., 2002; Le Carret et al. 2003**)** and even maintenance of cognitive function in the face of age-related brain and cognitive changes, which is in line with active (cognitive) reserve (Deary et al., 2000). Acknowledging that the findings of the current study are cross-sectional, is limited to certain variables, and

cannot speak to causality, the theoretical explanation accounting for the association between specific cognitive reserve proxies (education, estimated premorbid intelligence, occupational complexity with data) and cognitive performance is that a neural compensatory mechanism may exist, through the use of preserved crystallized intelligence and greater frontal lobe activation to reflect strategic aspects of episodic memory recall (Becker & Lim, 2003) and executive functions (Baudic et al., 2006) in healthy elderly patients with higher premorbid intelligence and education. Engagement of the prefrontal cortex by older adults, particularly by those with higher premorbid intelligence and education, can be an alternative network that is engaged to aid overall cognitive function (e.g., global cognition).

Hypothesis 2

Physical function moderated the relationship between premorbid verbal intelligence and language function only and did not modify the effects of either occupational complexity or education on any cognitive domain. Of note, both AMNART score and physical function were significant positive predictors of Language, while age was negatively related to physical function. Hence, while physical function is significant as a single predictor in correlation analyses, it does not add significantly to the prediction of the outcomes over and above the contributions made by age and AMNART. Physical function did not appear to have a moderating effect on other aspects of cognition, which is in contrast to a previous study that found significant moderating effects of physical function measures (e.g., gait speed) on verbal IQ and executive functioning in non-demented older adults, with individuals who have a higher CR possibly using brain

systems related to executive function more effectively to protect against decline in gait speed compared to those with lower CR (Holtzer, Wang, Liptin, & Verghese, 2012). Other studies that have examined moderating effects of physical functioning on CR and cognition found that the relationship between cognitive reserve (education, occupational cognitive complexity, cognitive leisure activity engagement) and MMSE scores was moderated by degree of grip strength, with those with greater grip strength performing better in global cognitive functioning (Ihle et al., 2017). In a follow-up study in 2018, functional fitness status (e.g., lower and upper body strength and flexibility, agility and balance, aerobic endurance) was found to moderate the relationship of CR (education and cognitive leisure activity) and MMSE scores. Our study did not find the above predictive, possibly due to the fact that physical functioning was measured differently using a composite score of the PPT and TUG tests, which measure several domains of functioning, including upper body strength and dexterity, mobility, stamina (PPT), ability to rise from a seated position, walk 10 feet, turn and return to their seat (TUG test).

A meta-analysis revealed significant, although small, effect sizes in favor of a positive association between performance on mobility measures and cognitive assessments after controlling for age, sex, and education (Demnitz et al., 2016). In our study, although physical functioning was positively correlated with cognitive performance in the univariate correlations, when added into the regression model with cognitive reserve measures and demographic controls, physical function was significantly associated only with psychomotor speed, and no interactions were observed. Perhaps we would have found more of a moderating role if assessing more specific measures of physical functioning that have been found to uniquely predict aspects of cognitive

functioning. For those studies that have examined physical functioning, it is becoming clear that some measures of performance-based physical function may be better markers than others of early cognitive decline. A review of healthy older adults by Demnitz and colleagues (2016) found that measures of gait and lower-extremity function were driving findings of better performance on tests of global cognition, executive function, memory and processing speed while most studies examining balance and cognition measures reported no significant results. Deterioration of specific motor functions, such as hand dexterity and grip strength, have also been associated with global cognition cross-sectionally and longitudinally (Kobayashi-Cuya et al., 2018). Rapid-paced walking tasks were found to be a more sensitive measure than self-paced walking speed in differentiating levels of cognition in older healthy adults as it was a more challenging task requiring more executive abilities that allowed for the distinction between individuals with higher versus lower levels of physical fitness to emerge (Fitzpatrick et al., 2007). Researchers have also found that each TUG subtask is unique in identifying early motor changes associated with specific cognitive decline and seems to require different cortical areas (Herman et al., 2011; Clouston et al., 2013). These possible mechanisms in different physical function subtasks may explain discrepancies in our results.

Overall, physical functioning did not reveal any protective effects of the variables representing cognitive reserve on cognition in older adults, with the exception of verbal intelligence on language skills. This suggests that language skills in old age may more strongly depend on accumulated cognitive reserve, such as premorbid verbal intelligence, during the life course for both individuals with high and low physical functioning status;

however, individuals with higher physical function benefitted more from having higher premorbid verbal intelligence.

People with higher physical functioning benefitted more from having higher premorbid intelligence because their verbal intelligence predicted language performance for higher physical functioning. Preliminarily, our findings do not corroborate Spini et al. (2017)'s "vulnerability framework" and Baltes and Baltes (1989) "Selective Optimization with Compensation (SOC)" model. The vulnerability framework posits that the relationship between cognitive reserve and cognitive functioning in older adults may be more pronounced for those who have fewer physiological resources and are physically weaker in old age, whereas the SOC model recognizes that aging often leads to losses and limitations in one or more health domains and the allowance for conditions to manifest. In applying our findings to both models, participants who had higher physiologic reserve (better scores on physical function test) benefitted from having high cognitive reserve (premorbid verbal intelligence) accumulated during their life course than their lower physically functioning counterparts. Individuals with higher physical functioning may utilize a "cross-compensation" mechanism to tap into their cognitive reserve to aid cognitive function more so than those with lower physical functioning. Activation of "cross-domain compensation" works in buffering against the natural tendency for older adults to lose physical resources in old age and may initiate cognitive reserve effects. The inclusion of physical functioning measures may—at least partly—account for the large variability in cognitive reserve–cognition relations debated in the literature (Ihle et al., 2017).

Hypothesis 3

Greater attention has been given to not only proxies of cognitive reserve (e.g., education and premorbid verbal intelligence) but the role that genetics plays in altering the cognitive aging process. The current findings show that the ApoE-4 genotype had a significant negative contribution to the prediction of global cognition, which is consistent with prior research (Wisdom et al., 2011). We did not find a significant main effect of ApoE-4 on individual cognitive domains, i.e., language, psychomotor speed, verbal memory, or executive function. Although previous findings have reported a significant, though relatively small negative effect on processing speed, episodic memory, and executive function in cross-sectional studies of healthy older adults, those effects did not control for the same covariates, such as gender (Ferencz et al., 2014). Furthermore, the current sample is healthier and more highly educated (*M* years of education = 16.69 vs. 12.29).

In addition to ApoE genotype, global cognition was predicted by younger age and premorbid verbal intelligence. ApoE genotype also significantly moderated the protective effects of occupational complexity with people on psychomotor speed. Additionally, marginally significant interactions with ApoE-4 genotype and complexity of work with people were observed with respect to global cognition and executive function. This suggests that a possible protective effect of cognitive reserve as measured by occupational complexity with People on psychomotor speed and global cognition may be reduced in individuals who are ApoE-4 carriers. Although other researchers have not found this interaction effect (López et al., 2017), it is important to note that these researchers examined moderating relationships between CR and cognitive performance in

either a middle-aged cognitively healthy population (Jonaitis et al., 2013) or with homozygous ApoE-4 genotype (Bracco et al., 2007).

Global cognitive functioning and processing speed have been found to be closely related to the structural integrity of white matter tracts associated with parietal and temporal cortices as well as left middle frontal gyrus (Turken, Whitfield-Gabrieli, Bammer, Baldo, Dronkers, & Gabrieli, 2008). It could be that ApoE-4 carriers and non-carriers differ in performances on cognitive measures that are associated with a distributed network rather than localized to specific cortical regions. Relative to non-carriers, ApoE-4 carriers have demonstrated changes in white matter integrity and an accelerated age-related loss of mean local interconnectivity and regional local interconnectivity decreases in the precuneus, medial orbitofrontal cortex, lateral parietal cortex (Brown et al., 2011), corpus callosum, inferior fronto-occipital and longitudinal fasciculi, and internal and external capsule (Cavedo et al., 2017). ApoE is a protein that transports cholesterol between cells in the brain, which plays a critical role in the neuronal growth, neuronal maintenance and repair, and synaptic plasticity in the CNS (Liu et al., 2013). ApoE-4 is strongly associated with poor efficiency at transporting brain cholesterol, which may lead to reduced long-term potentiation, delayed neuronal development, lower synaptic plasticity, and reduced clearance of amyloid-beta (O'Donoghue et al., 2018). Thus, ApoE-4 plays a modulatory role on white matter microstructure in elderly individuals at risk for AD suggesting early vulnerability and/or reduced resilience (Cavedo et al., 2017).

Although we did not find any occupational complexity factors to significantly contribute on their own to the prediction of cognitive performance, there was a significant

interaction effect of occupational complexity and ApoE-4 genotype on global cognition, language, and executive functioning, such that there appeared to be a protective effect of occupational complexity with things among ApoE-4 carriers but not in non-carriers. Some studies have found no differences between ApoE-4 carriers and non-carriers in the association between occupational complexity and AD risk (Green, 2013). It is possible that there may be a hidden protective effect of cognitive reserve on global cognition, language, and executive functioning for ApoE-4 carriers. Findings that the relation between occupational complexity with things and cognitive functioning in older adults may be more pronounced for those who are at genetic risk for AD may be explained by the vulnerability framework (Spini et al., 2017) and SOC model (Baltes & Baltes, 1989). In terms of the vulnerability framework, ApoE-4 carriers are a more vulnerable population relative to non-carriers, as they may lack resources to cope with age-related cognitive and physical decline in old age.

In applying the SOC model, it may be that engagement in heavy and sedentary work is less cognitively taxing for vulnerable populations, such as ApoE-4 carriers; thus, allowing carriers to conserve existing cognitive resources and reserve. Being in this line of work may also enable at-risk individuals to optimize their remaining capacities through a cross-domain compensatory mechanism that occurs between domains in the presence of depleted resources. This cross-compensation mechanism buffers against the adverse genetic effects related to neuronal growth inhibition, further supporting the idea of cognitive reserve. The need for occupational compensation in terms of CR would be disproportionately higher in vulnerable ApoE-4 carriers compared to less vulnerable non-carriers. In contrast, when having higher occupational complexity with people, the

protective effect of this CR variable on psychomotor speed was reduced in ApoE-4 carriers as this level of work complexity is higher in cognitive and social stimulation, and thus, more cognitively and mentally taxing and easily vulnerable to adverse genetic effects, making carriers more vulnerable to aging and pathological changes, brain atrophy, and dysfunction in brain networks (Arenaza-Urquijo et al. 2015; Mungas et al. 2018).

Additionally, inconsistent with previous findings (López et al., 2017), findings from the current study did not reveal that ApoE-4 genotype moderated the relationship between education and cognitive performance (e.g., global cognitive functioning, episodic memory, verbal fluency, and naming). This discrepancy may be again due to López et al. (2017)'s healthy community-dwelling participants who are of a different cultural and ethnic population in Madrid, Spain. The authors also utilized culturally adapted versions of neuropsychological tests while the current study used U.S.-based norms and measures.

Overall, our findings lend support for theoretical perspectives that different proxies of CR exhibit varying levels of benefits for individuals who are or are not genetically at risk for AD, such that high occupational complexity with things allows one to better cope with brain pathology (Stern, 2009), even in individuals who have a genetic predisposition for AD. However, the same CR proxy was not protective in ApoE-4 non-carriers, perhaps because they are not genetically vulnerable. Promoting cognitive reserve through certain occupational activities, particularly engaging in work that is higher in complexity with things (e.g., preparing, installing, and adjusting machines/equipment for operation; using tools or work aids to move, guide, or place objects in situations

appropriate for the task; starting, stopping, controlling and adjusting progress of machines, etc.), might be especially effective in subpopulations with high genetic risk of dementia. It could also help individuals maintain cognitive functioning for a longer lifetime period, even in people who carry the ApoE-4 gene.

There remain large discrepancies in the cross-sectional and longitudinal literature concerning ApoE-4's relation to cognitive decline in healthy individuals. One reason for potential discrepancy in our findings as well as in the literature is that some studies did not control for age. This is a necessary control because it has been suggested that the role of ApoE-4, as a risk factor for cognitive impairment and development of late-onset AD, may function differentially according to age (O'Donoghue et al., 2018). Another reason is that occupational complexity with data, people, and things may show different patterns of aggregate exposure between different geographical regions of the U.S., such as in primarily agricultural versus primarily industrial areas. For example, it may be the case that data complexity is protective (as found by Potter et al., 2007), but if individuals who are high in data complexity have a diverse mix of low versus high things complexity, making it so that data complexity effects would be undetectable (Green, 2013). Perhaps participants in our study are homogeneously low in data complexity, having made it much easier to see the effects of the high data and people complexity. It may be that the only way to test the "pure" effect of occupational complexity in each domain is to look at all three domains simultaneously, examining for example, the group that is "high" in only one domain but "low" in other domains (Green, 2013).

Limitations

A number of possible limitations in the current study should be considered. *First,* our study is limited by its cross-sectional design that does not allow for causal inferences. The directionality or temporality of the observed relationships cannot be established with present cross-sectional data. Thus, our analyses give information about interindividual differences in cognitive status but do not allow conclusions regarding the rate of cognitive decline between individuals with higher and lower cognitive reserve within specific cognitive domains (i.e., intraindividual changes over time), for which longitudinal research is needed.

Second, our cohort was exceptionally healthy with a relatively low rate of overall cognitive impairment and high mean of years of education (mean = 16.69 years). Thus, a more heterogeneous sample may reveal further associations and allow for greater generalizable to all participants. *Third,* although we examined physical functioning and ApoE-4 genotype status and adjusted for age and sex in our analyses, other factors we did not take into consideration include the presence of medical comorbidities, socioeconomic status, BMI, medications, and mood, which could affect the associations we found. One can argue that cognitive reserve, physical functioning, and ApoE-4 status may depend to some degree on many of these factors. Thus, controlling for these covariates in additional analyses suggests that these factors influenced the pattern of observed results.

Fourth, our smaller sample size also limited the number of variables we could include in models as confounders as well as our ability to test for interactions such as with age. Due to our small sample size, we did not examine potential mediators of cognitive reserve on neuropsychological performance, such as modifiable lifestyle factors

including cognitive leisure activity, physical activity, healthy diet, substance use such as cocaine or alcohol (Clare et al., 2017), sleep (Parker et al., 2020), and motivation level (Vallet et al., 2020). We also did not look into other factors that may affect physical and cognitive functioning. Researchers have proposed that having multiple chronic conditions and poor lifestyle factors may contribute to worsening of both physical and cognitive health and functions (Fabbri et al., 2016). ApoE-4 sensitivity and specificity are also considered low when used as a single marker (López et al. 2016), which our study is limited to. Mixed findings across studies may also be related to unaccounted modifiable factors that may modify ApoE effects on cognition, such as physical activity or functional status (Reas et al., 2019).

Fifth, in regard occupational complexity as marker of cognitive reserve, one may argue that this reflects the degree of intellectual involvement at work which may be directly dependent upon education (Ihle et al., 2017). Yet, some degree of overlap seems reasonable as, in general, education is a pre-requisite for most professions, and therefore, the level of job should, to some extent, be related to educational attainment. Empirically, **s**tudies have found that they nevertheless seem to be distinguishable constructs, as they had less than 40% of interindividual variance in common in the present sample (Ihle et al., 2017). This seems in line with evidence suggesting that in addition to educational attainment, the cognitive level of jobs may further contribute to the build-up of cognitive reserve across adulthood (Opdebeeck et al., 2016). *Furthermore*, the method that we used to measure occupational complexity in our study may have limited the associations found. The majority of extant studies have assessed occupational complexity by considering the occupation held for the longest period of an individual's working life. It

may be more beneficial to assess occupational complexity not only in this manner in order to account for lifetime accumulated experience, but to also assess occupational complexity at multiple time points from an individual's working life in order to truly assess the benefits that occupation may have for cognition (Obdebeeck et al., 2016).

Lastly, we examined the association between the individual proxies of cognitive reserve and cognitive performance. It is also possible that CR proxy variables are at least somewhat not independent of one another, but in some way interrelated. For example, education is not solely environmental and may be influenced by intelligence, as individuals with higher intelligence may obtain higher education in life (Richards & Sacker, 2003). Combining various proxy measures of cognitive reserve to form a ''reserve'' composite has been proposed as a means to resolve this shortcoming (Siedlecki, Stern, Reuben, Sacco, Elkind, & Wright, 2009). A CR composite score has been found to yield greater construct validity (Siedlecki et al., 2009). However, it is also important to note that although some variables are inter-related, each may impart independent effects as evidenced in previous sections of this review (Tucker & Stern, 2011).

