The Influence of Sex Differences on Educational Attainment and Occupational Complexity: Characterizing Cognitive Reserve and Cognitive Decline

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Thesis submitted to the University of Ottawa
in partial fulfillment of the requirements for the
MSc Interdisciplinary Health Sciences

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ABSTRACT

Background: Cognitive reserve (CR) has been associated with better cognitive function and lower risk of dementia in older people, yet it remains unclear whether sex moderates the association between CR and cognition. This study aims to identify whether sex influences both the relationships between brain-cognition and how CR proxies moderate the brain-cognition relationship.

Materials and Methods: Complete data on the measures of CR, education, occupation, and cognition were available for 189 healthy individuals aged 60 to 71 years (105 men and 84 women). Multiple linear regression models were used to investigate the potential effect of sex and CR proxies on the association between the brain and cognition measures.

Results: The results highlighted differences in speed/attention for males compared to females at high education and high occupational complexity. No significant sex differences in brain measures were observed in meanPutamen, meanCaudate, and meanHippocampal volume.

Conclusion/Significance: Traditional reserve contributors are influenced by gender and may be a result of different social determinants among men and women. Both sex-specific risk and protective factors for cognitive decline trajectories are critical for advancing knowledge for individualized interventions.

Keywords: Cognitive Reserve, Brain Reserve, Sex Differences, Gender Differences, Women.

RESUME

Contexte: La réserve cognitive (RC) a été associée à une meilleure fonction cognitive et à un risque plus faible de démence chez les personnes âgées, mais il reste à déterminer si le sexe modère l'association entre la RC et la cognition. Cette étude vise à déterminer si le sexe/genre influence à la fois les relations entre la cognition cérébrale et la manière dont les proxys CR modèrent la relation cerveau-cognition.

Matériels et méthodes: Des données complètes sur les mesures de RC, d'éducation, de profession et de cognition étaient disponibles pour 189 personnes en bonne santé âgées de 60 à 71 ans (105 hommes et 84 femmes). Des modèles de régression linéaire multiple ont été utilisés pour étudier l'effet potentiel des proxys de sexe et de RC sur l'association entre les mesures cognitives.

Résultats: Les résultats ont mis en évidence des différences de vitesse/d'attention pour les hommes par rapport aux femmes à haut niveau d'éducation et à complexité professionnelle élevée. Aucune différence entre les sexes dans les mesures du cerveau n'a été observée dans le volume moyen de Putamen, moyen caudé et moyen de l'hippocampe.

Conclusion/Importance: Les contributeurs traditionnels aux réserves sont influencés par le sexe et peuvent être le résultat de différents déterminants sociaux parmi les hommes et les femmes. Les facteurs de risque et de protection spécifiques au sexe/genre pour les trajectoires de déclin cognitif sont essentiels pour faire progresser les connaissances en vue d'interventions individualisées.

Mots-clés: réserve cognitive, réserve cérébrale, différences de sexe, différences de genre, femmes.

ACKNOWLDGEMENTS

The list of people that I must thank for getting me through my degree is quite long! Firstly, I would like to begin by thanking Allah SWT for the strength, guidance, and patience He has bestowed upon me for completing this project. Without His mercy and guidance, I would not be writing this note. I would also like to thank my mother for being my backbone. She has encouraged me all throughout my life and has been cheering me to continue expanding my knowledge. I am eternally grateful to you. To my sister, Yasmin, thank you for always being by my side through the highs and lows of completing this degree. You have always been my number one supporter and words can't describe my appreciation and love for you. Most importantly, I must say thank you to my husband, Adonis, who has shown me nothing but patience, love, and support through this entire experience. You're truly a blessing and I am forever grateful for your support.

To my supervisor, Dr. Jason Steffener, thank you for introducing me to the world of cognitive reserve and cognitive health research. Your mentorship and support has allowed me to grow personally and professionally throughout this entire experience. I would also like to extend my gratitude to my thesis advisory committee, Dr. Sarah Fraser and Dr. Tracey O'Sullivan, for dedicating their time and providing me the valuable feedback needed for me to confidently complete this project.

A special shoutout to my graduate school colleagues and friends. COVID-19 tried to take our experience away, but you all have made this degree a whole lot more fun and impactful. To our future endeavors and ever-expanding thirst for knowledge.

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LIST OF ABBREVIATIONS

STAC-r	Scaffolding Theory of Aging and Cognition-Revised
BR	Brain Reserve
CR	Cognitive Reserve
AD	Alzheimer's Disease
MT	Menopausal Transition
MRI	Magnetic Resonance Imaging
PD	Parkinson's Disease
IQ	Intelligence Quotient
fMRI	functional Magnetic Resonance Imaging
BM	Brain Maintenance
PET	Positron Emission Tomography
APOE	Apolipoprotein E
Aβ	Amyloid Beta
NART	National Adult Reading Test
WAIS-IV	Weschler Adult Intelligence Scale- IV
O_NET	Occupational Information Network
NP	Negative Priming
SRT	Selective Reminding Task
WAIS-R	Weschler Adult Intelligence Scale-Revised
WCST	Wisconsin Card Sorting Test
WAIS-III	Weschler Adult Intelligence Scale- III
SE-CASL	Spin-echo Continuos ASL
PLD	Post Labeling Delay
ERT	Estrogen Replacement Therapy
STEM	Science, Technology, Engineering, and Mathematics

CHAPTER 1: INTRODUCTION

1.1 Background

Individuals with cognitive impairments are at a higher risk of progressing to any form of dementia (Campbell et al., 2013). Dementia is often characterized by chronic and acquired loss of two or more cognitive abilities caused by brain disease or injury. Dementia is typically diagnosed when acquired cognitive impairment has reached a level of severity that could result in compromised social and/or occupational functioning. Aging is one of the main risk factors for all-cause dementia and the prevalence doubles every five years-of-age after age 65 (Hugo & Ganguli, 2014). In higher income countries, prevalence for dementia is approximately 5–10% in those aged 65+ years – usually higher amongst women than men – largely due to women having a higher life expectancy (Hugo & Ganguli, 2014). Dementia follows a pathway that begins many years before clinical diagnostic (Ávila-Villanueva et al., 2022). This pathway starts in the neocortex and continues through the allocortex, hippocampus, basal ganglia, midbrain, and cerebellum (Ávila-Villanueva et al., 2022). Mild cognitive impairment (MCI) is defined by performance that is categorized as lower than normal on objective neuropsychological testing of cognition, but with maintained daily functions (e.g., maintained abilities to function within society, and maintained activities of daily living such as for personal care) and therefore not consistent with dementia (Arvanitakis et al., 2019). MCI does not always progress to dementia, and a patient's cognitive status may fluctuate between MCI, normal cognition, and dementia (Arvanitakis et al., 2019).