In a recent meta-analysis by Obdebeeck, Martyr, & Clare (2016), the authors examined the strength in contribution of three key proxy measures of CR (educational level, engagement in cognitively stimulating activities, and occupational complexity)—individually and in combination—on cognitive functioning within specific cognitive domains (language, visuospatial ability, executive function, memory) in community-dwelling healthy older adults. All three proxies of CR, individually and in combination, demonstrated a modest positive association on cognitive performance, with engagement

in cognitive activities and occupational complexity showing the most variation across cognitive domains assessed. In other words, higher educational level by itself, and in combination with more complex occupational experience and greater engagement in cognitive-stimulating activities, were related to better performance on all cognitive domains assessed. These results support the notion that commonly used proxy variables of CR may share an underlying mechanism but that each proxy measure also provides unique contributions to CR in their associations with cognitive performance by domain. The similarities and differences in the patterns of association between the individual and combined proxy measures of CR and performance across cognitive domains in later life are consistent with the suggestion that experiences across the lifespan affect cognitive function in combination as well as individually (Opdebeeck et al., 2016). The findings suggest that a combination of experiences across the lifespan increases CR and may partly explain the differences in cognition observed (Stern, 2009; Tucker & Stern, 2011). Results from the meta-analysis are consistent with the findings of previous meta-analyses and studies, which showed a modest relationship between individual and combined CR proxy measures (education, occupational complexity, cognitively stimulating activities) with reduced cognitive decline and incidence of dementia (Obdebeeck et al., 2016).

In regard to the strengths of our study, although we did not collapse education, occupational complexity, and premorbid verbal intelligence into a composite CR measure, we utilized multiple measures of CR individually within our analyses to examine the strength of each three key proxy measures of CR in association with each cognitive domain. This provides information unique from the vast majority of studies that have used a single proxy measure to represent the entire construct of CR, which can also

be problematic as potential confounding variables are not accounted for. CR is a fluid construct conceptualized as a combination of experiences built over the lifespan (Stern, 2002; Opdebeeck et al., 2016). Hence, utilizing a single variable to measure CR may fail to capture the complete picture (Zahodne, Manly, Brickman, Siedlecki, DeCarli, & Stern, 2013). Secondly, we examined occupational complexity in three individual parts (people, data, and things) rather than using a composite score to explore the unique individual contribution to cognitive performance by domain.

Third, the PPT and TUG are direct observations of physical function. Therefore, an advantage of our study was that we were able to objectively quantify physical functioning capabilities of our participants. Previous studies have demonstrated the greater utility of objective performance-based measures in investigating relationships between physical and cognitive function. Use of performance-based measures has been noted to provide more objectivity in measurement and allow for variability in effort needed for different tasks (Guralnik et al., 1989). Assessing multiple domains of physical function also allows researchers to examine a range of complexity in tasks requiring the integration of motor, sensory, and cerebellar activities (Wang et al., 2006). Among older adults, the PPT has been shown to have excellent reliability (Reuben & Siu, 1990) and good to excellent validity with other tests of physical performance but moderate correlations with self-reports of physical abilities on questionnaires (Sherman & Reuben, 1998). Lastly, our study examines the interaction effects of ApoE-4 genotype and proxies of CR in healthy older adults, as little is known about the degree to which genetic vulnerability for AD alters the effect of CR on each cognitive domain.

Conclusions and Implications

Overall, the results of the present study provide new and important knowledge to the literature on cognitive reserve. The present demonstration of associations between proxies of cognitive reserve—consisting of years of education, estimated premorbid intelligence, and dimensions of occupational complexity (work with data, people, things)—and aspects of cognitive functioning builds on previous results and highlights the role of premorbid verbal intelligence in predicting cognitive function over and above the effects of education and occupational complexity factors, even after controlling for age and gender. This seems in line with the conceptual view that accumulated life experiences, as found in estimated verbal intelligence, may be a strong contributor to the build-up of cognitive reserve (Stern, 2009, 2012). Our findings extend previous literature by examining the individual contributions of each proxy of CR by simultaneously considering all three CR markers in analyses in relation to multiple cognitive measures.

There is a lack of research regarding the question of whether the protective influences of cognitive reserve factors on cognitive functioning in old age may be reduced in individuals with lower physical functioning and at risk for AD by considering multiple markers of CR and physical ability accumulated during the life-course in a sample of older adults. The present finding that lower physical function weakens the beneficial effect of premorbid verbal intelligence on language suggests that health-related physiological mechanisms may be an important factor in the relationship between cognitive reserve and cognitive performance in late life. Another factor contributing to interindividual differences in cognitive reserve is genetic risk. Our study suggests that the role of cognitive reserve is modified in ApoE-4 carriers in comparison to non-carriers.

The current study offers interesting prospects for future research. As the current findings emphasize the importance of certain occupations for conferring resilience or preserving cognitive health into old age, creating environmental and cognitive support to allow at-risk individuals to maintain physical and mental engagement until later in life is potentially important (Hyun, Katz, Lipton, & Sliwinski, 2019). Future studies would benefit from a longitudinal design to investigate if the results from this study also hold in the long term and to further investigate the directionality between factors (Sörman et al., 2019).

REFERENCES

Altman D. G. (2005). Categorizing continuous variables. In P. Armitage & T. Colton (Eds.), Encyclopedia of biostatistics (2nd ed., pp. 708-711). Hoboken, NJ: Wiley. doi: 10.1002/0470011815.b2a10012

American College Health Association (2002). National college health assessment: Reference group executive summary, Fall 2002. Retrieved from http://www.acha-ncha.org/docs/ACHA-NCHA_Reference_Group_ExecutiveSummary_Fall2002.pdf

Ahmed, M., & Boisvert, C. M. (2013). Mind stimulation therapy: Cognitive interventions for persons with schizophrenia. Routledge.

Akbaraly, T. N., Portet, F., Fustinoni, S., Dartigues, J. F., Artero, S., Rouaud, O., ... & Berr, C. (2009). Leisure activities and the risk of dementia in the elderly: results from the Three-City Study. Neurology, 73(11), 854-861.

Albert, M. S. (2002). Memory decline: The boundary between aging and age-related disease. Annals of Neurology, 51(3), 282-284.

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., ... & Snyder, P. J. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia, 7(3), 270-279.

Albert, M., Soldan, A., Gottesman, R., McKhann, G., Sacktor, N., Farrington, L., ... & Wang, M. C. (2014). Cognitive changes preceding clinical symptom onset of mild cognitive impairment and relationship to ApoE genotype. Current Alzheimer Research, 11(8), 773-784.

Albert, S. M., & Teresi, J. A. (1999). Reading ability, education, and cognitive status assessment among older adults in Harlem, New York City. American Journal of Public Health, 89(1), 95-97.

Alley, D., Suthers, K., & Crimmins, E. (2007). Education and cognitive decline in older Americans: Results from the AHEAD sample. Research on aging, 29(1), 73-94.

Alexander, G. E., Furey, M. L., Grady, C. L., Pietrini, P., Brady, D. R., Mentis, M. J., & Schapiro, M. B. (1997). Association of premorbid intellectual function with cerebral metabolism in Alzheimer's disease: implications for the cognitive reserve hypothesis. The American journal of psychiatry.

Alexandre, T. S., Meira, D. M., Rico, N. C., & Mizuta, S. K. (2012). Accuracy of Timed Up and Go Test for screening risk of falls among community-dwelling elderly. Brazilian Journal of Physical Therapy, 16(5), 381-388.

Alzheimer's Association. (2018). 2018 Alzheimer's disease facts and figures. Alzheimer's & Dementia, 14(3), 367-429.

Amieva, H., Mokri, H., Le Goff, M., Meillon, C., Jacqmin-Gadda, H., Foubert-Samier, A., ... & Dartigues, J. F. (2014). Compensatory mechanisms in higher-educated subjects with Alzheimer's disease: A study of 20 years of cognitive decline. Brain, 137(4), 1167-1175.

Andel, R., Crowe, M., Pedersen, N. L., Mortimer, J., Crimmins, E., Johansson, B., & Gatz, M. (2005). Complexity of work and risk of Alzheimer's disease: A population-based study of Swedish twins. The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 60(5), P251-P258.

Andel, R., Dávila-Roman, A. L., Grotz, C., Small, B. J., Markides, K. S., & Crowe, M. (2019). Complexity of work and incident cognitive impairment in Puerto Rican older adults. The Journals of Gerontology: Series B, 74(5), 785-795.

Andel, R., Kåreholt, I., Parker, M. G., Thorslund, M., & Gatz, M. (2007). Complexity of primary lifetime occupation and cognition in advanced old age. Journal of Aging and Health, 19(3), 397-415.

Anderson, N. D., & Craik, F. I. (2017). 50 years of cognitive aging theory. The Journals of Gerontology: Series B, 72(1), 1-6.

Andrejeva, N., Knebel, M., Dos Santos, V., Schmidt, J., Herold, C. J., Tudoran, R., ... & Gorenc-Mahmutaj, L. (2016). Neurocognitive deficits and effects of cognitive reserve in mild cognitive impairment. Dementia and geriatric cognitive disorders, 41(3-4), 199-209.

Angel, L., Fay, S., Bouazzaoui, B., Baudouin, A., & Isingrini, M. (2010). Protective role of educational level on episodic memory aging: An event-related potential study. Brain and cognition, 74(3), 312-323.

Annweiler, C., Schott, A. M., Van Kan, G. A., Rolland, Y., Blain, H., Fantino, B., ... & Beauchet, O. (2011). The Five-Times-Sit-to-Stand test, a marker of global cognitive functioning among community-dwelling older women. The journal of nutrition, health & aging, 15(4), 271.

Ansiau, D., Marquié, J. C., Soubelet, A., & Ramos, S. (2005). Relationships between cognitive characteristics of the job, age, and cognitive efficiency. In International Congress Series (Vol. 1280, pp. 43-48). Elsevier.

Anstey, K. J., & Christensen, H. (2000). Education, activity, health, blood pressure and apolipoprotein E as predictors of cognitive change in old age: A review. Gerontology, 46(3), 163-177.

Anstey, K. J., & Low, L. F. (2004). Normal cognitive changes in aging. Australian Family Physician, 33(10), 783.

Arenaza-Urquijo, E. M., Gonneaud, J., Fouquet, M., Perrotin, A., Mézenge, F., Landeau, B., ... & Chételat, G. (2015a). Interaction between years of education and APOE ε4 status on frontal and temporal metabolism. Neurology, 85(16), 1392-1399.

Arenaza-Urquijo, E. M., Wirth, M., & Chételat, G. (2015b). Cognitive reserve and lifestyle: moving towards preclinical Alzheimer's disease. Frontiers in aging neuroscience, 7, 134.

Arendt, T. (2003). Synaptic plasticity and cell cycle activation in neurons are alternative effector pathways: The 'Dr. Jekyll and Mr. Hyde concept' of Alzheimer's disease or the yin and yang of neuroplasticity. Progress in neurobiology, 71(2-3), 83-248.

Atkinson, H. H., Cesari, M., Kritchevsky, S. B., Penninx, B. W., Fried, L. P., Guralnik, J. M., & Williamson, J. D. (2005). Predictors of combined cognitive and physical decline. Journal of the American Geriatrics Society, 53(7), 1197-1202.

Atkinson, H. H., Rapp, S. R., Williamson, J. D., Lovato, J., Absher, J. R., Gass, M., ... & Espeland, M. A. (2010). The relationship between cognitive function and physical performance in older women: results from the women's health initiative memory study. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences, 65(3), 300-306.

Aud, M. A., & Rantz, M. J. (2005). Admissions to skilled nursing facilities from assisted living facilities. Journal of Nursing Care Quality, 20(1), 16-25.

Bäckman, L., Almkvist, O., Andersson, J., Nordberg, A., Winblad, B., Reineck, R., & Långström, B. (1997). Brain activation in young and older adults during implicit and explicit retrieval. Journal of Cognitive neuroscience, 9(3), 378-391.

Baillieux, H., De Smet, H. J., Paquier, P. F., De Deyn, P. P., & Mariën, P. (2008). Cerebellar neurocognition: Insights into the bottom of the brain. Clinical neurology and neurosurgery, 110(8), 763-773.

Balci, B. D., Yenger, G., & Angin, S. (2011). The relationship between physical performance, cognition and depression in Alzheimer type of dementia. Journal of Neurological Sciences (Turkish), 28(1), 051-057.

Baltes, P. B., & Baltes, M. M. (1989). Selective optimization with compensation-a psychological model of successful aging. Zeitschrift fur Padagogik, 35(1), 85-105.

Baltes, P. B., Cornelius, S. W., Spiro, A., Nesselroade, J. R., & Willis, S. L. (1980). Integration versus differentiation of fluid/crystallized intelligence in old age. Developmental Psychology, 16(6), 625.

Barberger-Gateau, P., & Fabrigoule, C. (1997). Disability and cognitive impairment in the elderly. Disability and rehabilitation, 19(5), 175-193.

Bartzokis, G. (2004). Age-related myelin breakdown: A developmental model of cognitive decline and Alzheimer's disease. Neurobiology of aging, 25(1), 5-18.

Barulli, D. J., Rakitin, B. C., Lemaire, P., & Stern, Y. (2013). The influence of cognitive reserve on strategy selection in normal aging. Journal of the International Neuropsychological Society, 19(7), 841-844.

Baudic, S., Barba, G. D., Thibaudet, M. C., Smagghe, A., Remy, P., & Traykov, L. (2006). Executive function deficits in early Alzheimer's disease and their relations with episodic memory. Archives of Clinical Neuropsychology, 21(1), 15-21.

Beauchet, O., Annweiler, C., Callisaya, M. L., De Cock, A. M., Helbostad, J. L., Kressig, R. W., ... & Allali, G. (2016). Poor gait performance and prediction of dementia: Results from a meta-analysis. Journal of the American Medical Directors Association, 17(6), 482-490.

Becker, S., & Lim, J. (2003). A computational model of prefrontal control in free recall: Strategic memory use in the California Verbal Learning Task. Journal of Cognitive Neuroscience, 15(6), 821-832.

Bennett, D. A., Wilson, R. S., Schneider, J. A., Evans, D. A., De Leon, C. M., Arnold, S. E., ... & Bienias, J. L. (2003). Education modifies the relation of AD pathology to level of cognitive function in older persons. Neurology, 60(12), 1909-1915.

Berardi, Raja Parasuraman, James V. Haxby, A. (2001). Overall vigilance and sustained attention decrements in healthy aging. Experimental aging research, 27(1), 19-39.

Best, J. R., Davis, J. C., & Liu-Ambrose, T. (2015). Longitudinal analysis of physical performance, functional status, physical activity, and mood in relation to executive function in older adults who fall. Journal of the American Geriatrics Society, 63(6), 1112-1120.

Bherer, L., Belleville, S., & Peretz, I. (2001). Education, age, and the Brown-Peterson technique. Developmental Neuropsychology, 19(3), 237-251.

Bickel, H., & Cooper, B. (1994). Incidence and relative risk of dementia in an urban elderly population: findings of a prospective field study. Psychological Medicine, 24(1), 179-192.

Binder, E. F., Storandt, M., & Birge, S. J. (1999). The relation between psychometric test performance and physical performance in older adults. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences, 54(8), M428-M432.

Ble, A., Volpato, S., Zuliani, G., Guralnik, J. M., Bandinelli, S., Lauretani, F., ... & Ferrucci, L. (2005). Executive function correlates with walking speed in older persons: The InCHIANTI study. Journal of the American Geriatrics Society, 53(3), 410-415.

Bohannon, R. W., & Schaubert, K. (2005). Long-term reliability of the timed up-and-go test among community-dwelling elders. Journal of Physical Therapy Science, 17(2), 93-96.

Boots, E. A., Schultz, S. A., Almeida, R. P., Oh, J. M., Koscik, R. L., Dowling, M. N., ... & Okonkwo, O. C. (2015). Occupational complexity and cognitive reserve in a middle-aged cohort at risk for Alzheimer's disease. Archives of Clinical Neuropsychology, 30(7), 634-642.