Neural and cognitive decline, and their manifested stages (MCI and Dementia), are often initiated as a result of aging in humans. The prevalence of dementia is projected to almost quadruple in the next 30 years. It is estimated that one in 85 individuals worldwide will be affected by the disease (Brookmeyer et al., 2007). Although efficacious treatment for dementia has not been found, evidence suggests that dementia might be delayed, or even prevented, by certain modifiable risk factors (Li et al., 2021b). Thus, understanding this transitional stage, from normal to declining aging, is essential in identifying the modifiable and non-modifiable risk factors that will aid in the understanding of the progression of mild cognitive impairment to dementia.

Alzheimer's disease (AD) is the most common form of dementia, where the most common clinical presentation of AD is a slow onset and gradually progressive loss of memory. Typically,

it manifests as the inability to learn new information, particularly autobiographical information, such as recent events in ones' life (Hugo & Ganguli, 2014). This is because AD preferentially affects brain networks involved in episodic memory (Hugo & Ganguli, 2014). Clinicopathological studies show a large amount of variability surrounding pathological AD-related impairment, suggesting that the brain has the capacity to buffer the effects of neuropathology (Fratiglioni & Wang, 2007). The Scaffolding theory of aging and cognition-revised model (STAC-r) (Figure 1) is a conceptual model that provides a dynamic guide to both neuropsychological and compensatory neural processes that collaboratively predict cognitive function over time. The STAC-r model suggests the presence of two pathways serving as providing beneficial and protective brain functioning. This model therefore considers inter-individual variability and nonlinearity in individual cognitive trajectories. The first pathway considers the direct enhancement and preservation of brain structures and function through methods of direct neural enhancement by promoting efficient connectivity, increasing cortical thickness, synaptic density, and other indictors of brain health (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014). This is a concept that was later defined as Brain Reserve (BR). The second pathway describes the concept of Cognitive Reserve (CR) which is considered a less direct mechanism, where life course enrichment factors aid in the formation of additional neural protection that allows for the maintenance of cognitive performance despite pathological disease burden by means of increasing the brain's capacity for compensatory means (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014).

An example of life course enrichment is high educational attainment where it leads to enhanced compensatory scaffolding, so despite neural degradation, cognitive function remains intact or is improved (Park & Reuter-Lorenz, 2009) (Reuter-Lorenz & Park, 2014). These aspects in the STAC-r model will be the main focus of this study, encompassing both structural and neural compensation, as they have parallel definitions to the concepts of CR and BR against the effects of cognitive decline. The concept of CR refers to an individual's capacity to maintain normal cognitive function despite the presence of brain pathology (Yaakov Stern, 2010). CR is essentially the difference observed between the degree of age-related neural changes and the manifestation of cognitive symptoms (Yaakov Stern, 2010).

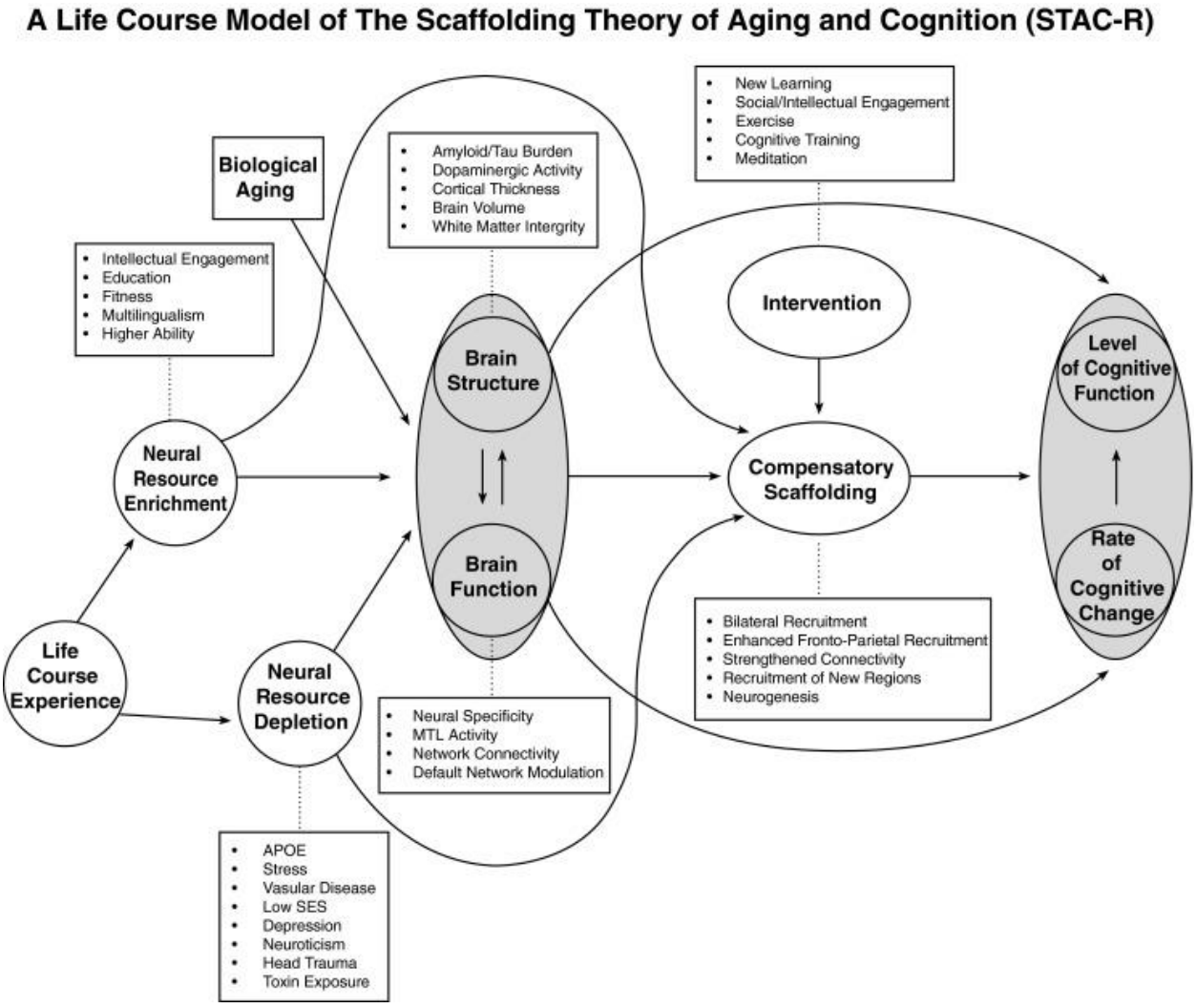

Figure 1: A conceptual model of the scaffolding theory of aging and cognition-revised (STAC-r)

BR refers to the passive model that emphasizes quantitative measures of structural and neural capacity (number of neurons/synapses and overall brain volume) that reflects cognitive performance in efforts of delaying age/disease related neural decline (Yaakov Stern et al., 2019). Life experiences, such as education level and occupational attainment, are related to the prevention or the minimization of the pathology that is associated with cognitive decline through the process of increased cognitive reserve and utilization of additional functional resources (Yaakov Stern,

2010). The clinical implications of cognitive reserve are that individuals with low cognitive reserve have worse clinical manifestation of a neurodegenerative disease, such as AD, when compared to those with higher cognitive reserve. Thus, individuals with an equivalent level of clinical pathology may present different levels of cognitive ability (Yaakov Stern, 2010). Reserve was initially thought to be an indicator of brain change as a result of clinical outcome, but recent studies suggest life experiences may act as moderators in minimizing or damping pathology. CR is a construct that, although cannot be measured directly, can be operationalized by proxy indicators (Yaakov Stern, 2010). Proxy indicators such as education and occupational complexity, or rather the combination of many life factors, can be indexed as measures of CR (Clare et al., 2017). A recurring factor that has an association with cognitive decline is low educational attainment (Fratiglioni & Wang, 2007). Lower occupational complexity is said to also be associated with increased incidence of cognitive impairment and may directly affect cognition through lower CR (Evans et al., 1997; Yaakov Stern et al., 1994).

In the upcoming sections, the complexity of sex and gender differences in health and their influence on CR and BR among men and women will be discussed. In scientific literature, the terms “sex” and “gender” are often used synonymously. However, they have different definitions. The term sex is often used to group people into dichotomous groups: females and males. This variation is on the basis of an individual’s reproductive system. Gender refers to the psychosocial and cultural differences between men and women (eg, access to education and occupation). Since it is not clear whether the brain and behavioral differences discussed in this thesis are sex or gender-based, the term sex/gender is used throughout the text when referencing previous CR research.

Cognitive impairment research has often considered the biological differences when addressing sex/gender differences, but it is important to note that consideration of social determinant differences can aid in understanding the gender-based health differences that extend as a consequence of social disadvantage (e.g.: education and occupation differences) (Okamoto et al., 2021). Sex/gender could prompt differences in the accumulation of reserve resulting in the variations in the manifestation of AD symptomology and prevention measures, which if understood, would allow for sex/gender-specific lifestyle interventions to diminish the burden of AD. Exposure to sex hormones early in development was found to have permanent effects on sex-

related behavior, and reproductive anatomy and function (Berenbaum & Beltz, 2016). Therefore, early development is considered a sensitive period for the role of hormones in organizing the brain (Berenbaum & Beltz, 2016). Sex differences in brain function and structure stem from sex determining genes and fetal hormonal programming, in which these differences have important implications for brain-based disease risk and investigational approaches (Mazure & Swendsen, 2016; Rocca et al., 2014). Neuroimaging studies have shown that cortical atrophy in regions such as medial temporal, posterior cingulate, and the striatum are affected in early stages of AD (Lee et al., 2019). Consideration of these specific regions is important when investigating CR because they demonstrate structural and functional changes that can be used to map out baseline functionality and deviations when studying functional neuroplasticity (Bartsch & Wulff, 2015).

The impact of gender inequity on dementia risk is likely to be the basis behind women having a higher incidence of dementia in comparison to men (Nebel et al., 2018). In the past century, women had fewer opportunities for higher education and complex occupational attainment. This resulted in more women being affected by this risk factor (Nebel et al., 2018). This impact is likely accounted for by the sociocultural shifts that impact both men and women through time. The women who discovered they could carry out "men's work" and get paid a higher wage have led to more women refusing to return to their roles as housewives (Lamb, 2012). This movement led to a change in what is considered the feminine role, so the roles of women were re-defined and professional barriers were broken (Lamb, 2012).

Therefore, future research should be less gender-specific while investigating the topic of reserve to capture the true extent of women's role in resisting AD (Subramaniapillai et al., 2021). When educational attainment improved for women throughout the 20th century, both in form (high school, college, etc.) and number of years, a dramatic shift in female tertiary education graduates and education level in the workplace has increased (Chusseau & Hellier, 2013a).

In terms of genetic predispositions, women have a higher probability of silent cerebral ischemic and white matter changes linked to diseases such as hypertension and diabetes in comparison to men (Rahman et al., 2019). Another sex-dependent biomarker for AD is polymorphism in the apolipoprotein E (APOE) gene, which is one of the main risk factors for developing late onset Alzheimer's disease (Husain et al., 2021). APOE plays a critical role in both the metabolism and transportation of the lipids that play a role in the maintenance of synaptic

plasticity as well as in synaptogenesis (Hsu et al., 2019). APOE-ε4 is associated with accelerated cognitive aging, where the risk factor can result both familial and sporadic forms of AD. The presence of the gene was observed to be associated with greater risk of poorer functional status and lower cognitive function (Hsu et al., 2019). APOE- ε4 can result in the reduction in cerebral metabolic rate of glucose, leading to the unconfined spread and increase in amyloid-beta plaques (Aβ) and neuritic tangles pathology, which consequently accelerates cognitive decline (Mosconi et al., 2008; Sundermann et al., 2020).