Bosma, H., van Boxtel, M. P., Ponds, R. W., Houx, P. J., Burdorf, A., & Jolles, J. (2003). Mental work demands protect against cognitive impairment: MAAS prospective cohort study. Experimental aging research, 29(1), 33-45.

Bracco, L., Piccini, C., Baccini, M., Bessi, V., Biancucci, F., Nacmias, B., ... & Sorbi, S. (2007). Pattern and progression of cognitive decline in Alzheimer's disease: Role of premorbid intelligence and ApoE genotype. Dementia and geriatric cognitive disorders, 24(6), 483-491.

Braun, U., Schäfer, A., Walter, H., Erk, S., Romanczuk-Seiferth, N., Haddad, L., ... & Meyer-Lindenberg, A. (2015). Dynamic reconfiguration of frontal brain networks during executive cognition in humans. Proceedings of the National Academy of Sciences, 112(37), 11678-11683.

Brewster, P. W., Melrose, R. J., Marquine, M. J., Johnson, J. K., Napoles, A., MacKay-Brandt, A., ... & Mungas, D. (2014). Life experience and demographic influences on cognitive function in older adults. Neuropsychology, 28(6), 846

Bright, P., Jaldow, E. L. I., & Kopelman, M. D. (2002). The National Adult Reading Test as a measure of premorbid intelligence: A comparison with estimates derived from demographic variables. Journal of the International Neuropsychological Society, 8(6), 847-854.

Brookmeyer, R., Gray, S., & Kawas, C. (1998). Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. American journal of public health, 88(9), 1337-1342.

Brookmeyer, R., Johnson, E., Ziegler-Graham, K., & Arrighi, H. M. (2007). Forecasting the global burden of Alzheimer's disease. Alzheimer's & dementia, 3(3), 186-191.

Brown, J. A., Terashima, K. H., Burggren, A. C., Ercoli, L. M., Miller, K. J., Small, G. W., & Bookheimer, S. Y. (2011). Brain network local interconnectivity loss in

aging APOE-4 allele carriers. Proceedings of the National Academy of Sciences, 108(51), 20760-20765.

Bruandet, A., Richard, F., Bombois, S., Maurage, C. A., Masse, I., Amouyel, P., & Pasquier, F. (2008). Cognitive decline and survival in Alzheimer's disease according to education level. Dementia and geriatric cognitive disorders, 25(1), 74-80.

Bryan, J., Luszcz, M. A., & Crawford, J. R. (1997). Verbal knowledge and speed of information processing as mediators of age differences in verbal fluency performance among older adults. Psychology and aging, 12(3), 473.

Buchman, A. S., Boyle, P. A., Leurgans, S. E., Barnes, L. L., & Bennett, D. A. (2011). Cognitive function is associated with the development of mobility impairments in community-dwelling elders. The American Journal of Geriatric Psychiatry, 19(6), 571-580.

Buracchio, T., Dodge, H. H., Howieson, D., Wasserman, D., & Kaye, J. (2010). The trajectory of gait speed preceding mild cognitive impairment. Archives of neurology, 67(8), 980-986.

Burns, J. M., Cronk, B. B., Anderson, H. S., Donnelly, J. E., Thomas, G. P., Harsha, A., ... & Swerdlow, R. H. (2008). Cardiorespiratory fitness and brain atrophy in early Alzheimer disease. Neurology, 71(3), 210-216.

Burke, D. M., MacKay, D. G., & James, L. E. (2000). Theoretical approaches to language and aging. In Models of Cognitive Aging (Perfect, T. and Maylor, E., eds), pp. 204–237, Oxford University Press.

Burke, D. M., & Shafto, M. A. (2011). Language and aging. In The handbook of aging and cognition (pp. 381-451). Psychology Press.

Butler, T. L., Fraser, G. E., Beeson, W. L., Knutsen, S. F., Herring, R. P., Chan, J., ... & Bennett, H. (2008). Cohort profile: The Adventist health study-2 (AHS-2). International journal of epidemiology, 37(2), 260-265.

Cabeza, R. (2001). Cognitive neuroscience of aging: contributions of functional neuroimaging. Scandinavian journal of psychology, 42(3), 277-286.

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: The HAROLD model. Psychology and aging, 17(1), 85-100.

Cabeza, R., Daselaar, S. M., Dolcos, F., Prince, S. E., Budde, M., & Nyberg, L. (2004). Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. Cerebral cortex, 14(4), 364-375.

Cabeza, R., Grady, C. L., Nyberg, L., McIntosh, A. R., Tulving, E., Kapur, S., ... & Craik, F. I. (1997). Age-related differences in neural activity during memory encoding and retrieval: A positron emission tomography study. Journal of neuroscience, 17(1), 391-400.

Cader, S., Cifelli, A., Abu-Omar, Y., Palace, J., & Matthews, P. M. (2006). Reduced brain functional reserve and altered functional connectivity in patients with multiple sclerosis. Brain, 129(2), 527-537.

Caffo, A. O., Lopez, A., Spano, G., Saracino, G., Stasolla, F., Ciriello, G., ... & Bosco, A. (2016). The role of pre-morbid intelligence and cognitive reserve in predicting cognitive efficiency in a sample of Italian elderly. Aging clinical and experimental research, 28(6), 1203-1210.

Callisaya, M. L., Blizzard, C. L., Wood, A. G., Thrift, A. G., Wardill, T., & Srikanth, V. K. (2015). Longitudinal relationships between cognitive decline and gait slowing: the Tasmanian Study of Cognition and Gait. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences, 70(10), 1226-1232.

Campisi, J., & di Fagagna, F. D. A. (2007). Cellular senescence: When bad things happen to good cells. Nature reviews Molecular cell biology, 8(9), 729.

Canevelli, M., Grande, G., Lacorte, E., Quarchioni, E., Cesari, M., Mariani, C., ... &

Vanacore, N. (2016). Spontaneous reversion of mild cognitive impairment to normal cognition: A systematic review of literature and meta-analysis. Journal of the American Medical Directors Association, 17(10), 943-948.

Capitani, E., Barbarotto, R., & Laiacona, M. (1996). Does education influence the age-related cognitive decline? A further inquiry. Developmental Neuropsychology, 12(2), 231-240.

Carlson, M. C., Fried, L. P., Xue, Q. L., Bandeen-Roche, K., Zeger, S. L., & Brandt, J. (1999).

Association between executive attention and physical functional performance in community-dwelling older women. The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 54(5), S262-S270.

Carlson, M. C., Hasher, L., Connelly, S. L., & Zacks, R. T. (1995). Aging, distraction, and the benefits of predictable location. Psychology and aging, 10(3), 427.

Carmelli, D., Swan, G. E., LaRue, A., & Eslinger, P. J. (1997). Correlates of change in cognitive function in survivors from the Western Collaborative Group Study. Neuroepidemiology, 16(6), 285-29.

Carolina, F., Hermida P, D., Tartaglini, M. F., Dorina, S., Verónica, S., & Allegri Ricardo, F. (2016). Cognitive Reserve in Patients with Mild Cognitive Impairment: The Importance of Occupational Complexity as a Buffer of Declining Cognition in Older Adults. AIMS Medical Science, 3(1), 77-95.

Carriere, J. S., Cheyne, J. A., Solman, G. J., & Smilek, D. (2010). Age trends for failures of sustained attention. Psychology and Aging, 25(3), 569.

Caselli, R. J., Dueck, A. C., Osborne, D., Sabbagh, M. N., Connor, D. J., Ahern, G. L., ... & Locke, D. E. (2009). Longitudinal modeling of age-related memory decline and the APOE ε4 effect. New England Journal of Medicine, 361(3), 255-263

Cavedo, E., Lista, S., Rojkova, K., Chiesa, P. A., Houot, M., Brueggen, K., ... & Alzheimer Precision Medicine Initiative. (2017). Disrupted white matter structural networks in healthy older adult APOE ε4 carriers–An international multicenter DTI study. Neuroscience, 357, 119-133.

Ceci's, J. (1996). On intelligence: A bioecological treatise on intellectual development.Centers for Disease Control and Prevention, & Alzheimer's Association. (2007). Healthy brain initiative: A national public health road map to maintaining cognitive health. In Healthy brain initiative: A national public health road map to maintaining cognitive health. Alzheimer's Association.

Cervilla, J. A., Prince, M., Joels, S., Lovestone, S., & Mann, A. (2000). Long-term predictors of cognitive outcome in a cohort of older people with hypertension. The British journal of psychiatry, 177(1), 66-71.

Cesari, M., Kritchevsky, S. B., Newman, A. B., Simonsick, E. M., Harris, T. B., Penninx, B. W., ... & Health, Aging and Body Composition Study. (2009). Added value of physical performance measures in predicting adverse health-related events: Results from the Health, Aging and Body Composition Study. Journal of the American Geriatrics Society, 57(2), 251-259.

Chanraud, S., Zahr, N., Sullivan, E. V., & Pfefferbaum, A. (2010). MR diffusion tensor imaging: A window into white matter integrity of the working brain. Neuropsychology review, 20(2), 209-225.

Chen, H. Y., & Tang, P. F. (2016). Factors contributing to Single-and Dual-Task timed "up & go" test performance in middle-aged and older adults who are active and dwell in the community. Physical therapy, 96(3), 284-292.

Chen, G., Yang, K., & Han, Y. (2020). APOE ε4 Allele Modulates: The Differential Effects of Education on Cognition in Alzheimer's Continuum: The SILCODE Study.

Christensen, H. (2001). What cognitive changes can be expected with normal ageing?. Australian & New Zealand Journal of Psychiatry, 35(6), 768-775.

Christensen, H., Anstey, K. J., Leach, L. S., & Mackinnon, A. J. (2008). Intelligence, education, and the brain reserve hypothesis. The handbook of aging and cognition, 3, 133-188.

Christensen, H., Hofer, S. M., MacKinnon, A. J., Korten, A. E., Jorm, A. F., & Henderson, A. S. (2001). Age is no kinder to the better educated: Absence of an association investigated using latent growth techniques in a community sample. Psychological medicine, 31(1), 15-28.

Christensen, H., Korten, A. E., Jorm, A. F., Henderson, A. S., Jacomb, P. A., Rodgers, B., & Mackinnon, A. J. (1997). Education and decline in cognitive performance: Compensatory but not protective. International journal of geriatric psychiatry, 12(3), 323-330.

Christensen, H., Mackinnon, A. J., Korten, A. E., Jorm, A. F., Henderson, A. S., Jacomb,

P., & Rodgers, B. (1999). An analysis of diversity in the cognitive performance of elderly community dwellers: Individual differences in change scores as a function of age. Psychology and aging, 14(3), 365.

Clare, L., Wu, Y. T., Teale, J. C., MacLeod, C., Matthews, F., Brayne, C., ... & CFAS-Wales Study Team. (2017). Potentially modifiable lifestyle factors, cognitive reserve, and cognitive function in later life: A cross-sectional study. PLoS medicine, 14(3), e1002259.

Clouston, S. A., Brewster, P., Kuh, D., Richards, M., Cooper, R., Hardy, R., ... & Hofer, S. M. (2013). The dynamic relationship between physical function and cognition in longitudinal aging cohorts. Epidemiologic reviews, 35(1), 33-50.

Coffey, C. E., Saxton, J. A., Ratcliff, G., Bryan, R. N., & Lucke, J. F. (2000). Relation of education to brain size in normal aging: implications for the reserve hypothesis. Neurology, 53(1), 189-189.

Cohen, A. D., Price, J. C., Weissfeld, L. A., James, J., Rosario, B. L., Bi, W., ... & Wolk, D. A. (2009). Basal cerebral metabolism may modulate the cognitive effects of Aβ in mild cognitive impairment: An example of brain reserve. Journal of Neuroscience, 29(47), 14770-14778.

Colangeli, S., Boccia, M., Verde, P., Guariglia, P., Bianchini, F., & Piccardi, L. (2016). Cognitive reserve in healthy aging and Alzheimer's disease: A meta-analysis of fMRI studies. American Journal of Alzheimer's Disease & Other Dementias®, 31(5), 443-449.

Colcombe, S. J., Kramer, A. F., McAuley, E., Erickson, K. I., & Scalf, P. (2004). Neurocognitive aging and cardiovascular fitness. Journal of Molecular Neuroscience, 24(1), 9-14.

Cooper, R., Hardy, R., Sayer, A. A., Ben-Shlomo, Y., Birnie, K., Cooper, C., ... & HALCyon Study Team. (2011). Age and gender differences in physical capability levels from mid-life onwards: The harmonisation and meta-analysis of data from eight UK cohort studies. PloS one, 6(11), e27899.

Coppin, A. K., Shumway-Cook, A., Saczynski, J. S., Patel, K. V., Ble, A., Ferrucci, L., & Guralnik, J. M. (2006). Association of executive function and performance of dual-task physical tests among older adults: Analyses from the InChianti study. Age and ageing, 35(6), 619-624.

Corder, E. H., Saunders, A. M., Risch, N. J., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., ... & Small, G. W. (1994). Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nature genetics, 7(2), 180.

Corder, E. H., Saunders, A. M., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Small, G., ... & Pericak-Vance, M. A. (1993). Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science, 261(5123), 921-923.

Corral, M., Rodriguez, M., Amenedo, E., Sanchez, J. L., & Diaz, F. (2006). Cognitive reserve, age, and neuropsychological performance in healthy participants. Developmental Neuropsychology, 29(3), 479-491.

Correa Ribeiro, P. C., Lopes, C. S., & Lourenço, R. A. (2013). Complexity of lifetime occupation and cognitive performance in old age. Occupational medicine, 63(8), 556-562.

Cowan, N., & Alloway, T. (2009). Development of working memory in childhood.

Cox, S. R., Dickie, D. A., Ritchie, S. J., Karama, S., Pattie, A., Royle, N. A., ... & Starr, J. M. (2016). Associations between education and brain structure at age 73 years, adjusted for age 11 IQ. Neurology, 87(17), 1820-1826.

Craik, F. I. (1977). Age differences in human memory. Handbook of the psychology of aging, 384–420.

Craik, F. I. M. (1983). On the transfer of information from temporary to permanent memory. Philosophical Transactions of the Royal Society of London. B, Biological Sciences, 302(1110), 341-359.

Craik, F. I., & Bialystok, E. (2006). Cognition through the lifespan: Mechanisms of change. Trends in cognitive sciences, 10(3), 131-138.

Craik, F. I., Klix, F., & Hagendorf, H. (1986). A functional account of age differences in memory (pp. 409-422).

Crowe, M., Andel, R., Wadley, V. G., Okonkwo, O. C., Sawyer, P., & Allman, R. M. (2008). Life-space and cognitive decline in a community-based sample of African American and Caucasian older adults. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 63(11), 1241-1245.

Cullum, S., Huppert, F. A., McGee, M., Dening, T., Ahmed, A., Paykel, E. S., & Brayne, C. (2000). Decline across different domains of cognitive function in normal ageing: Results of a longitudinal population-based study using CAMCOG. International journal of geriatric psychiatry, 15(9), 853-862.

Cummings, J. L. (2003). The neuropsychiatry of Alzheimer's disease and related dementias. CRC Press.

Daley, M. J., & Spinks, W. L. (2000). Exercise, mobility and aging. Sports medicine, 29(1), 1-12.

Dansereau, A., Hunter, S. W., Gomez, F., Guralnik, J. M., DePaul, V. G., & Auais, M. (2020). Global cognition predicts the incidence of poor physical performance among older adults: A cross-national study. Geriatrics & gerontology international, 20(3), 218-222.

Darby, R. R., Brickhouse, M., Wolk, D. A., & Dickerson, B. C. (2017). Effects of cognitive reserve depend on executive and semantic demands of the task. J Neurol Neurosurg Psychiatry, 88(9), 794-802.

Darowski, E. S., Helder, E., Zacks, R. T., Hasher, L., & Hambrick, D. Z. (2008). Age-related differences in cognition: The role of distraction control. Neuropsychology, 22(5), 638.

Dartigues, J. F., Gagnon, M., Letenneur, L., Barberger-Gateau, P., Commenges, D., Evaldre, M., & Salamon, R. (1992). Principal lifetime occupation and cognitive impairment in a French elderly cohort (Paquid). American Journal of Epidemiology, 135(9), 981-988.

Darwish, H., Farran, N., Assaad, S., & Chaaya, M. (2018). Cognitive reserve factors in a developing country: Education and occupational attainment lower the risk of dementia in a sample of Lebanese older adults. Frontiers in aging neuroscience, 10, 277.

Daselaar, S., Veltman, D. J., Rombouts, S. A. R. B., Raaijmakers, J. G. W., & Jonker, C. (2003). Neuroanatomical correlates of episodic encoding and retrieval in young and elderly subjects. Brain, 126(1), 43-56.

Davidson, P. S., & Glisky, E. L. (2002). Neuropsychological correlates of recollection and familiarity in normal aging. Cognitive, Affective, & Behavioral Neuroscience, 2(2), 174-186.

Deary, I. J., Whalley, L. J., Lemmon, H., Crawford, J. R., & Starr, J. M. (2000). The stability of individual differences in mental ability from childhood to old age: Follow-up of the 1932 Scottish Mental Survey. Intelligence, 28(1), 49-55.

Dekhtyar, S., Marseglia, A., Xu, W., Darin-Mattsson, A., Wang, H. X., & Fratiglioni, L. (2019). Genetic risk of dementia mitigated by cognitive reserve: A cohort study. Annals of neurology, 86(1), 68-78.

Dekhtyar, S., Wang, H. X., Scott, K., Goodman, A., Koupil, I., & Herlitz, A. (2015). A life-course study of cognitive reserve in dementia—from childhood to old age. The American Journal of Geriatric Psychiatry, 23(9), 885-896.

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (2000). California Verbal Learning Test–Second Edition (CVLT-II). San Antonio, TX: The Psychological Corporation.

Demnitz, N., Esser, P., Dawes, H., Valkanova, V., Johansen-Berg, H., Ebmeier, K. P., & Sexton, C. (2016). A systematic review and meta-analysis of cross-sectional studies examining the relationship between mobility and cognition in healthy older adults. Gait & posture, 50, 164-17

Desai, A. K., Grossberg, G. T., & Chibnall, J. T. (2010). Healthy brain aging: A road map. Clinics in Geriatric Medicine, 26(1), 1-16.

Diamond, Adele. "The early development of executive functions." Lifespan cognition: Mechanisms of change (2006): 70-95.

Dobbs, A. R., & Rule, B. G. (1989). Adult age differences in working memory. Psychology and aging, 4(4), 500.

Doi, T., Tsutsumimoto, K., Nakakubo, S., Kim, M. J., Kurita, S., Hotta, R., & Shimada, H. (2019). Physical Performance Predictors for Incident Dementia Among Japanese Community-Dwelling Older Adults. Physical Therapy, 99(9), 1132-1140.

Donix, M., Burggren, A. C., Suthana, N. A., Siddarth, P., Ekstrom, A. D., Krupa, A. K., ... & Small, G. W. (2010). Family history of Alzheimer's disease and hippocampal structure in healthy people. American Journal of Psychiatry, 167(11), 1399-1406.

Doraiswamy, P. M., Sperling, R. A., Coleman, R. E., Johnson, K. A., Reiman, E. M., Davis, M. D., ... & Carpenter, A. (2012). Amyloid-β assessed by florbetapir F 18 PET and 18-month cognitive decline: A multicenter study. Neurology, 79(16), 1636-1644.

Drachman, D. A. (2006). Aging of the brain, entropy, and Alzheimer disease. Neurology, 67(8), 1340-1352.

Drag, L. L., & Bieliauskas, L. A. (2010). Contemporary review 2009: Cognitive aging. Journal of geriatric psychiatry and neurology, 23(2), 75-93.

Draganski, B., Lutti, A., & Kherif, F. (2013). Impact of brain aging and neurodegeneration on cognition: evidence from MRI. Current opinion in neurology, 26(6), 640-645.

DSM-V-TR, A.P.A. (2013). Diagnostic and statistical manual of mental disorders.

Dumurgier, J., & Tzourio, C. (2020). Epidemiology of neurological diseases in older adults. Revue neurologique.

Early, D. R., Widaman, K. F., Harvey, D., Beckett, L., Park, L. Q., Farias, S. T., ... & Mungas, D. (2013). Demographic predictors of cognitive change in ethnically diverse older persons. Psychology and aging, 28(3), 633.

Economou, A. (2009). Memory score discrepancies by healthy middle-aged and older individuals: The contributions of age and education. Journal of the International Neuropsychological Society, 15(06), 963-972.

Elderkin-Thompson, V., Ballmaier, M., Hellemann, G., Pham, D., & Kumar, A. (2008). Executive function and MRI prefrontal volumes among healthy older adults. Neuropsychology, 22(5), 626.

Evans, D. A., Hebert, L. E., Beckett, L. A., Scherr, P. A., Albert, M. S., Chown, M. J., ... & Taylor, J. O. (1997). Education and other measures of socioeconomic status and risk of incident Alzheimer disease in a defined population of older persons. Archives of neurology, 54(11), 1399-1405.

Fabbri, E., An, Y., Zoli, M., Tanaka, T., Simonsick, E. M., Kitner-Triolo, M. H., ... & Ferrucci, L. (2016). Association between accelerated multimorbidity and age-related cognitive decline in older Baltimore longitudinal study of aging participants without dementia. Journal of the American Geriatrics Society, 64(5), 965-972.

Farmer, M. E., Kittner, S. J., Rae, D. S., Bartko, J. J., & Regier, D. A. (1995). Education and change in cognitive function: The epidemiologic catchment area study. Annals of epidemiology, 5(1), 1-7.

Farrer, L. A., Cupples, L. A., Haines, J. L., Hyman, B., Kukull, W. A., Mayeux, R., ... & Van Duijn, C. M. (1997). Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: A meta-analysis. Jama, 278(16), 1349-1356.

Feldberg, C., Hermida, P. D., Maria Florencia, T., Stefani, D., Somale, V., &Allegri, R. F. (2016). Cognitive reserve in patients with mild cognitive impairment: The

importance of occupational complexity as a buffer of declining cognition in older adults. AIMS Medical Science, 3(1), 77-95.

Ferencz, B., Laukka, E. J., Welmer, A. K., Kalpouzos, G., Angleman, S., Keller, L., ... & Bäckman, L. (2014). The benefits of staying active in old age: Physical activity counteracts the negative influence of PICALM, BIN1, and CLU risk alleles on episodic memory functioning. Psychology and Aging, 29(2), 440.

Ferrari, C., Xu, W. L., Wang, H. X., Winblad, B., Sorbi, S., Qiu, C., & Fratiglioni, L. (2013). How can elderly apolipoprotein E ε4 carriers remain free from dementia?. Neurobiology of aging, 34(1), 13-21.

Fillit, H. M., Butler, R. N., O'Connell, A. W., Albert, M. S., Birren, J. E., Cotman, C. W., ... & Perls, T. T. (2002). Achieving and maintaining cognitive vitality with aging. In Mayo Clinic Proceedings (Vol. 77, No. 7, pp. 681-696). Elsevier.

Finkel, D., Andel, R., Gatz, M., & Pedersen, N. L. (2009). The role of occupational complexity in trajectories of cognitive aging before and after retirement. Psychology and aging, 24(3), 563.

Fisher, G. G., Stachowski, A., Infurna, F. J., Faul, J. D., Grosch, J., & Tetrick, L. E. (2014). Mental work demands, retirement, and longitudinal trajectories of cognitive functioning. Journal of occupational health psychology, 19(2), 231.

Fitzpatrick, A. L., Buchanan, C. K., Nahin, R. L., DeKosky, S. T., Atkinson, H. H., Carlson, M. C., & Williamson, J. D. (2007). Associations of gait speed and other measures of physical function with cognition in a healthy cohort of elderly persons. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 62(11), 1244-1251.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). “Mini-mental state”: A practical method for grading the cognitive state of patients for the clinician. Journal of psychiatric research, 12(3), 189-198.

Forstmeier, S., Maercker, A., Maier, W., van den Bussche, H., Riedel-Heller, S., Kaduszkiewicz, H., ... & Luppa, M. (2012). Motivational reserve: Motivation-related occupational abilities and risk of mild cognitive impairment and Alzheimer disease. Psychology and aging, 27(2), 353.

Fortenbaugh, F. C., DeGutis, J., Germine, L., Wilmer, J. B., Grosso, M., Russo, K., & Esterman, M. (2015). Sustained attention across the life span in a sample of 10,000: dissociating ability and strategy. Psychological Science, 26(9), 1497-1510.

Foubert-Samier, A., Catheline, G., Amieva, H., Dilharreguy, B., Helmer, C., Allard, M., & Dartigues, J. F. (2012). Education, occupation, leisure activities, and brain reserve: A population-based study. Neurobiology of aging, 33(2), 423-e15.

Franzen, M. D., Burgess, E. J., & Smith-Seemiller, L. (1997). Methods of estimating premorbid functioning. Archives of Clinical Neuropsychology, 12(8), 711-738.

Fratiglioni, L., Ahlbom, A., Viitanen, M., & Winblad, B. (1993). Risk factors for late-onset Alzheimer's disease: A population-based, case-control study. Annals of neurology, 33(3), 258-266.

Fritsch, T., McClendon, M. J., Smyth, K. A., Lerner, A. J., Friedland, R. P., & Larsen, J. D. (2007). Cognitive functioning in healthy aging: The role of reserve and lifestyle factors early in life. The Gerontologist, 47(3), 307-322.

Fukuyama, H., Ouchi, Y., Matsuzaki, S., Nagahama, Y., Yamauchi, H., Ogawa, M., ... & Shibasaki, H. (1997). Brain functional activity during gait in normal subjects: A SPECT study. Neuroscience letters, 228(3), 183-186.

Fyffe, D. C., Mukherjee, S., Barnes, L. L., Manly, J. J., Bennett, D. A., & Crane, P. K. (2011). Explaining differences in episodic memory performance among older African Americans and whites: the roles of factors related to cognitive reserve and test bias. Journal of the International Neuropsychological Society, 17(4), 625-638.

Gagliardi, C., Papa, R., Postacchini, D., & Giuli, C. (2016). Association between cognitive status and physical activity: Study profile on baseline survey of The My Mind Project. International journal of environmental research and public health, 13(6), 585.

Gale, C. R., Allerhand, M., Sayer, A. A., Cooper, C., & Deary, I. J. (2014). The dynamic relationship between cognitive function and walking speed: The English Longitudinal Study of Ageing. Age, 36(4), 9682.

Garibotto, V., Borroni, B., Sorbi, S., Cappa, S. F., Padovani, A., & Perani, D. (2012). Education and occupation provide reserve in both ApoE ε4 carrier and noncarrier patients with probable Alzheimer's disease. Neurological Sciences, 33(5), 1037-1042.

Garrett, D. D., Grady, C. L., & Hasher, L. (2010). Everyday memory compensation: The impact of cognitive reserve, subjective memory, and stress. Psychology and Aging, 25(1), 74.

Gathercole, S. E., Pickering, S. J., Knight, C., & Stegmann, Z. (2004). Working memory skills and educational attainment: Evidence from national curriculum assessments at 7 and 14 years of age. Applied Cognitive Psychology, 18(1), 1-16.

Gatto, N.M., Garcia-Cano, J., Irani, C., Liu, T., Arakaki, C., Fraser, G., Wang, C., & Lee, G.J. (2020). Observed physical function is associated with better cognition among elderly adults: The Adventist Health Study-2.

Gazzaley, A., & D'Esposito, M. (2005). BOLD functional MRI and cognitive aging. Cognitive neuroscience of aging: Linking cognitive and cerebral aging, 107-131.

Giannouli, E., Bock, O., & Zijlstra, W. (2018). Cognitive functioning is more closely related to real-life mobility than to laboratory-based mobility parameters. European journal of ageing, 15(1), 57-65.

Gillain, S., Warzee, E., Lekeu, F., Wojtasik, V., Maquet, D., Croisier, J. L., ... & Petermans, J. (2009). The value of instrumental gait analysis in elderly healthy, MCI or Alzheimer's disease subjects and a comparison with other clinical tests used in single and dual-task conditions. Annals of physical and rehabilitation medicine, 52(6), 453-474.

Giogkaraki, E., Michaelides, M. P., & Constantinidou, F. (2013). The role of cognitive reserve in cognitive aging: Results from the neurocognitive study on aging. Journal of Clinical and Experimental Neuropsychology, 35(10), 1024-1035.

Glisky, E. L. (2007). Changes in cognitive function in human aging. Brain aging: Models, methods, and mechanisms, 3-20.

Gow, A. J., Avlund, K., & Mortensen, E. L. (2014). Occupational characteristics and cognitive aging in the Glostrup 1914 Cohort. Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 69(2), 228-236.

Grady, C. L., & Craik, F. I. (2000). Changes in memory processing with age. Current opinion in neurobiology, 10(2), 224-231.

Greene, D. R. (2013). Relationship between occupational complexity and dementia risk in late life: A population study.

Green, R. C., Cupples, L. A., Go, R., Benke, K. S., Edeki, T., Griffith, P. A., ... & Farrer, L. A. (2002). Risk of dementia among white and African American relatives of patients with Alzheimer disease. Jama, 287(3), 329-336.

Gregoire, J., & Van Der Linden, M. (1997). Effect of age on forward and backward digit spans. Aging, neuropsychology, and cognition, 4(2), 140-149.

Grigsby, J., Kaye, K., Baxter, J., Shetterly, S. M., & Hamman, R. F. (1998). Executive cognitive abilities and functional status among community-dwelling older persons in the San Luis Valley Health and Aging Study. Journal of the American Geriatrics Society, 46(5), 590-596.

Groot, C., van Loenhoud, A. C., Barkhof, F., van Berckel, B. N., Koene, T., Teunissen, C. C., ... & Ossenkoppele, R. (2018). Differential effects of cognitive reserve and brain reserve on cognition in Alzheimer disease. Neurology, 90(2), e149-e156.

Gross, A. L., Mungas, D. M., Crane, P. K., Gibbons, L. E., MacKay-Brandt, A., Manly, J. J., ... & Potter, G. G. (2015). Effects of education and race on cognitive decline: An integrative study of generalizability versus study-specific results. Psychology and aging, 30(4), 863.

Gunstad, J., Paul, R. H., Brickman, A. M., Cohen, R. A., Arns, M., Roe, D., ... & Gordon, E. (2006). Patterns of cognitive performance in middle-aged and older adults: A cluster analytic examination. Journal of geriatric psychiatry and neurology, 19(2), 59-64.

Guralnik, J. M., Branch, L. G., Cummings, S. R., & Curb, J. D. (1989). Physical performance measures in aging research. Journal of gerontology, 44(5), M141-M146.

Guralnik, J. M., Simonsick, E. M., Ferrucci, L., Glynn, R. J., Berkman, L. F., Blazer, D. G., ... & Wallace, R. B. (1994). A short physical performance battery assessing lower extremity function: Association with self-reported disability and prediction of mortality and nursing home admission. Journal of gerontology, 49(2), M85-M94.

Haaland, K. Y., Price, L., & Larue, A. (2003). What does the WMS–III tell us about memory changes with normal aging?. Journal of the International Neuropsychological Society, 9(01), 89-96.

Hakiki, B., Pancani, S., Portaccio, E., Molino-Lova, R., Sofi, F., Macchi, C., & Cecchi, F. (2020). Impact of occupational complexity on cognitive decline in the oldest-old. Aging & mental health, 1-6.

Hall, C. B., Derby, C., LeValley, A., Katz, M. J., Verghese, J., & Lipton, R. B. (2007). Education delays accelerated decline on a memory test in persons who develop dementia. Neurology, 69 (17), 1657-1664.

Harada, C. N., Love, M. C. N., & Triebel, K. L. (2013). Normal cognitive aging. Clinics in geriatric medicine, 29(4), 737-752.

Haug, H., Barmwater, U., Eggers, R., Fischer, D., Kuhl, S., & Sass, N. L. (1983). Anatomical changes in aging brain: Morphometric analysis of the human prosencephalon. Aging, 21, 1-12.

Haug, H., & Eggers, R. (1991). Morphometry of the human cortex cerebri and corpus striatum during aging. Neurobiology of aging, 12(4), 336-338.