Female carriers had an increased risk of developing AD, as well as accelerated progression of the disease, as well as greater severity in associated symptoms have been reported between females and males carrying the *APOE4* allele (Hsu et al., 2019). Interactions between genetic and modifiable factors could play a role in mitigating AD progression (Arenaza-Urquijo et al., 2015). An example of this is the interaction between educational attainment and APOE genotype; educational attainment was found to reduce the effects of *APOE-ε4* on metabolism, independent of Aβ deposition in cognitively normal adults (Arenaza-Urquijo et al., 2015). Thus, education plays a role in mitigating the deterioration of episodic memory as a consequence of AD, even in *APOE-ε4* carriers (Arenaza-Urquijo et al., 2015).

Menopausal Transition (MT) is a female-specific risk factor for AD. The effects of MT can be seen when post-menopausal women exhibit an increased AD burden through means of increased amyloid-beta deposits, reduced glucose metabolism, and grey matter volume loss when compared to pre-menopausal women, and men at the same age (Rahman et al., 2019). Postmenopausal women experience a reduction of estrogen affecting brain metabolism which has been found to contribute to an increased risk of AD progression (Zhao L, Mao Z, 2016). Lack of estrogenic activation triggers not only the signature menopause symptoms, but also causes a shift in compensatory bioenergetic methods of the brain, causing cognitive compromise and increased risk of late-onset AD (Zhao L, Mao Z, 2016). Men do not experience this severe loss of estrogen hormone because testosterone can be metabolized to estrogen, even later in life (Feldman et al., 2002).

In the current study, biological and sociocultural influence in CR proxy variables were explored with sex influencing CR proxies. Data suggests that sex/gender differences are present, both in type of education attained and subsequently in job complexity (van Hek et al.,

2016). This supplemental measure would contribute to the understanding of sociocultural and biological preserves of reserve and its mediation of cognitive trajectories that surround life experiences. This study integrates full brain data into a comprehensive model of Cognitive Reserve and cognitive aging.

1.2 Purpose

The purpose of this study is to investigate how biological and sociocultural preserves of reserve are affected by sex (e.g. education and occupational attainment) and whether these differences translate to sex differences in the relationships between the brain and cognitive measures.

The first aim is to identify whether CR proxies equally predict cognitive measures. **We hypothesize that higher CR proxy values of education and occupational complexity will jointly and independently result in higher cognition scores.**

The second aim is to identify whether sex differences exist in commonly used proxies of reserve. **We hypothesize that sex influences CR by interacting with the CR proxy resulting in differences in cognition. Therefore, values of CR proxies will differ between the sexes.**

The third aim is to identify whether sex-related differences in the proxies of reserve are explained by sex influence on the brain-cognition relationship. **We hypothesize that sex differences in cognitive functioning are a result of sex influence on CR proxies' protective capacity. We hypothesize that women have disadvantaged cognitive outcomes compared to men when considering differences in CR proxies. Therefore, the moderating effects of CR proxies on the relationship between neural and cognitive measures will itself be moderated by sex.**

These objectives will be met by combining brain-based data, acquired with the use of Magnetic Resonance Imaging (MRI) measures, and CR proxies **with an effort to link biological factors as preservers to cognitive reserve** .

1.3 Hypotheses

Cognition: In line with CR studies, we hypothesize that higher CR proxy values of education and occupational complexity will jointly and independently predict higher cognition scores.

1. **Sex:** We hypothesize that sex and CR proxies interact when predicting cognitive function.
2. **Sex and Cognition:** The effect of brain volume on cognitive scores is jointly and independently moderated by CR proxy variables and sex.

CHAPTER 2: LITERATURE REVIEW

2.1 Cognitive Aging and Cognitive Decline

As the developed nations in the world are experiencing exponential increases in the proportion of older adults in their population due to falling birth rates combined with increased longevity, it is projected that by 2050 there will be many more older adults in developed countries (~26%) than children under 15 (Cohen, 2003). This shift presents opportunities to investigate emerging neurodegenerative diseases and possible mitigating measures as they become more prevalent in populations worldwide (Harada et al., 2013). The term cognitive aging describes a pattern of mild age-related decline in cognitive functions (Whalley et al., 2004). In the general population, average levels of cognitive function increase normatively across childhood, peak at some point in adulthood, and decline into old age (Whalley et al., 2004). It is imperative to understand the effects of age on cognition due to the rising number of adults over the age of sixty-five and the increasing prevalence of age-related neurodegenerative (Murman, 2015). In later life, a reduction in in cognitive domains such as fluid reasoning, mental speed, memory are abilities neuroscientist often attribute to age-related decline in healthy adults (Goh & Park, 2009). Consequently, the shift from age-related decline to neurodegenerative cognitive decline is often marked by degenerative memory loss that could be a preclinical marker of AD and other forms of dementia (Resnick et al., 2004).

Despite previous understanding that cognitive decline and chronological age share a linear relationship, it is now understood that a more complex relationship is shared with various life-style factors influencing the relationship. Neurodegenerative disorders like AD and Parkinson's Disease (PD) do not normally manifest as a repercussion of age for all, but they do appear as an age-dependent manner and can also share similar symptomology with normal aging (Dumas, 2015). These similarities make it difficult to completely distinguish between early signs and symptoms of disease and that of normal age-related decline (Dumas, 2015). In recent decades, the availability of magnetic resonance imaging (MRI) has provided an insight on changes in the brain, both anatomically and functionally, that occur due to normal aging as well as during neurological cognitive decline (Cabeza et al., 2018). MRI studies have observed that normal aging often involves grey matter volume loss and functional changes in areas that involve high cognitive functions; those reductions are found in regions such as the prefrontal, medial temporal, and parietal cortices (Cabeza et al., 2018).

2.1.1 Developmental Origins of Health and Disease and Neurodegeneration

The Developmental Origins of Health and Disease hypothesis proposes that factors influencing early life, from preconception to approximately 2 years, play a role in programming the physical and physiological aspects of the fetus/infant. This programming serves a form of risk reduction in the development of disease in later life.