Head, D., Buckner, R. L., Shimony, J. S., Williams, L. E., Akbudak, E., Conturo, T. E., ... & Snyder, A. Z. (2004). Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in dementia of the Alzheimer type: Evidence from diffusion tensor imaging. Cerebral cortex, 14(4), 410-423.

Head, D., Rodrigue, K. M., Kennedy, K. M., & Raz, N. (2008). Neuroanatomical and cognitive mediators of age-related differences in episodic memory. Neuropsychology, 22(4), 491.

Hebert, L. E., Bienias, J. L., Aggarwal, N. T., Wilson, R. S., Bennett, D. A., Shah, R. C., & Evans, D. A. (2010). Change in risk of Alzheimer disease over time. Neurology, 75(9), 786-791.

Hebert, L. E., Weuve, J., Scherr, P. A., & Evans, D. A. (2013). Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. Neurology, 80(19), 1778-1783.

Hedden, T., & Gabrieli, J. D. (2004). Insights into the ageing mind: A view from cognitive neuroscience. Nature reviews neuroscience, 5(2), 87.

Helmer, C., Letenneur, L., Rouch, I., Richard-Harston, S., Barberger-Gateau, P., Fabrigoule, C., ... & Dartigues, J. F. (2001). Occupation during life and risk of dementia in French elderly community residents. Journal of Neurology, Neurosurgery & Psychiatry, 71(3), 303-309.

Helzner, E. P., Scarmeas, N., Cosentino, S., Portet, F., & Stern, Y. (2007). Leisure activity and cognitive decline in incident Alzheimer disease. Archives of Neurology, 64(12), 1749-1754.

Hendrie, H. C., Albert, M. S., Butters, M. A., Gao, S., Knopman, D. S., Launer, L. J., ... & Wagster, M. V. (2006). The NIH cognitive and emotional health project: report of the critical evaluation study committee. Alzheimer's & Dementia, 2(1), 12-32.

Herman, T., Giladi, N., & Hausdorff, J. M. (2011). Properties of the 'timed up and go' test: More than meets the eye. Gerontology, 57(3), 203-210.

Hertzog, C., Dixon, R. A., Hultsch, D. F., & MacDonald, S. W. (2003). Latent change models of adult cognition: Are changes in processing speed and working memory associated with changes in episodic memory?. Psychology and aging, 18(4), 755.

Heyman, A., Wilkinson, W. E., Stafford, J. A., Helms, M. J., Sigmon, A. H., & Weinberg, T. (1984). Alzheimer's disease: A study of epidemiological aspects. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 15(4), 335-341.

Holtzer, R., Epstein, N., Mahoney, J. R., Izzetoglu, M., & Blumen, H. M. (2014). Neuroimaging of mobility in aging: A targeted review. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences, 69(11), 1375-1388.

Holtzer, R., Verghese, J., Xue, X., & Lipton, R. B. (2006). Cognitive processes related to gait velocity: Results from the Einstein Aging Study. Neuropsychology, 20(2), 215.

Holtzer, R., Wang, C., Lipton, R., & Verghese, J. (2012). The protective effects of executive functions and episodic memory on gait speed decline in aging defined in the context of cognitive reserve. Journal of the American Geriatrics Society, 60(11), 2093-2098.

Horn, J. L. (1970). Organization of data on life-span development of human abilities. In Life-span developmental psychology (pp. 423-466). Academic Press.

Horn, J. L., & Cattell, R. B. (1967). Age differences in fluid and crystallized intelligence. Acta psychologica, 26, 107-129.

Horn, J. L., & Donaldson, G. (1976). On the myth of intellectual decline in adulthood. American Psychologist, 31(10), 701.

Howard, E. P., Morris, J. N., Steel, K., Strout, K. A., Fries, B. E., Moore, A., & Garms-

Homolová, V. (2016). Short-term lifestyle strategies for sustaining cognitive status. BioMed research international, 2016.

Hsiung, G. Y. R., Sadovnick, A. D., & Feldman, H. (2004). Apolipoprotein E ε4 genotype as a risk factor for cognitive decline and dementia: data from the Canadian Study of Health and Aging. Cmaj, 171(8), 863-867.

Hugo, J., & Ganguli, M. (2014). Dementia and cognitive impairment: epidemiology, diagnosis, and treatment. Clinics in geriatric medicine, 30(3), 421-442.

Huh, Y., Yang, E. J., Lee, S. A., Lim, J. Y., Kim, K. W., & Paik, N. J. (2011). Association between executive function and physical performance in older Korean adults: findings from the Korean Longitudinal Study on Health and Aging (KLoSHA). Archives of gerontology and geriatrics, 52(3), e156-e161.

Hultsch, D. F., Hertzog, C., Small, B. J., & Dixon, R. A. (1999). Use it or lose it: engaged lifestyle as a buffer of cognitive decline in aging?. Psychology and aging, 14(2), 245.

Hyman, B. T., Phelps, C. H., Beach, T. G., Bigio, E. H., Cairns, N. J., Carrillo, M. C., ... & Mirra, S. S. (2012). National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimer's & dementia, 8(1), 1-13.

Hyun, J., Katz, M. J., Lipton, R. B., & Sliwinski, M. J. (2019). Mentally challenging occupations are associated with more rapid cognitive decline at later stages of cognitive aging. The Journals of Gerontology: Series B.

Iachini, T., Iavarone, A., Senese, V. P., Ruotolo, F., & Ruggiero, G. (2009). Visuospatial memory in healthy elderly, AD and MCI: A review. Current aging science, 2(1), 43-59.

Ihle, A., Gouveia, É. R., Gouveia, B. R., Freitas, D. L., Jurema, J., Odim, A. P., & Kliegel, M. (2017). The relation of education, occupation, and cognitive activity to cognitive status in old age: The role of physical frailty. International psychogeriatrics, 29(9), 1469-1474.

Ihle, A., Gouveia, É. R., Gouveia, B. R., Freitas, D. L., Jurema, J., Ornelas, R. T., ... & Kliegel, M. (2018). The relation of education and cognitive activity to mini-mental state in old age: The role of functional fitness status. European journal of ageing, 15(2), 123-131.

Inzitari, M., Newman, A. B., Yaffe, K., Boudreau, R., De Rekeneire, N., Shorr, R., ... & Rosano, C. (2007). Gait speed predicts decline in attention and psychomotor speed in older adults: The health aging and body composition study. Neuroepidemiology, 29(3-4), 156-162.

Isingrini, M., Taconnat, L. (2008) Episodic memory, frontal functioning, and aging. Revue neurologique, 164 (Suppl 3): S91–5.

Jefferson, A. L., Gibbons, L. E., Rentz, D. M., Carvalho, J. O., Manly, J., Bennett, D. A., & Jones, R. N. (2011). A life course model of cognitive activities, socioeconomic status, education, reading ability, and cognition. Journal of the American Geriatrics Society, 59(8), 1403-1411.

Jonaitis, E., La Rue, A., Mueller, K. D., Koscik, R. L., Hermann, B., & Sager, M. A. (2013). Cognitive activities and cognitive performance in middle-aged adults at risk for Alzheimer's disease. Psychology and aging, 28(4), 1004.

Jonker, C., Schmand, B., Lindeboom, J., Havekes, L. M., & Launer, L. J. (1998). Association Between Apolipoprotein Eϵ4 and the Rate of Cognitive Decline in Community-Dwelling Elderly Individuals with and Without Dementia. Archives of Neurology, 55(8), 1065-1069.

Jorm, A. F., & Jolley, D. (1998). The incidence of dementia: A meta-analysis. Neurology, 51(3), 728-733.

Jorm, A. F., Mather, K. A., Butterworth, P., Anstey, K. J., Christensen, H., & Easteal, S. (2007). APOE genotype and cognitive functioning in a large age-stratified population sample. Neuropsychology, 21(1), 1.

Kalmijn, S., Feskens, E. J., Launer, L. J., & Kromhout, D. (1997). Longitudinal study of the effect of apolipoprotein e4 allele on the association between education and cognitive decline in elderly men. Bmj, 314(7073), 34.

Kaiser, N. C., Miller, K. J., Siddarth, P., Ercoli, L. M., & Small, G. W. (2013). The impact of age and Alzheimer's disease risk factors on memory performance over time. Aging Health, 9(1), 115-124.

Karp, A., Kåreholt, I., Qiu, C., Bellander, T., Winblad, B., & Fratiglioni, L. (2004). Relation of education and occupation-based socioeconomic status to incident Alzheimer's disease. American journal of epidemiology, 159(2), 175-183.

Katzman, R., Terry, R., DeTeresa, R., Brown, T., Davies, P., Fuld, P., ... & Peck, A. (1988). Clinical, pathological, and neurochemical changes in dementia: A subgroup with preserved mental status and numerous neocortical plaques. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 23(2), 138-144.

Kaup, A. R., Xia, F., Launer, L. J., Sidney, S., Nasrallah, I., Erus, G., ... & Yaffe, K. (2018). Occupational cognitive complexity in earlier adulthood is associated with brain structure and cognitive health in midlife: The CARDIA study. Neuropsychology, 32(8), 895.

Kohn, M. L., & Schooler, C. (1983). Work and personality: An inquiry into the impact of social stratification. Greenwood.

Kim, J., Basak, J. M., & Holtzman, D. M. (2009). The role of apolipoprotein E in Alzheimer's disease. Neuron, 63(3), 287-303.

Kobayashi-Cuya, K. E., Sakurai, R., Suzuki, H., Ogawa, S., Takebayashi, T., & Fujiwara, Y. (2018). Observational evidence of the association between handgrip strength, hand dexterity, and cognitive performance in community-dwelling older adults: A systematic review. Journal of epidemiology, JE20170041.

Kobayashi, S., Ohashi, Y., & Ando, S. (2002). Effects of enriched environments with different durations and starting times on learning capacity during aging in rats assessed by a refined procedure of the Hebb-Williams maze task. Journal of neuroscience research, 70(3), 340-346.

Kramer, A. F., Bherer, L., Colcombe, S. J., Dong, W., & Greenough, W. T. (2004). Environmental influences on cognitive and brain plasticity during aging. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 59(9), M940-M957.

Krausz, Y., Bonne, O., Gorfine, M., Karger, H., Lerer, B., & Chisin, R. (1998). Age-related changes in brain perfusion of normal subjects detected by 99m Tc-HMPAO SPECT. Neuroradiology, 40(7), 428-434.

Kravitz, J., Kim, J., Faust-Socher, A., Rogers, S., & Miller, K. (2008). Mild cognitive impairment: Current trends for early detection and treatment.

Kroger, E., Andel, R., Lindsay, J., Benounissa, Z., Verreault, R., & Laurin, D. (2008). Is complexity of work associated with risk of dementia? The Canadian Study of Health and Aging. American journal of epidemiology, 167(7), 820-830.

Lam, L. C., Ong, P. A., Dikot, Y., Sofiatin, Y., Wang, H., Zhao, M., ... & Fu, J. L. (2015). Intellectual and physical activities, but not social activities, are associated with better global cognition: A multi-site evaluation of the cognition and lifestyle activity study for seniors in Asia (CLASSA). Age and ageing, 44(5), 835-840.

Lane, A. P., Windsor, T. D., Andel, R., & Luszcz, M. A. (2017). Is occupational complexity associated with cognitive performance or decline? Results from the Australian Longitudinal Study of Ageing. Gerontology, 63(6), 550-559.

Langa, K. M., Larson, E. B., Crimmins, E. M., Faul, J. D., Levine, D. A., Kabeto, M. U., & Weir, D. R. (2017). A comparison of the prevalence of dementia in the United States in 2000 and 2012. JAMA internal medicine, 177(1), 51-58.

Lautenschlager, N. T., Cupples, L. A., Rao, V. S., Auerbach, S. A., Becker, R., Burke, J., ... & Green, R. C. (1996). Risk of dementia among relatives of Alzheimer's disease patients in the MIRAGE study: What is in store for the oldest old?. Neurology, 46(3), 641-650.

Le Carret, N., Auriacombe, S., Letenneur, L., Bergua, V., Dartigues, J. F., & Fabrigoule, C. (2005). Influence of education on the pattern of cognitive deterioration in AD patients: The cognitive reserve hypothesis. Brain and cognition, 57(2), 120-126.

Le Carret, N., Lafont, S., Letenneur, L., Dartigues, J. F., Mayo, W., & Fabrigoule, C. (2003). The effect of education on cognitive performances and its implication for the constitution of the cognitive reserve. Developmental neuropsychology, 23(3), 317-337.

Lee, G. J. (2016). PSYC 516 Neuropsychological Assessment: Memory [PowerPoint slides].

Lenehan, M. E., Summers, M. J., Saunders, N. L., Summers, J. J., & Vickers, J. C. (2015). Relationship between education and age-related cognitive decline: A review of recent research. Psychogeriatrics, 15(2), 154-162.

Lerche, S., Gutfreund, A., Brockmann, K., Hobert, M. A., Wurster, I., Sünkel, U., ... & Berg, D. (2018). Effect of physical activity on cognitive flexibility, depression and RBD in healthy elderly. Clinical neurology and neurosurgery, 165, 88-93.

Leung, G. T., Fung, A. W., Tam, C. W., Lui, V. W., Chiu, H. F., Chan, W. M., & Lam, L. C. (2010). Examining the association between participation in late-life leisure activities and cognitive function in community-dwelling elderly Chinese in Hon Kong. International Psychogeriatrics, 22(1), 2-13

Lezak, M. D., Howieson, D. B., Loring, D. W., & Fischer, J. S. (2004). Neuropsychological assessment. Oxford University Press, USA.

Lezak, M., Howieson, D., & Loring, D. (2012). Neuropsychological assessment. 5th ed Oxford University Press. Oxford, New York, ISBN, 10, 9780195395525.

Li, C. Y., Wu, S. C., & Sung, F. C. (2002). Lifetime principal occupation and risk of cognitive impairment among the elderly. Industrial health, 40(1), 7-13.

Lim, Y. Y., Ellis, K. A., Pietrzak, R. H., Ames, D., Darby, D., Harrington, K., ... & Szoeke, C. (2012). Stronger effect of amyloid load than APOE genotype on cognitive decline in healthy older adults. Neurology, 79(16), 1645-1652.

Lindenberger, U., & Reischies, F. M. (1999). Limits and potentials of intellectual functioning in old age. The Berlin aging study: Aging from, 70, 329-359.

Lipnicki, D. M., Crawford, J. D., Dutta, R., Thalamuthu, A., Kochan, N. A., Andrews, G., ... & Stephan, B. C. (2017). Age-related cognitive decline and associations with sex, education and apolipoprotein E genotype across ethnocultural groups and geographic regions: A collaborative cohort study. PLoS medicine, 14(3), e1002261.

Liu-Ambrose, T. Y., Ashe, M. C., Graf, P., Beattie, B. L., & Khan, K. M. (2008). Increased risk of falling in older community-dwelling women with mild cognitive impairment. Physical therapy, 88(12), 1482-1491.

Liu, C. C., Kanekiyo, T., Xu, H., & Bu, G. (2013). Apolipoprotein E and Alzheimer disease: Risk, mechanisms and therapy. Nature Reviews Neurology, 9(2), 106.

Liu, Y., Ma, W., Li, M., Han, P., Cai, M., Wang, F., ... & Yu, Y. (2021). Relationship between physical performance and mild cognitive impairment in Chinese community-dwelling older adults. Clinical Interventions in Aging, 16, 119.

López, M. E., Turrero, A., Cuesta, P., Lopez-Sanz, D., Bruna, R., Marcos, A., ... & Maestu, F. (2016). Searching for primary predictors of conversion from mild cognitive impairment to Alzheimer's disease: A multivariate follow-up study. Journal of Alzheimer's Disease, 52(1), 133-143.

López, M. E., Turrero, A., Delgado, M. L., Rodríguez-Rojo, I. C., Arrazola, J., Barabash, A., ... & Fernández, A. (2017). APOE ε4 genotype and cognitive reserve effects on the cognitive functioning of healthy elders. Dementia and geriatric cognitive disorders, 44(5-6), 328-342.

Lowe, D. A., & Rogers, S. A. (2011). Estimating premorbid intelligence among older adults: The utility of the AMNART. Journal of aging research, 2011.

Lyketsos, C. G., Chen, L. S., & Anthony, J. C. (1999). Cognitive decline in adulthood: An 11.5-year follow-up of the Baltimore Epidemiologic Catchment Area study. American Journal of Psychiatry, 156(1), 58-65.