The development of the human brain begins in utero and continues through adolescence and early adulthood (Ernst & Korelitz, 2009). However, neurogenesis is predominantly completed approximately halfway through gestation. Throughout the course of pregnancy, the fetal brain is capable of producing up to 250,000 neurons per minute on average. In this critical developmental phase, pre-and postnatally, the brain is vulnerable to environmental factors such as stress or undernutrition (de Rooij, 2022). The brain utilizes an adaptation process that, from an evolutionary perspective, provides the fetus/infant the capability to adapt itself to expected environmental influences within a single generation. This distinction is different from that of genetic adaptation, which refers to the developmental plasticity that may take several generational cycles to be effective. The brain's ability to cause permanent modifications as a result of extrinsic

environmental challenges may aid and be beneficial to the fetus/infant on a short-term basis, but may have a negative impact in later life resulting in increased risk of disease (de Rooij, 2022).

Previous studies have demonstrated that various socio-environmental factors may influence late-life disease risk. For example, place of birth, which somewhat reflects early life environment, can influence dementia risk. Rural vs urban area, specifically those born in high infant mortality regions, have an increased risk for dementia (Baker et al., 1993; Gilsanz et al., 2017; Glymour et al., 2011; Jean et al., 1996; Scazufca et al., 2008). This extends to early-life poor socio-economic living conditions which has been observed to influence late life cognitive impairments and increase risk for dementia, especially those with family history of dementia or APOE-E4 carriership (Herd et al., 2021; Moceri et al., 2001; Mortimer et al., 1998; Zhang et al., 2008). Another factor that elevates the risk for dementia is the experience of adverse events during early-life and childhood. A study conducted using a large Japanese sample indicated individuals who experiences three or more adverse childhood experiences had almost double the risk of developing dementia in comparison to their counterparts who experienced no adverse events (Tani et al., 2020).

This theory demonstrates that early life factors and experiences are associated with cognitive decline and dementia in later life via reserve capacity. Reserve capacity is established and largely constructed during early-life and socio-environmental exposures that may negatively affect the construction of reserve capacity (de Rooij, 2022).

2.2 Reserve

It has become apparent over the last few decades that individual differences in age-related cognitive decline are influenced by complex interactions involving both genetic and environmental factors. These complex interactions have led to variability in cognitive decline trajectories, leading to variabilities in the clinical manifestation of symptoms and the severity of dementia. Variability in cognitive-decline trajectories is driven and explained by three interacting mechanisms: reserve, maintenance, and compensation (Cabeza et al., 2018). Defining terms such as cognitive reserve (CR), brain reserve (BR), and brain maintenance (BM) are not static, since the conceptual

framework involving defining, measuring, and studying those terms is still evolving (Yaakov Stern et al., 2020). An explanation of all three mechanisms will be addressed in the upcoming sections.

The overarching definition of 'reserve' was initially defined by Dr. Yaakov Stern, as a cumulative increase in neural resources that mitigate the effects of brain decline due to aging or age-related disease. There are debates between authors where some prefer using more specific terms distinguishing between BR and CR, while others believe the distinction between the two are not mutually exclusive and therefore prefer using the overarching term 'reserve' (Harrison et al., 2015). It is important to note when using the general term 'reserve', there are various aspects of reserve including CR and BR which require different methodologies and technologies for their measurements. The understanding of why certain individuals present differences in pathological damage and clinical expression of disease is still unclear, so the 'reserve' hypothesis aims to address this knowledge gap (Harrison et al., 2015).

2.3 Cognitive Reserve Hypothesis

The concept of CR was argued by Dr. Yaakov Stern to be referred as an active model, which refers to the variability in how individuals can manage brain damage. An extension of this definition is CR refers to the efficiency, capacity, and flexibility of cognition that allows for differential susceptibility in cognitive processes as a response to brain aging, pathology, or insult (Harrison et al., 2015). The brain manages to utilize protective measures that has been forming over the life course in efforts of responding or compensating for the neuropathological damage that could be a consequence of disease (Harrison et al., 2015). The CR hypothesis involves two components: neural reserve and neural compensation. Neural reserve refers to the Inter-individual variability in the form of differing efficiency, capacity, or flexibility in the brain networks or cognitive paradigms that underlie task performance in the healthy brain. In essence, an individual whose networks are more efficient, have greater capacity, or are more cognitively flexible might be more capable in coping with the disruption imposed by brain pathology (Yaakov Stern, 2010)(Harrison et al., 2015). On the other hand, neural compensation refers to the brain redirecting neural traffic to areas of the brain not previously used to compensate for any form of damage or

insult (Harrison et al., 2015). These concepts further explain CR and provide a link between the concepts of CR and BR.

Different life-experiences such as higher education, participating in leisure activities, and high occupational complexity supply the expansion of reserve, allowing for risk reduction of dementia in old age (Harrison et al., 2015). CR is typically operationalized using proxies like educational attainment, amongst the other factors, that have been proposed to contribute to CR positively (Hersi et al., 2017; Siedlecki et al., 2009). Evidence shows that greater educational attainment was found to be associated with a reduced risk of developing AD.

Since the CR model is a relatively new concept there is no standard established to defining CR, so the weighted contribution for each proxy indicator is not yet determined (Harrison et al., 2015). Therefore, the lack of consensus for defining CR creates barriers in comparing different studies and contributing to lack of homogeneity across study designs (Harrison et al., 2015). Similarly, another issue that creates difficulty in CR studies is the sparsity of CR indicators across the life course; some indicators are acquired early in life, during childhood and adolescence (ex: levels of education), and as a result contribute to later life indicators and CR build up (ex: occupation/occupational complexity) (Harrison et al., 2015). The inability to define the level of contribution of CR proxies has led to the assumption that some proxies carry a heavier influence on CR due to the static or dynamic nature of the measure. Measures that are considered static refer to a timed contribution to CR, while occupational attainment and years of education are considered examples of static measures. Proxy measures such as literacy, engagement in cognitive activities, intellectual engagement, and social engagement are considered dynamic CR measures since they are constantly changing. The variance between the two measures have solidified the importance of intellectual engagement across a lifespan.

2.4 Cognitive Reserve Measures

The role of composite proxy measures is to provide a proxy of CR, since CR can rarely be assessed directly. CR is commonly represented by proxies that reflect life experience factors known to increase reserve; this allows these factors to act as buffers against brain pathology or damage. As a result, CR is measured in proxies, which often are measures of life experiences such

as educational attainment, occupation type and complexity, and participating in stimulating activities (Grotz et al., 2017). Studies often attempt to characterize and measure functional brain processes through a set of methodology (Yaakov Stern et al., 2020) which are often subcategorized under three major methods: socio-behavioural proxies of CR, residual approaches as a way of quantifying CR, and neural implementation of CR, which will be described in the upcoming sections.