Mahley, R. W., Weisgraber, K. H., & Huang, Y. (2009). Apolipoprotein E: Structure determines function, from atherosclerosis to Alzheimer's disease to AIDS. Journal of lipid research, 50(Supplement), S183-S188.

Malek-Ahmadi, M. (2016). Reversion from mild cognitive impairment to normal cognition. Alzheimer Disease & Associated Disorders, 30(4), 324-330.

Malmstrom, T. K., Wolinsky, F. D., Andresen, E. M., Philip Miller, J., & Miller, D. K. (2005). Cognitive ability and physical performance in middle-aged African Americans. Journal of the American Geriatrics Society, 53(6), 997-1001.

Manly, J. J., Schupf, N., Tang, M. X., & Stern, Y. (2005). Cognitive decline and literacy among ethnically diverse elders. Journal of geriatric psychiatry and neurology, 18(4), 213-217.

Manly, J. J., Touradji, P., Tang, M. X., & Stern, Y. (2003). Literacy and memory decline among ethnically diverse elders. Journal of clinical and experimental neuropsychology, 25(5), 680-690.

Mathias, S., Nayak, U. S., & Isaacs, B. (1986). Balance in elderly patients: The" get-up and go" test. Archives of physical medicine and rehabilitation, 67(6), 387-389.

Mathuranath, P. S., Cherian, J. P., Mathew, R., George, A., Alexander, A., & Sarma, S. P. (2007). Mini mental state examination and the Addenbrooke's cognitive examination: Effect of education and norms for a multicultural population. Neurology India, 55(2), 106.

Mattay, V. S., Fera, F., Tessitore, A., Hariri, A. R., Das, S., Callicott, J. H., & Weinberger, D. R. (2002). Neurophysiological correlates of age-related changes in human motor function. Neurology, 58(4), 630-635.

Mayer, R. E., & Moreno, R. (1998). A split-attention effect in multimedia learning: Evidence for dual processing systems in working memory. Journal of educational psychology, 90(2), 312.

Mayeux, R., Sano, M., Chen, J., Tatemichi, T., & Stern, Y. (1991). Risk of dementia in first-degree relatives of patients with Alzheimer's disease and related disorders. Archives of neurology, 48(3), 269-273.

Mayeux, R., Small, S. A., Tang, M. X., Tycko, B., & Stern, Y. (2001). Memory performance in healthy elderly without Alzheimer’s disease: effects of time and apolipoprotein-E. Neurobiology of aging, 22(4), 683-689.

Mayeux, R., Stern, Y., Ottman, R., Tatemichi, T. K., Tang, M. X., Maestre, G., ... & Ginsberg, H. (1993). The apolipoprotein ε4 allele in patients with Alzheimer's disease. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 34(5), 752-754.

Maylor, E. A. (1996). Age-related impairment in an event-based prospective-memory task. Psychology and aging, 11(1), 74.

Mazer, J. A., Vinje, W. E., McDermott, J., Schiller, P. H., & Gallant, J. L. (2002). Spatial frequency and orientation tuning dynamics in area V1. Proceedings of the National Academy of Sciences, 99(3), 1645-1650.

Mazzeo, S., Padiglioni, S., Bagnoli, S., Bracco, L., Nacmias, B., Sorbi, S., & Bessi, V. (2019). The dual role of cognitive reserve in subjective cognitive decline and mild cognitive impairment: A 7-year follow-up study. Journal of neurology, 266(2), 487-497.

McDowd, J. M., & Craik, F. I. (1988). Effects of aging and task difficulty on divided attention performance. Journal of Experimental Psychology: Human Perception and Performance, 14(2), 267.

McGough, E. L., Kelly, V. E., Logsdon, R. G., McCurry, S. M., Cochrane, B. B., Engel, J. M., & Teri, L. (2011). Associations between physical performance and executive function in older adults with mild cognitive impairment: gait speed and the timed “up & go” test. Physical therapy, 91(8), 1198-1207.

Medaglia, J. D., Pasqualetti, F., Hamilton, R. H., Thompson-Schill, S. L., & Bassett, D. S. (2017). Brain and cognitive reserve: Translation via network control theory. Neuroscience & Biobehavioral Reviews, 75, 53-64.

Meguro, K., Shimada, M., Yamaguchi, S., Ishizaki, J., Ishii, H., Shimada, Y., ... & Sekita, Y. (2001). Cognitive function and frontal lobe atrophy in normal elderly adults: Implications for dementia not as aging-related disorders and the reserve hypothesis. Psychiatry and Clinical Neurosciences, 55(6), 565-572.

Mendez, M. F., Underwood, K. L., Zander, B. A., Mastri, A. R., Sung, J. H., & Frey, W. H. (1992). Risk factors in Alzheimer's disease: A clinicopathologic study. Neurology, 42(4), 770-770.

Meng, X., & D’arcy, C. (2012). Education and dementia in the context of the cognitive reserve hypothesis: A systematic review with meta-analyses and qualitative analyses. PloS one, 7(6), e38268.

Mielke, M. M., Roberts, R. O., Savica, R., Cha, R., Drubach, D. I., Christianson, T., ... & Petersen, R. C. (2013). Assessing the temporal relationship between cognition and gait: slow gait predicts cognitive decline in the Mayo Clinic Study of Aging. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences, 68(8), 929-937.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions

to complex “frontal lobe” tasks: A latent variable analysis. Cognitive psychology, 41(1), 49-100.

Morris, N., & Jones, D. M. (1990). Memory updating in working memory: The role of the central executive. British journal of psychology, 81(2), 111-121.

Morrison, J. H., & Hof, P. R. (1997). Life and death of neurons in the aging brain. Science, 278(5337), 412-419.

Mortamais, M., Portet, F., Brickman, A. M., Provenzano, F. A., Muraskin, J., Akbaraly, T. N., ... & de Champfleur, N. M. (2014). Education modulates the impact of white matter lesions on the risk of mild cognitive impairment and dementia. The American Journal of Geriatric Psychiatry, 22(11), 1336-1345.

Mortimer, J. A., Snowdon, D. A., & Markesbery, W. R. (2003). Head circumference, education and risk of dementia: Findings from the Nun Study. Journal of clinical and experimental neuropsychology, 25(5), 671-679.

Muir-Hunter, S. W., Clark, J., McLean, S., Pedlow, S., Van Hemmen, A., Montero Odasso, M., & Overend, T. (2014). Identifying balance and fall risk in community-dwelling older women: The effect of executive function on postural control. Physiotherapy Canada, 66(2), 179-186.

Müller, N. C., Genzel, L., Konrad, B. N., Pawlowski, M., Neville, D., Fernández, G., ... & Dresler, M. (2016). Motor skills enhance procedural memory formation and protect against age-related decline. PloS one, 11(6), e0157770.

Mungas, D., Gavett, B., Fletcher, E., Farias, S. T., DeCarli, C., & Reed, B. (2018). Education amplifies brain atrophy effect on cognitive decline: implications for cognitive reserve. Neurobiology of aging, 68, 142-150.

Murphy, S. L., Xu, J., Kochanek, K. D., & Arias, E. (2018). Mortality in the United States, 2017.

Narazaki, K., Matsuo, E., Honda, T., Nofuji, Y., Yonemoto, K., & Kumagai, S. (2014). Physical fitness measures as potential markers of low cognitive function in Japanese community-dwelling older adults without apparent cognitive problems. Journal of sports science & medicine, 13(3), 590.

Ngandu, T., von Strauss, E., Helkala, E. L., Winblad, B., Nissinen, A., Tuomilehto, J., ... & Kivipelto, M. (2007). Education and dementia: What lies behind the association?. Neurology, 69(14), 1442-1450.

Nilsson, L. G. (2003). Memory function in normal aging. Acta Neurologica Scandinavica, 107(s179), 7-13.

Nishita, Y., Tange, C., Tomida, M., Ando, F., & Shimokata, H. (2013). Does high educational level protect against intellectual decline in older adults?: A 10-year longitudinal study. Japanese Psychological Research, 55(4), 378-389.

Nolde, S. F., Johnson, M. K., & D'Esposito, M. (1998). Left prefrontal activation during episodic remembering: An event-related fMRI study. NeuroReport, 9(15), 3509-3514.

Nordin, E., Rosendahl, E., & Lundin-Olsson, L. (2006). Timed "Up & Go" Test: Reliability in older people dependent in activities of daily living—focus on cognitive state. Physical therapy, 86(5), 646-655.

Nyberg, L., Lövdén, M., Riklund, K., Lindenberger, U., & Bäckman, L. (2012). Memory aging and brain maintenance. Trends in cognitive sciences, 16(5), 292-305.

O'Brien, R. J., & Wong, P. C. (2011). Amyloid precursor protein processing and Alzheimer's disease. Annual review of neuroscience, 34, 185-204.

O'Donoghue, M. C., Murphy, S. E., Zamboni, G., Nobre, A. C., & Mackay, C. E. (2018). APOE genotype and cognition in healthy individuals at risk of Alzheimer's disease: A review. Cortex, 104, 103-123.

O'Hara, R., Yesavage, J. A., Kraemer, H. C., Mauricio, M., Friedman, L. F., & Murphy Jr, G. M. (1998). The APOEə 4 allele Is Associated with Decline on Delayed Recall Performance in Community-Dwelling Older Adults. Journal of the American Geriatrics Society, 46(12), 1493-1498.

Okonkwo, O. C., Crowe, M., Wadley, V. G., & Ball, K. (2008). Visual attention and self-regulation of driving among older adults. International Psychogeriatrics, 20(1), 162-173.

Oltra-Cucarella, J., Sánchez-SanSegundo, M., Lipnicki, D. M., Sachdev, P. S., Crawford,J. D., Pérez-Vicente, J. A., ... & Alzheimer's Disease Neuroimaging Initiative. (2018). Using Base Rate of Low Scores to Identify Progression from Amnestic Mild Cognitive Impairment to Alzheimer's Disease. Journal of the American Geriatrics Society, 66(7), 1360-1366.

Oosterman, J. M., Vogels, R. L., van Harten, B., Gouw, A. A., Poggesi, A., Scheltens, P., ... & Scherder, E. J. (2010). Assessing mental flexibility: neuroanatomical and neuropsychological correlates of the Trail Making Test in elderly people. The Clinical Neuropsychologist, 24(2), 203-219.

Opdebeeck, C., Martyr, A., & Clare, L. (2016). Cognitive reserve and cognitive function in healthy older people: A meta-analysis. Aging, Neuropsychology, and Cognition, 23(1), 40-60.

Osone, A., Arai, R., Hakamada, R., & Shimoda, K. (2016). Cognitive and brain reserve in conversion and reversion in patients with mild cognitive impairment over 12 months of follow-up. Journal of clinical and experimental neuropsychology, 38(10), 1084-1093.

Owsley, C., & McGwin Jr, G. (2004). Association between visual attention and mobility in older adults. Journal of the American Geriatrics Society, 52(11), 1901-1906.

Painter, P., Stewart, A. L., & Carey, S. (1999). Physical functioning: definitions, measurement, and expectations. Advances in renal replacement therapy, 6(2), 110-123.

Pandya, S. Y., Lacritz, L. H., Weiner, M. F., Deschner, M., & Woon, F. L. (2017). Predictors of reversion from mild cognitive impairment to normal cognition. Dementia and geriatric cognitive disorders, 43(3-4), 204-214.

Papadakis, M. A., Grady, D., Tierney, M. J., Black, D., Wells, L., & Grunfeld, C. (1995). Insulin-like growth factor 1 and functional status in healthy older men. Journal of the American Geriatrics Society, 43(12), 1350-1355.

Park, D. C. (2000). The basic mechanisms accounting for age-related decline in cognitive function. Cognitive aging: A primer, 11, 3-19.

Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: Aging and neurocognitive scaffolding. Annual review of psychology, 60, 173-196.

Parker, D., Bucks, R. S., Rainey-Smith, S. R., Hodgson, E., Fine, L., Sohrabi, H. R., ... & Weinborn, M. (2020). Sleep Mediates Age-Related Executive Function for Older Adults with Limited Cognitive Reserve. Journal of the International Neuropsychological Society, 1-11.

Paykel, E. S., Brayne, C., Huppert, F. A., Gill, C., Barkley, C., Gehlhaar, E., ... & O'Connor, D. (1994). Incidence of dementia in a population older than 75 years in the United Kingdom. Archives of General Psychiatry, 51(4), 325-332.

Peel, N. M., Alapatt, L. J., Jones, L. V., & Hubbard, R. E. (2019). The association between gait speed and cognitive status in community-dwelling older people: A systematic review and meta-analysis. The Journals of Gerontology: Series A, 74(6), 943-948.

Penke, L., Maniega, S. M., Murray, C., Gow, A. J., Hernández, M. C. V., Clayden, J. D., ... & Deary, I. J. (2010). A general factor of brain white matter integrity predicts information processing speed in healthy older people. Journal of Neuroscience, 30(22), 7569-7574.

Perneczky, R., Drzezga, A., Diehl-Schmid, J., Li, Y., & Kurz, A. (2007). Gender differences in brain reserve. Journal of neurology, 254(10), 1395.

Perneczky, R., Wagenpfeil, S., Lunetta, K. L., Cupples, L. A., Green, R. C., DeCarli, C., ... & Kurz, A. (2010). Head circumference, atrophy, and cognition: implications for brain reserve in Alzheimer disease. Neurology, 75(2), 137-142.

Persad, C. C., Jones, J. L., Ashton-Miller, J. A., Alexander, N. B., & Giordani, B. (2008). Executive function and gait in older adults with cognitive impairment. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 63(12), 1350-1355.

Petersen, R. C., Doody, R., Kurz, A., Mohs, R. C., Morris, J. C., Rabins, P. V., ... & Winblad, B. (2001). Current concepts in mild cognitive impairment. Archives of neurology, 58(12), 1985-1992.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. Archives of neurology, 56(3), 303-308.

Pettigrew, C., Soldan, A., Li, S., Lu, Y., Wang, M. C., Selnes, O. A., ... & Research Team the BIOCARD. (2013). Relationship of cognitive reserve and APOE status to the emergence of clinical symptoms in preclinical Alzheimer's disease. Cognitive neuroscience, 4(3-4), 136-142.

Pillai, J. A., McEvoy, L. K., Hagler Jr, D. J., Holland, D., Dale, A. M., Salmon, D. P., ... & Fennema-Notestine, C. (2012). Higher education is not associated with greater cortical thickness in brain areas related to literacy or intelligence in normal aging or mild cognitive impairment. Journal of clinical and experimental neuropsychology, 34(9), 925-935.

Plassman, B. L., Langa, K. M., Fisher, G. G., Heeringa, S. G., Weir, D. R., Ofstedal, M. B., ... & Steffens, D. C. (2007). Prevalence of dementia in the United States: The aging, demographics, and memory study. Neuroepidemiology, 29(1-2), 125-132.

Plumet, J., Gil, R., & Gaonac'h, D. (2005). Neuropsychological assessment of executive functions in women: effects of age and education. Neuropsychology, 19(5), 566.

Podsiadlo, D., & Richardson, S. (1991). The timed "Up & Go": A test of basic functional mobility for frail elderly persons. Journal of the American geriatrics Society, 39(2), 142-148.

Potter, G. G., Helms, M. J., Burke, J. R., Steffens, D. C., & Plassman, B. L. (2007). Job demands and dementia risk among male twin pairs. Alzheimer's & Dementia, 3(3), 192-199.

Potter, G. G., Plassman, B. L., Helms, M. J., Foster, S. M., & Edwards, N. W. (2006). Occupational characteristics and cognitive performance among elderly male twins. Neurology, 67(8), 1377-1382.

Price, L., Said, K., & Haaland, K. Y. (2004). Age-associated memory impairment of logical memory and visual reproduction. Journal of clinical and experimental neuropsychology, 26(4), 531-538.

Prince, M., Bryce, R., Albanese, E., Wimo, A., Ribeiro, W., & Ferri, C. P. (2013). The global prevalence of dementia: A systematic review and metaanalysis. Alzheimer's & dementia, 9(1), 63-75.

Proust-Lima, C., Amieva, H., Letenneur, L., Orgogozo, J. M., Jacqmin-Gadda, H., & Dartigues, J. F. (2008). Gender and education impact on brain aging: A general cognitive factor approach. Psychology and aging, 23(3), 608.

Puente, A. N., Lindbergh, C. A., & Miller, L. S. (2015). The relationship between cognitive reserve and functional ability is mediated by executive functioning in older adults. The Clinical Neuropsychologist, 29(1), 67-81.

Raji, M. A., Ostir, G. V., Markides, K. S., & Goodwin, J. S. (2002). The interaction of cognitive and emotional status on subsequent physical functioning in older Mexican Americans: findings from the Hispanic established population for the epidemiologic study of the elderly. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 57(10), M678-M682.

Ramnath, U., Rauch, L., Lambert, E. V., & Kolbe-Alexander, T. L. (2018). The relationship between functional status, physical fitness and cognitive performance in physically active older adults: A pilot study. PloS one, 13(4), e0194918.

Ravdin, L. D., & Katzen, H. L. (Eds.). (2013). Handbook on the Neuropsychology of Aging and Dementia (pp. 4-5). New York, NY, USA: Springer.

Raz, N. (2005). The aging brain observed in vivo: differential changes and their modifiers.

Raz, N., Gunning-Dixon, F. M., Head, D., Dupuis, J. H., & Acker, J. D. (1998). Neuroanatomical correlates of cognitive aging: evidence from structural magnetic resonance imaging. Neuropsychology, 12(1), 95.

Raz, N., Gunning, F. M., Head, D., Dupuis, J. H., McQuain, J., Briggs, S. D., ... & Acker,

J. D. (1997). Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. Cerebral cortex (New York, NY: 1991), 7(3), 268-282.

Reas, E. T., Laughlin, G. A., Bergstrom, J., Kritz-Silverstein, D., Barrett-Connor, E., & McEvoy, L. K. (2019). Effects of APOE on cognitive aging in community-dwelling older adults. Neuropsychology, 33(3), 406.

Rentz, D. M., Locascio, J. J., Becker, J. A., Mo ran, E. K., Eng, E., Buckner, R. L., ... & Johnson, K. A. (2010). Cognition, reserve, and amyloid deposition in normal aging. Annals of neurology, 67(3), 353-364.

Reuben, D. B., & Siu, A. L. (1990). An objective measure of physical function of elderly outpatients: The Physical Performance Test. Journal of the American Geriatrics Society, 38(10), 1105-1112.

Reuter-Lorenz, P. A., Jonides, J., Smith, E. E., Hartley, A., Miller, A., Marshuetz, C., & Koeppe, R. A. (2000). Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. Journal of cognitive neuroscience, 12(1), 174-187.

Reuter-Lorenz, P. A., & Mikels, J. A. (2006). The aging mind and brain: Implications of enduring plasticity for behavioral and cultural change. Lifespan development and the brain: The perspective of biocultural co-constructivism, 255-276.

Reuter-Lorenz, P. A., & Sylvester, C. Y. C. (2005). The cognitive neuroscience of working memory and aging. Cognitive neuroscience of aging: Linking cognitive and cerebral aging, 186-217.

Richard, E., Van den Heuvel, E., van Charante, E. P. M., Achthoven, L., Vermeulen, M., Bindels, P. J., & Van Gool, W. A. (2009). Prevention of dementia by intensive vascular care (PreDIVA): A cluster-randomized trial in progress. Alzheimer Disease & Associated Disorders, 23(3), 198-204.

Richards, M., Sacker, A., & Deary, I. J. (2013). Lifetime antecedents of cognitive reserve. In Cognitive Reserve (pp. 54-69). Psychology Press.

Richards, M., Shipley, B., Fuhrer, R., & Wadsworth, M. E. (2004). Cognitive ability in childhood and cognitive decline in mid-life: longitudinal birth cohort study. Bmj, 328(7439), 552.

Riedel, B. C., Thompson, P. M., & Brinton, R. D. (2016). Age, APOE and sex: Triad of risk of Alzheimer's disease. The Journal of steroid biochemistry and molecular biology, 160, 134-147.

Riley, K. P., Snowdon, D. A., Saunders, A. M., Roses, A. D., Mortimer, J. A., & Nanayakkara, N. (2000). Cognitive function and apolipoprotein E in very old adults: Findings from the Nun Study. The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 55(2), S69-S75.

Rioux, P., Desgranges, B., Marchal, G., Petit-Taboué, M. C., Dary, M., Lechevalier, B., & Baron, J. C. (1995). Healthy aging, memory subsystems and regional cerebral oxygen consumption. Neuropsychologia, 33(7), 867-887.

Rizzo, N. S., Jaceldo-Siegl, K., Sabate, J., & Fraser, G. E. (2013). Nutrient profiles of vegetarian and nonvegetarian dietary patterns. Journal of the Academy of Nutrition and Dietetics, 113(12), 1610-1619.

Rodriguez, F. S., Roehr, S., Pabst, A., Kleineidam, L., Fuchs, A., Wiese, B., ... & Riedel-Heller, S. G. (2021). Effects of APOE e4-allele and mental work demands on cognitive decline in old age: Results from the German Study on Ageing, Cognition, and Dementia in Primary Care Patients (AgeCoDe). International Journal of Geriatric Psychiatry, 36(1), 152-162.

Roe, C. M., Fagan, A. M., Grant, E. A., Hassenstab, J., Moulder, K. L., Dreyfus, D. M., ... & Morris, J. C. (2013). Amyloid imaging and CSF biomarkers in predicting cognitive impairment up to 7.5 years later. Neurology, 80(19), 1784-1791.

Rogers, S. A., Kang, C. H., & Miller, K. J. (2007). Cognitive profiles of aging and aging-related conditions.

Roldán-Tapia, L., García, J., Cánovas, R., & León, I. (2012). Cognitive reserve, age, and their relation to attentional and executive functions. Applied Neuropsychology: Adult, 19(1), 2-8.

Roos, P. A., & Treiman, D. J. (1980). DOT scales for the 1970 Census classification. Work, jobs, and occupations: A critical review of occupational titles, 336-389.

Rosano, C., Brach, J., Studenski, S., Longstreth Jr, W. T., & Newman, A. B. (2007). Gait variability is associated with subclinical brain vascular abnormalities in high-functioning older adults. Neuroepidemiology, 29(3-4), 193-200.

Rosano, C., Studenski, S. A., Aizenstein, H. J., Boudreau, R. M., Longstreth Jr, W. T., & Newman, A. B. (2011). Slower gait, slower information processing and smaller prefrontal area in older adults. Age and ageing, 41(1), 58-64.

Royall, D. R., Palmer, R., Chiodo, L. K., & Polk, M. J. (2005). Normal rates of cognitive change in successful aging: The freedom house study. Journal of the International Neuropsychological Society, 11(7), 899-909.

Rubenstein, L. Z., Schairer, C., Wieland, G. D., & Kane, R. (1984). Systematic biases in functional status assessment of elderly adults: effects of different data sources. Journal of Gerontology, 39(6), 686-691.

Runge, S. K., Small, B. J., McFall, G. P., & Dixon, R. A. (2014). APOE moderates the association between lifestyle activities and cognitive performance: evidence of genetic plasticity in aging. Journal of the International Neuropsychological Society, 20(5), 478-486

Ryan, J. J., Lopez, S. J., & Paolo, A. M. (1996). Digit span performance of persons 75–96 years of age: Base rates and associations with selected demographic variables. Psychological assessment, 8(3), 324.

Sachs-Ericsson, N. J., Sawyer, K. A., Corsentino, E. A., Collins, N. A., & Blazer, D. G. (2010). APOE ϵ 4 allele carriers: Biological, psychological, and social variables associated with cognitive impairment. Aging & mental health, 14(6), 679-691.

Salat, D. H. (2011). The declining infrastructure of the aging brain. Brain connectivity, 1(4), 279-293.

Saling, M. M. (2009). Verbal memory in mesial temporal lobe epilepsy: beyond material specificity. Brain, 132(3), 570-582.

Salmon, D. P., Ferris, S. H., Thomas, R. G., Sano, M., Cummings, J. L., Sperling, R. A., ... & Aisen, P. S. (2013). Age and apolipoprotein E genotype influence rate of cognitive decline in nondemented elderly. Neuropsychology, 27(4), 391.

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. Psychological review, 103(3), 403.

Salthouse, T. A. (2010). Selective review of cognitive aging. Journal of the International neuropsychological Society, 16(05), 754-760.

Salthouse, T. A., & Babcock, R. L. (1991). Decomposing adult age differences in working memory. Developmental psychology, 27(5), 763.

Salthouse, T. A., Berish, D. E., & Siedlecki, K. L. (2004). Construct validity and age sensitivity of prospective memory. Memory & Cognition, 32(7), 1133-1148.

Sattler, C., Erickson, K. I., Toro, P., & Schröder, J. (2011). Physical fitness as a protective factor for cognitive impairment in a prospective population-based study in Germany. Journal of Alzheimer's Disease, 26(4), 709-718.

Saunders, A. M., Strittmatter, W. J., Schmechel, D., George-Hyslop, P. S., Pericak-Vance, M. A., Joo, S. H., ... & Hulette, C. (1993). Association of apolipoprotein E allele ϵ4 with late-onset familial and sporadic Alzheimer's disease. Neurology, 43(8), 1467-1467.

Scarmeas, N., Albert, S. M., Manly, J. J., & Stern, Y. (2006). Education and rates of cognitive decline in incident Alzheimer’s disease. Journal of Neurology, Neurosurgery & Psychiatry, 77(3), 308-316.

Scarmeas, N., & Stern, Y. (2004). Cognitive reserve: Implications for diagnosis and prevention of Alzheimer’s disease. Current neurology and neuroscience reports, 4(5), 374-380.

Schaie, K. W. (1994). The course of adult intellectual development. American psychologist, 49(4), 304.

Schaie, K. W. (2005). Developmental influences on adult intelligence: The Seattle longitudinal study. Oxford University Press.

Scherr, P. A., Albert, M. S., Funkenstein, H. H., Cook, N. R., Hennekens, C. H., Branch, L. G., ... & Evans, D. A. (1988). Correlates of cognitive function in an elderly community population. American Journal of Epidemiology, 128(5), 1084-1101.

Schmand, B., Smit, J. H., Geerlings, M. I., & Lindeboom, J. (1997). The effects of intelligence and education on the development of dementia. A test of the brain reserve hypothesis. Psychological medicine, 27(6), 1337-1344.

Schooler, C., & Mulatu, M. S. (2001). The reciprocal effects of leisure time activities and intellectual functioning in older people: A longitudinal analysis. Psychology and aging, 16(3), 466.

Schooler, C., Mulatu, M. S., & Oates, G. (2004). Occupational self-direction, intellectual functioning, and self-directed orientation in older workers: Findings and implications for individuals and societies. American Journal of Sociology, 110(1), 161-197.

Seeman, T. E., Huang, M. H., Bretsky, P., Crimmins, E., Launer, L., & Guralnik, J. M. (2005). Education and APOE-e4 in longitudinal cognitive decline: MacArthur Studies of Successful Aging. The Journals of Gerontology Series B: Psychological sciences and social sciences, 60(2), P74-P83.

Selkoe, D. J. (2001). Alzheimer's disease: genes, proteins, and therapy. Physiological reviews, 81(2), 741-766.

Sheridan, P. L., & Hausdorff, J. M. (2007). The role of higher-level cognitive function in gait: executive dysfunction contributes to fall risk in Alzheimer’s disease. Dementia and geriatric cognitive disorders, 24(2), 125-137.

Sherman, S. E., & Reuben, D. (1998). Measures of functional status in community-dwelling elders. Journal of general internal medicine, 13(12), 817-823.

Siedlecki, K. L., Stern, Y., Reuben, A., Sacco, R. L., Elkind, M. S., & Wright, C. B. (2009). Construct validity of cognitive reserve in a multiethnic cohort: The Northern Manhattan Study. Journal of the International Neuropsychological Society, 15(4), 558-569.

Singh-Manoux, A., Kivimaki, M., Glymour, M. M., Elbaz, A., Berr, C., Ebmeier, K. P., ... & Dugravot, A. (2012). Timing of onset of cognitive decline: Results from Whitehall II prospective cohort study. Bmj, 344, d7622.

Singh-Manoux, A., Marmot, M. G., Glymour, M., Sabia, S., Kivimäki, M., & Dugravot, A. (2011). Does cognitive reserve shape cognitive decline?. Annals of neurology, 70(2), 296-304.

Singh, P. P., Singh, M., & Mastana, S. S. (2006). APOE distribution in world populations with new data from India and the UK. Annals of human biology, 33(3), 279-308.

Sliwinski, M., & Buschke, H. (1999). Cross-sectional and longitudinal relationships among age, cognition, and processing speed. Psychology and aging, 14(1), 18.

Small, B. J., Basun, H., & Bäckman, L. (1998). Three-year changes in cognitive performance as a function of apolipoprotein E genotype: evidence from very old adults without dementia. Psychology and aging, 13(1), 80.

Small, B. J., Rosnick, C. B., Fratiglioni, L., & Bäckman, L. (2004). Apolipoprotein E and cognitive performance: A meta-analysis. Psychology and aging, 19(4), 592.

Small, S. A., Stern, Y., Tang, M., & Mayeux, R. (1999). Selective decline in memory function among healthy elderly. Neurology, 52(7), 1392-1392.

Smart, E. L., Gow, A. J., & Deary, I. J. (2014). Occupational complexity and lifetime cognitive abilities. Neurology, 83(24), 2285-2291.

Smith, G. E., Bohac, D. L., Waring, S. C., Kokmen, E., Tangalos, E. G., Ivnik, R. J., & Petersen, R. C. (1998). Apolipoprotein E genotype influences cognitive 'phenotype' in patients with Alzheimer's disease but not in healthy control subjects. Neurology, 50(2), 355-362.

Soldan, A., Pettigrew, C., Cai, Q., Wang, J., Wang, M. C., Moghekar, A., ... & BIOCARD Research Team. (2017). Cognitive reserve and long-term change in cognition in aging and preclinical Alzheimer's disease. Neurobiology of aging, 60, 164-172.

Soldan, A., Pettigrew, C., Li, S., Wang, M. C., Moghekar, A., Selnes, O. A., ... & BIOCARD Research Team. (2013). Relationship of cognitive reserve and cerebrospinal fluid biomarkers to the emergence of clinical symptoms in preclinical Alzheimer's disease. Neurobiology of aging, 34(12), 2827-2834.

Sörman, D. E., Hansson, P., Pritschke, I., & Ljungberg, J. K. (2019). Complexity of primary lifetime occupation and cognitive processing. Frontiers in psychology, 10, 1861.

Soubra, R., Chkeir, A., & Novella, J. L. (2019). A Systematic Review of Thirty-One Assessment Tests to Evaluate Mobility in Older Adults. BioMed Research International, 2019.

Spini, D., Bernardi, L., & Oris, M. (2017). Toward a life course framework for studying vulnerability. Research in Human Development, 14(1), 5-25.

Springer, M. V., McIntosh, A. R., Winocur, G., & Grady, C. L. (2005). The relation between brain activity during memory tasks and years of education in young and older adults. Neuropsychology, 19(2), 181.

Starr, J. M., Leaper, S. A., Murray, A. D., Lemmon, H. A., Staff, R. T., Deary, I. J., & Whalley, L. J. (2003). Brain white matter lesions detected by magnetic resosnance imaging are associated with balance and gait speed. Journal of Neurology, Neurosurgery & Psychiatry, 74(1), 94-98.

Starr, J. M., & Lonie, J. (2007). The influence of pre-morbid IQ on Mini-Mental State Examination score at time of dementia presentation. International Journal of Geriatric Psychiatry: A journal of the psychiatry of late life and allied sciences, 22(4), 382-384.

Starr, J. M., & Lonie, J. (2008). Estimated pre-morbid IQ effects on cognitive and functional outcomes in Alzheimer disease: A longitudinal study in a treated cohort. BMC psychiatry, 8(1), 27.

Steffen, T. M., Hacker, T. A., & Mollinger, L. (2002). Age-and gender-related test performance in community-dwelling elderly people: Six-Minute Walk Test, Berg Balance Scale, Timed Up & Go Test, and gait speeds. Physical therapy, 82(2), 128-137.