2.4.1 Socio-Behavioral Proxies of CR

Measures under this category can be categorized as 'formative' (Jones et al., 2011; Yaakov Stern et al., 2020), meaning they aim to provide information on experiences having the ability to influence the development of CR. These socio-behavioural proxies include education (years), overall Intelligent Quotient (IQ), occupational complexity, engagement in leisure activity, and engagement in physical activity. A study conducted by Le Carret (2003) reports socio-behavioral proxies protect psychological performance in late life and specifically education and occupational complexity were seen to establish lifelong capabilities in supporting attention and conceptualizing problems (Le Carret et al., 2003).

It is critical to note that due to CR being influenced by various exposures throughout an individual's lifespan, proxies need to be considered in the degree they account for individual differences and not as direct measures of CR. Each component proxy should be analyzed and studied in various ways to account for the effects of each individual factor on CR (Yaakov Stern et al., 2020).

2.4.2 Residual Approaches as a Way of Quantifying CR

The residual approach is another method for quantifying CR. This approach entails the use of demographic and brain predictors of cognition and then corresponds to the variance in cognition specific predictors and outcomes that are being measured in the model. Several limitations could arise with the use of this method: firstly, the introduction of variability across studies due to the use of different sets of predictors and outcomes variables. secondly, the use of brain measure can

only partially capture the underlying brain physiology and pathology, and so essentially memory scores are taken and the effects of brain and demographics are removed and what is left is a proxy of CR (B. R. Reed et al., 2010; Yaakov Stern et al., 2020).

2.4.3 Neural Implementation of CR

The most common method in capturing the neural implementation of CR is the use of functional imaging (Yaakov Stern et al., 2003, 2020). The main use of this approach is to identify the brain networks that reflect CR (Yaakov Stern et al., 2020). Functional Magnetic Resonance Imaging (fMRI) studies try to capture the variability between individual during tasks; this accounts for the CR differences in task performance that is an effect of brain changes on cognition at the level of age or disease related changes (Y. Stern, 2013; Yaakov Stern et al., 2020). Identifying activated networks and their expression during tasks may allow for a direct measure of CR through means of identifying which new subcortical regions were activated during these tasks (Yaakov Stern et al., 2020).

2.5 Brain Reserve Hypothesis

The brain reserve (BR) hypothesis proposes neurobiological standing (i.e., number of neurons, synapses, or even brain density) provide an explanation of the individual variations with brain aging and pathology (Satz, 1993) (Yaakov Stern et al., 2020). The variations implied by BR explain structural characteristics of the brain that can be used an indicator of cognition, and how this allows some people to better cope with cognitive aging and neuropathological aging before any clinical or cognitive impairments manifest (Fratiglioni & Wang, 2007). This protective capacity suggests structural and functional compensations can act as a buffer to mitigate the effects of neuropathology (Fratiglioni & Wang, 2007; Yoon et al., 2021).

Unlike CR, BR was initially considered a fixed and passive construct, referring to the constant neurobiological state at a given time (Yaakov Stern et al., 2020). However, studies have shown BR is actually dynamic, and life experiences can aid to maintain brain integrity (Yoon et al., 2021). A number of studies observed an increase in cognitive activity is associated with preserved whole brain volume as well as hippocampal volume (Yaakov Stern, 2017). These observations show the true dynamic nature of the brain and how BR can aid in reducing the

incidence of dementia (Yoon et al., 2021). Thus, this introduces an important underlying concept named brain maintenance (BM) (Nyberg et al., 2012); this concept will be further explained in section 2.7.

2.6 Brain Reserve Measures

In theory, BR refers to all anatomical or structural components of the brain that can be measured using in vivo or post mortem techniques (Yaakov Stern et al., 2020). In particular, this definition is exclusive of neuropathology related to AD, since BR is hypothesized to be protective in those effected areas (Yaakov Stern et al., 2020).

Various research has incorporated measures that observe grey matter volume, cortical surface areas, cortical thickness, Positron Emission Tomography (PET) measures of synaptic integrity, or white matter properties (Cabeza et al., 2018; Yaakov Stern et al., 2020). Utilizing these techniques to measure BR is challenging, since pathology and BR can be expressed in the same brain areas, making differentiation between the two concepts difficult (Cabeza et al., 2018). In the context of the reserve hypotheses , task-related fMRI can be employed to identify brain networks that link cognitive task responses with CR (Anthony & Lin, 2017). BR and CR are concepts that are cyclic in influence, where an increase in one will influence an increase in the other.

2.7 Brain Maintenance

Brain maintenance (BM) is a concept that is interconnected with other concepts like CR and BR. It describes the individual differences that reflect the various cognitive abilities with cognitive decline trajectories (Nilsson & Lövdén, 2018). BM essentially highlights the recurring notion that the brain is modifiable based on life experiences (Yaakov Stern et al., 2020). That is, the less brain changes with age – whether structurally, chemically, or even functionally – the less its cognitive ability is hindered (Nilsson & Lövdén, 2018). BM is measured using similar techniques as BR (Yaakov Stern et al., 2020). The only important consideration is that BM is best measured longitudinally, to illustrate the brain's ability to preserve against different circumstances

(Yaakov Stern et al., 2020); if measurement longitudinally is not attainable, an alternative measure is to opt for the residual approach, which compares the expected baseline status at a specified age with the individual's current brain status (Yaakov Stern et al., 2020).

2.8 Sex/Gender Differences in the Cognitive Reserve Hypothesis

The impact of sex and gender inequity on dementia risk is one possibility for women being at a greater disadvantage in comparison to men regarding known AD risk factors (Nebel et al., 2018). Of the 5.2 million people currently living with AD in the US, 3.3 million are women. Studies have shown that women, as opposed to men, have a significantly higher incidence of age-related decline and greater cognitive deterioration, and that distinction increases with age. In addition to differences in prevalence of AD, the severity and progression of the disease between both sexes is documented, in which older women show a significantly faster age-related decline and cognitive deterioration; this finding is only significant at ages over 70 years. Sex/gender differences stem from biological factors (e.g., sex hormones), health factors (e.g., cardiovascular risk), and social factors (e.g., education level and occupational complexity) theorized to contribute to the risk of dementia (Levine et al., 2021a).