Steffen, T. M., & Mollinger, L. A. (2005). Age-and gender-related test performance in community-dwelling adults. Journal of Neurologic Physical Therapy, 29(4), 181-188.

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. Journal of the International Neuropsychological Society, 8(3), 448-460.

Stern, Y. (2006). Cognitive reserve and Alzheimer disease. Alzheimer's Disease and Associated Disorders, 20, 112-117.

Stern, Y. (2009). Cognitive reserve. Neuropsychologia, 47(10), 2015-2028.

Stern, Y., Albert, S., Tang, M. X., & Tsai, W. Y. (1999). Rate of memory decline in AD is related to education and occupation: cognitive reserve?. Neurology, 53(9), 1942-1942.

Stern, Y., Gurland, B., Tatemichi, T. K., Tang, M. X., Wilder, D., & Mayeux, R. (1994). Influence of education and occupation on the incidence of Alzheimer's disease. Jama, 271(13), 1004-1010.

Strittmatter, W. J., Saunders, A. M., Schmechel, D., Pericak-Vance, M., Enghild, J., Salvesen, G. S., & Roses, A. D. (1993). Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proceedings of the National Academy of Sciences, 90(5), 1977-1981.

Studenski, S., Perera, S., Patel, K., Rosano, C., Faulkner, K., Inzitari, M., ... & Nevitt, M. (2011). Gait speed and survival in older adults. Jama, 305(1), 50-58.

Sullivan, E. V., & Pfefferbaum, A. (2006). Diffusion tensor imaging and aging. Neuroscience & Biobehavioral Reviews, 30(6), 749-761.

Tabachnick, B. G., & Fidell, L. S. (2013). Using multivariate statistics (6th ed.). Pearson.

Tabbarah, M., Crimmins, E. M., & Seeman, T. E. (2002). The relationship between cognitive and physical performance: MacArthur Studies of Successful Aging. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 57(4), M228-M235.

Tang, E. Y., Harrison, S. L., Errington, L., Gordon, M. F., Visser, P. J., Novak, G., ... & Stephan, B. C. (2015). Current developments in dementia risk prediction modelling: An updated systematic review. PLoS One, 10(9), e0136181.

Taylor, K. I., Salmon, D. P., Rice, V. A., Bondi, M. W., Hill, L. R., Ernesto, C. R., & Butters, N. (1996). Longitudinal examination of American National Adult Reading Test (AMNART) performance in dementia of the Alzheimer type (DAT): Validation and correction based on degree of cognitive decline. Journal of Clinical and Experimental Neuropsychology, 18(6), 883-891.

Telonio, A., Blanchet, S., Maganaris, C. N., Baltzopoulos, V., Villeneuve, S., & McFadyen, B. J. (2014). The division of visual attention affects the transition point from level walking to stair descent in healthy, active older adults. Experimental gerontology, 50, 26-33.

Thomas, K. R., Eppig, J. S., Weigand, A. J., Edmonds, E. C., Wong, C. G., Jak, A. J., ... & Bondi, M. W. (2019). Artificially low mild cognitive impairment to normal reversion rate in the Alzheimer's Disease Neuroimaging Initiative. Alzheimer's & Dementia, 15(4), 561-569.

Thorvaldsson, V., Skoog, I., & Johansson, B. (2017). IQ as moderator of terminal decline in perceptual and motor speed, spatial, and verbal ability: Testing the cognitive reserve hypothesis in a population-based sample followed from age 70 until death. Psychology and aging, 32(2), 148

Tian, Q., An, Y., Resnick, S. M., & Studenski, S. (2016). The relative temporal sequence of decline in mobility and cognition among initially unimpaired older adults:

Results from the Baltimore Longitudinal Study of Aging. Age and ageing, 46(3), 445-451.

Tolea, M. I., Morris, J. C., & Galvin, J. E. (2015). Longitudinal associations between physical and cognitive performance among community-dwelling older adults. PloS one, 10(4), e0122878.

Toots, A., Taylor, M. E., Lord, S. R., & Close, J. C. (2019). Associations between gait speed and cognitive domains in older people with cognitive impairment. Journal of Alzheimer's Disease, 71(s1), S15-S21.

Treitz, F. H., Heyder, K., & Daum, I. (2007). Differential course of executive control changes during normal aging. Aging, Neuropsychology, and Cognition, 14(4), 370-393.

Tsang, P. S. (1998). Age, attention, expertise, and time-sharing performance. Psychology and aging, 13(2), 323.

Tucker-Drob, E. M., Johnson, K. E., & Jones, R. N. (2009). The cognitive reserve hypothesis: A longitudinal examination of age-associated declines in reasoning and processing speed. Developmental psychology, 45(2), 431.

Tucker, A., & Stern, Y. (2011). Cognitive reserve in aging. Current Alzheimer Research, 8(4), 354-360.

Tukey, J. W. (1977). Exploratory data analysis. Reading, MA: Addison-Wesley.Tulving, E. (2002). Episodic memory: From mind to brain. Annual review of psychology, 53(1), 1-25.

Tun, P. A., & Lachman, M. E. (2008). Age differences in reaction time and attention in a national telephone sample of adults: education, sex, and task complexity matter. Developmental psychology, 44(5), 1421.

Tupler, L. A., Krishnan, K. R. R., Greenberg, D. L., Marcovina, S. M., Payne, M. E., MacFall, J. R., ... & Doraiswamy, P. M. (2007). Predicting memory decline in normal elderly: genetics, MRI, and cognitive reserve. Neurobiology of aging, 28(11), 1644-1656.

Turken, U., Whitfield-Gabrieli, S., Bammer, R., Baldo, J. V., Dronkers, N. F., & Gabrieli, J. D. (2008). Cognitive processing speed and the structure of white matter pathways: Convergent evidence from normal variation and lesion studies. Neuroimage, 42(2), 1032-1044. United States. Bureau of the Census. (2010). The Next Four Decades: The Older Population in the United States: 2010 to 2050: Population Estimates and Projections. US Census Bureau.

Vaarst, J., Boyle, E., Vestergaard, S., Hvid, L. G., Strotmeyer, E. S., Glynn, N. W., & Caserotti, P. (2021). Does physical performance and muscle strength predict

future personal and nursing care services in community-dwelling older adults aged 75+?. Scandinavian Journal of Public Health, 1403494820979094.

Vadikolias, K., Tsiakiri-Vatamidis, A., Tripsianis, G., Tsivgoulis, G., Ioannidis, P., Serdari, A., ... & Piperidou, C. (2012). Mild cognitive impairment: effect of education on the verbal and nonverbal tasks performance decline. Brain and behavior, 2(5), 620-627.

Valenzuela, M. J., & Sachdev, P. (2006a). Brain reserve and cognitive decline: A non-parametric systematic review. Psychological medicine, 36(8), 1065-1073.

Valenzuela, M. J., & Sachdev, P. (2006b). Brain reserve and dementia: A systematic review. Psychological medicine, 36(4), 441-454.

Vallet, F., Mella, N., Ihle, A., Beaudoin, M., Fagot, D., Ballhausen, N., ... & Desrichard, O. (2020). Motivation as a mediator of the relation between cognitive reserve and cognitive performance. The Journals of Gerontology: Series B, 75(6), 1199-1205.

Van Dijk, K. R., Van Gerven, P. W., Van Boxtel, M. P., Van der Elst, W., & Jolles, J. (2008). No protective effects of education during normal cognitive aging: results from the 6-year follow-up of the Maastricht Aging Study. Psychology and aging, 23(1), 119.

Van Duijn, C. M., Clayton, D., Chandra, V., Fratiglioni, L., Graves, A. B., Heyman, A., ... & Rocca, W. A. (1991). Familial aggregation of Alzheimer's disease and related disorders: A collaborative re-analysis of case-control studies. International journal of epidemiology, 20(Supplement_2), S13-S20.

Van Exel, E., Gussekloo, J., De Craen, A. J. M., Bootsma-Van Der Wiel, A., Houx, P., Knook, D. L., & Westendorp, R. G. J. (2001). Cognitive function in the oldest old: Women perform better than men. Journal of Neurology, Neurosurgery & Psychiatry, 71(1), 29-32.

Van Gerven, P. W., Van Boxtel, M. P., Ausems, E. E., Bekers, O., & Jolles, J. (2012). Do apolipoprotein E genotype and educational attainment predict the rate of cognitive decline in normal aging? A 12-year follow-up of the Maastricht Aging Study. Neuropsychology, 26(4), 459.

Van Hooren, S. A. H., Valentijn, A. M., Bosma, H., Ponds, R. W. H. M., Van Boxtel, M. P. J., & Jolles, J. (2007). Cognitive functioning in healthy older adults aged 64–81: A cohort study into the effects of age, sex, and education. Aging, Neuropsychology, and Cognition, 14(1), 40-54.

Vellas, B., Carrie, I., Gillette-Guyonnet, S., Touchon, J., Dantoine, T., Dartigues, J. F., ... & Bories, L. (2014). MAPT study: A multidomain approach for preventing Alzheimer’s disease: design and baseline data. The journal of prevention of Alzheimer's disease, 1(1), 13.

Vélez-Coto, M., Andel, R., Pérez-García, M., & Caracuel, A. (2021). Complexity of work with people: Associations with cognitive functioning and change after retirement. Psychology and Aging.

Verghese, J., Lipton, R. B., Hall, C. B., Kuslansky, G., Katz, M. J., & Buschke, H. (2002). Abnormality of gait as a predictor of non-Alzheimer's dementia. New England Journal of Medicine, 347(22), 1761-1768.

Verghese, J., Wang, C., & Holtzer, R. (2011). Relationship of clinic-based gait speed measurement to limitations in community-based activities in older adults. Archives of physical medicine and rehabilitation, 92(5), 844-846.

Verghese, J., Wang, C., Lipton, R. B., & Holtzer, R. (2013). Motoric cognitive risk syndrome and the risk of dementia. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences, 68(4), 412-418

Verhaeghen, P., & Cerella, J. (2002). Aging, executive control, and attention: A review of meta-analyses. Neuroscience & Biobehavioral Reviews, 26(7), 849-857.

Voineskos, A. N., Rajji, T. K., Lobaugh, N. J., Miranda, D., Shenton, M. E., Kennedy, J. L., & Mulsant, B. H. (2012). Age-related decline in white matter tract integrity and cognitive performance: A DTI tractography and structural equation modeling study. Neurobiology of aging, 33(1), 21-34.

Voelcker-Rehage, C., Godde, B., & Staudinger, U. M. (2010). Physical and motor fitness are both related to cognition in old age. European Journal of Neuroscience, 31(1), 167-176.

Waite, L. M., Grayson, D. A., Piguet, O., Creasey, H., Bennett, H. P., & Broe, G. A. (2005). Gait slowing as a predictor of incident dementia: 6-year longitudinal data from the Sydney Older Persons Study. Journal of the neurological sciences, 229, 89-93.

Wang, L., Larson, E. B., Bowen, J. D., & van Belle, G. (2006). Performance-based physical function and future dementia in older people. Archives of internal medicine, 166(10), 1115-1120.

Wechsler, D. (2008). Wechsler adult intelligence scale–Fourth Edition (WAIS–IV). San Antonio, TX: NCS Pearson, 22, 498.

Wecker, N. S., Kramer, J. H., Hallam, B. J., & Delis, D. C. (2005). Mental flexibility: Age effects on switching. Neuropsychology, 19(3), 345.

West, R. L. (1996). An application of prefrontal cortex function theory to cognitive aging. Psychological bulletin, 120(2), 272.

West, R. (2000). In defense of the frontal lobe hypothesis of cognitive aging. Journal of the International Neuropsychological Society, 6(6), 727-729.

West, R., & Bowry, R. (2005). Effects of aging and working memory demands on prospective memory. Psychophysiology, 42(6), 698-712.

West, S. G., Finch, J. F., & Curran, P. J. (1995). Structural equation models with non-normal variables: problems and remedies. In R. J. Hoyle (Ed.), Structural equation modeling: Concepts, issues and applications (pp 56-75). Sage Publications, Inc.

Whitman, G. T., Tang, T., Lin, A., & Baloh, R. W. (2001). A prospective study of cerebral white matter abnormalities in older people with gait dysfunction. Neurology, 57(6), 990-994.

Wight, R. G., Aneshensel, C. S., & Seeman, T. E. (2002). Educational attainment, continued learning experience, and cognitive function among older men. Journal of Aging and Health, 14(2), 211-236.

Wilson, R. (2011). Mental stimulation and brain health: complex, challenging activities can support cognitive health in older adults. Generations, 35(2), 58-62.

Winnock, M., Letenneur, L., Jacqmin-Gadda, H., Dallongeville, J., Amouyel, P., & Dartigues, J. F. (2002). Longitudinal analysis of the effect of apolipoprotein E ε4 and education on cognitive performance in elderly subjects: the PAQUID study. Journal of Neurology, Neurosurgery & Psychiatry, 72(6), 794-797.

Wirth, M., Villeneuve, S., La Joie, R., Marks, S. M., & Jagust, W. J. (2014). Gene–environment interactions: lifetime cognitive activity, APOE genotype, and beta-amyloid burden. Journal of Neuroscience, 34(25), 8612-8617.

Wisdom, N. M., Callahan, J. L., & Hawkins, K. A. (2011). The effects of apolipoprotein E on non-impaired cognitive functioning: A meta-analysis. Neurobiology of aging, 32(1), 63-74.

Wolinsky, F. D., Callahan, C. M., Fitzgerald, J. F., & Johnson, R. J. (1993). Changes in functional status and the risks of subsequent nursing home placement and death. Journal of gerontology, 48(3), S94-101.

Won, H., Singh, D. K. A., Din, N. C., Badrasawi, M., Manaf, Z. A., Tan, S. T., ... & Shahar, S. (2014). Relationship between physical performance and cognitive performance measures among community-dwelling older adults. Clinical epidemiology, 6, 343.

Xu, W., Tan, L., Wang, H. F., Jiang, T., Tan, M. S., Tan, L., ... & Yu, J. T. (2015). Meta-analysis of modifiable risk factors for Alzheimer's disease. J Neurol Neurosurg Psychiatry, 86(12), 1299-1306.

Yaffe, K., Weston, A., Graff-Radford, N. R., Satterfield, S., Simonsick, E. M., Younkin, S. G., ... & Harris, T. B. (2011). Association of plasma β-amyloid level and cognitive reserve with subsequent cognitive decline. Jama, 305(3), 261-266.

Ye, B. S., Seo, S. W., Cho, H., Kim, S. Y., Lee, J. S., Kim, E. J., ... & Park, K. W. (2013). Effects of education on the progression of early-versus late-stage mild cognitive impairment. International psychogeriatrics, 25(4), 597-606.

Ylikoski, R., Ylikoski, A., Keskivaara, P., Tilvis, R., Sulkava, R., & Erkinjuntti, T. (1999). Heterogeneity of congnitive profiles in aging: successful aging, normal aging, and individuals at risks for cognitive decline. European Journal of Neurology, 6(6), 645-652.

Zahodne, L. B., Glymour, M. M., Sparks, C., Bontempo, D., Dixon, R. A., MacDonald, S. W., & Manly, J. J. (2011). Education does not slow cognitive decline with aging: 12-year evidence from the Victoria Longitudinal Study. Journal of the International Neuropsychological Society, 17(6), 1039-1046.

Zahodne, L. B., Manly, J. J., Brickman, A. M., Siedlecki, K. L., DeCarli, C., & Stern, Y. (2013). Quantifying cognitive reserve in older adults by decomposing episodic memory variance: replication and extension. Journal of the International Neuropsychological Society, 19(8), 854-862.

Zec, R. F. (1995). The neuropsychology of aging. Experimental gerontology, 30(3-4), 431-442.

Zelinski, E., Dalton, S., & Hindin, S. (2011). Cognitive changes in healthy older adults. Generations, 35(2), 13-20. Zhang, X., Li, C., & Zhang, M. (1999). Psychosocial risk factors of Alzheimer's disease. Zhonghua yi xue za zhi, 79(5), 335-338.

Zimmermann, T. D., & Meier, B. (2006). The rise and decline of prospective memory performance across the lifespan. Quarterly Journal of Experimental Psychology, 59(12), 2040-2046.

Zimprich, D. (2002). Cross-sectionally and longitudinally balanced effects of processing speed on intellectual abilities. Experimental Aging Research, 28(3), 231-251.