Sex differences in reserve were previously described in AD patients, where women are more negatively affected by previously known AD risk factors. The Apolipoprotein E (APOE) ε4 allele – a non-causative mutation – is considered the most significant risk factor associated with dementia as well as late onset AD. The presence of this allele in women can not only increase risk of accelerated cognitive decline, but also reduce the protective effects associated with life experiences such as education. Sex differences become more apparent in AD neuropathology subsequent to initial disease processes, such as Amyloid Beta (Aβ) deposition. This distinction becomes more severe in women when neuronal injury and cognitive decline commences (Babapour Mofrad & van der Flier, 2019).

Importantly, sex hormones play an important role in AD protection and progression. The "Estrogen Hypothesis" proposes reproductive hormones influence and contribute to the sex differences in AD, where hormones such as estrogen play a protective role against AD-dementia (Rahman et al., 2019). Lower lifetime exposure to ovarian hormones contribute to the

understanding of why women are more likely to be diagnosed with AD. Estrogen generates and maintains hippocampal function during aging, improves cerebral blood flow, and synapse formation in hippocampal dendritic spine (Murphy & Segal, 1996). These protective properties are compromised during menopause or during estradiol level reduction. Estradiol plays a critical role in Ca^{2+} homeostasis and downstream signaling that promotes neuroprotection through long-term and acute reactions (Babapour Mofrad & van der Flier, 2019). Menopausal transition (MT) is the mechanism through which menopausal decline in estrogen is apparent, where reduction in estrogen could interfere with cognitive functioning and neuroprotection capabilities (Babapour Mofrad & van der Flier, 2019). The effects of MT can be seen in which pre and postmenopausal women exhibit an increased AD burden through means of increased Amyloid-beta deposits, reduced glucose metabolism, and grey matter volume loss when compared to premenopausal women and men at the same age (Rahman et al., 2019). Lack of estrogenic activation triggers not only the signature menopause symptoms, but also causes a shift in compensatory bioenergetic methods of the brain, causing cognitive compromise and increased risk of late-onset AD (Zhao L, Mao Z, 2016). Men do not experience this severe loss of estrogen hormone because testosterone can be metabolized to estrogen, even in later life (Feldman et al., 2002).

2.8.1 Gender Differences in Cognitive Reserve

Sociocultural aspects (i.e., gender differences) have been shown to contribute to variations and altering of CR trajectories. Gender has been strongly linked with the concept of CR, where due to gender norms factors such as education, occupational complexity/type, are principally male causing variability in neural protection against AD- related symptoms and disease (Mielke et al., 2014). The impact of sex and subsequent gender inequity on dementia risk is likely the basis behind women being at a greater disadvantage to men (Nebel et al., 2018).This impact likely accounts for the sociocultural shifts impacting both men and women through time. Sociocultural shifts refer back to the Sociocultural Evolution Theory; this theory discusses the process involved in changing social roles and, in turn, creating new roles by correcting and altering the cultural components that influence them (Klüver et al., 2003).

In the past century, men have had numerous opportunities for higher education and higher occupational attainment than women. For example, during war times, millions of American

women had opted to work, often taking positions in industrial factories to help with the war effort. The women who discovered that they could carry out male gendered roles and get paid a higher wage have led to more women refusing to return to their roles as housewives (Lamb, 2012). This movement led to a change in what is considered the feminine role, and so the roles of women were redefined and professional barriers were broken (Lamb, 2012). As per the 1955 census, women were represented in all the 446 professions listed, but often obtained jobs that were customarily a female gendered occupation, such as secretarial, clerical, teaching, nursing, and sales representatives (Lamb, 2012). Men, on the other hand, typically would have had jobs with what would be considered higher occupational complexity, such as lawyers, engineering, and other Science, Technology, Engineering, and Mathematics (STEM) roles (Subramaniapillai Sivaniya , Almey Anne , Rajah M. Natasha, 2001).

As mentioned, women during the 1950s typically engaged in more stimulating non-professional type work such as being homemakers, a possible hindrance in the ability to build to cognitive reserve when compared to their male counterparts (C. Stern & Munn, 2010). Leisure activities as a form of cognitive and physical activities have been suggested to lower risk of dementia by increasing neuronal reserves (Rocca, 2017; Vemuri et al., 2012). While these stimulating activities do help in protecting and increasing CR, its impact is far less significant in comparison to education/occupation (Vemuri et al., 2012). Many of the existing research on occupational complexity between sexes excludes homemakers, leading to restricted views on the complexity of the role women took during that time period (Marioni et al., 2014). Therefore, in future research, gendered bias while investigating the topic of reserve should consider less gender-specific measures to capture the true extent of women's' role in resisting AD (Subramaniapillai Sivaniya , Almey Anne , Rajah M. Natasha, 2001). The dynamic trends for incidence of dementia could be explained by studying the impact and role of those sociocultural factors amongst different birth cohorts (Rocca, 2017). Moreover, cohort effects in educational and occupational attainment could play an important role in the understanding of different late-life cognitive trajectories and risk of AD (Gerstorf et al., 2011).

3.1 Cohort Differences:

When considering gender differences, it is important to have considerations of cohort differences that may arise where historical processes and contextual factors shape aspects of individual development. Research suggests mean-level differences in cognition and health is often favourable for later-born cohorts, than earlier born cohorts; this is significant when examined at the same age range (Gerstorf et al., 2011). Cohort differences highlight key factors of life span theory regarding the malleability and plasticity of ontogenetic development. This allows for central indicators of life expectancy, education, health, and gender to be solely studied (Gerstorf et al., 2011). Cohort effects at advanced stages of age or in the context of mortality-related processes indicate that sociocultural factors have some effect even among particularly vulnerable individuals of the population (Gerstorf et al., 2011). Implications of prolonging healthy aging and extending the phase of productive aging are a cause of positive cohort differences at the level of cognitive function that occur over a period of time. Longitudinal studies of older adults have focused on cohort differences in cognitive aging trajectories. A study conducted by (Zelinski & Kennison, 2007) applied growth models to data from the Long Beach Longitudinal Study (LBLS) and reported that the rate of cognitive aging from age 55 to age 87 on measures of reasoning, spatial abilities, and vocabulary showed minimal differences between age-matched cohorts born 1893-1923 and those born 1908-1940. Furthermore, a study using data from the national General Social Survey (GSS) conducted by Bowles, Grimm, and McArdle (2005), found cohort differences in the rate and steepness of decline in vocabulary knowledge; this difference was apparent in cohorts born before 1940. However, differences were not significant at overlapping age ranges (Bowles et al., 2005). Older adults from different age groups may have experienced different educational, professional, or cultural factors throughout their lives that have an impact on their CR level. Sociocultural and environmental impact on CR, and its influence on cognitive performance, can be investigated using birth cohorts. The use of birth cohorts allows for grouping of individuals based on commonalities in their life experiences, which could have lasting effects on their cognitive function and subsequent brain development (Turcotte et al., 2022).

Over the past century, especially during the beginning of the 20th century, pivotal historical events, such as World Wars, pandemics, and economic crises, have posed an impact on societies and triggered a shift toward sociocultural changes that impacted individual development on a wider

scale. Societal shift as a result of historical events provoked a rise in extremely unfavourable living conditions, suspension of educational attainment measures, and lack of health and social care early in life (Turcotte et al., 2022). Following this decline, from 1910 to 1940, educational attainment and graduation rates increased in most of the United States, where the median year of education attained for adults (25 years and older) increased from 8.1 to 8.6, and later exponentially increasing to 12.3 years during the 1940s and 1950s (Turcotte et al., 2022). This rise in educational attainment may have facilitated higher levels of complexity in occupational attainment and promoted higher intellectual capacities. These secular trends are observed where proxies of CR improved across birth cohorts, with more individuals having higher educational attainment, higher occupational complexity, and higher verbal IQ at older ages, and thus higher CR, compared to their earlier-born counterparts (Turcotte et al., 2022). This shift can be also seen in favour of women, where findings show that the Flynn effect (i.e., the observed rise over time in standardized intelligence test scores) is greater for women than for men, suggesting that women benefit more than men from improved living conditions and societal changes (Turcotte et al., 2022).

Cohort intergenerational effects in cognitive abilities are evident where a great shift is observed between the younger and older birth cohorts; that shift was more evident for women than men. When educational attainment, both in type and number of years, increased in favor of women in the early seventies, a dramatic shift in number of tertiary education graduates and the education level in the workplace has increased (Chusseau & Hellier, 2013b). This highlights the pivotal gender-specific sociocultural changes that occurred over time (C. Stern & Munn, 2010). Therefore, over time, altered epidemiological patterns for AD and dementia can be observed as a result of the changing trends of intellectual lifestyle and occupational opportunities amongst men and women.

This study was conducted to assess the sex differences in later-life trajectories that are a result of both biological and sociocultural preservers of CR between men and women. A secondary aim of the study was to evaluate whether sex moderates the role of CR. Women are hypothesized to accumulate less CR across the lifespan as a result of inequitable access to education and subsequently occupational complexity.

CHAPTER 3: METHODS

3.1 Study Participants

The current study used a subset of the participants from a previous study (Yaakov Stern et al., 1994). Demographic features, age, education (years) means , National American Reading Test (NART) scores, and high vs low occupational and educational level proportions by sex are summarized in Table 1. One hundred and eighty-nine healthy participants aged 60 to 70 years of age (N= 189) (105 men and 84 women; mean (± s.d.) age = 65.0 ± 3.0; years of education = 16.2 ± 2.3 (all right-handed)) were recruited through random market-mailing within 10 miles of the Columbia University Medical Center (Yaakov Stern et al., 1994). This recruitment approach intends to obviate cohort effects that might be present by using convenience. This study was approved by the Internal Review Board of the College of Physicians and Surgeons of Columbia University, and written informed consent was obtained from all participants before study participation; the nature and risks of the study were explained afterward. Participants were compensated for their participation in the study (Yaakov Stern et al., 1994). All subjects were required to be native English speakers, strongly right-handed, and have at least a fourth-grade reading level. Subjects were screened for MRI contraindications and hearing or visual impairment that would impede testing. Subjects were free of medical or psychiatric conditions that could affect cognition (Yaakov Stern et al., 1994).

Table 1: Summary of demographic features in the whole cohort and comparison between males and females

Variable	*Male*	*Female*
No. subjects	105	84
Age y, mean ± SE	65 ± 0.298	65 ± 0.315
NARTIQ , mean ± SE	118 ± 0.791	119 ± 1.04
Education y, mean ± SE	16.1 ± 0.226	16.3 ± 0.260
Education , low/high	64/41	51/33
Occupation, high/low	0.108 ± 0.131	-0.113 ± 0.103

[a] *Higher scores correspond to higher occupational complexity*

3.2 Measure of Reserve

Education is the strongest marker for innate intelligence, which could be due to a combination of genetics and/or life exposure (Scarmeas & Stern, 2003). Typically, CR is operationalized and measured using two methods. Firstly, an MRI approach, which tries to identify brain region volume differences (BR) as a result of variations in CR proxies. Another common approach to measure CR is indirectly with sociobehavioral proxy indicators. This study utilized the indirect approach of sociobehavioral proxy indicators. Education and occupational complexity were considered the main proxies for CR. The study also utilized MRI data as a supplementary measure of brain volume differences associated with sociobehavioral proxies.

3.3 Variables of Interest

Variables such as sex (male/female), age (60- $\geq$ 71), education level (years), job complexity, and the mean of 3 brain regions (Putamen, Caudate, and Hippocampus) were deemed the main variables of interest of this study. The mean of these subcortical regions just refers to the average of the two-hemisphere volumes. These variables were chosen due to their known

contribution to CR. Participants were asked to provide the occupation of the longest duration in their lifetime (Habeck et al., 2019b). Job complexity was studied using occupational attainment as quantified by the detailed characterization in the Occupational Information Network (O_NET[1]), which is an online resource regulated by the US Department of Labor. Nine variables depicting different occupations with their different attributes were quantified (Habeck et al., 2019b). To generate 9 principal components which provided descriptions for complexity, motor, social, physical, creativity, managing, business, attention, and engineering, principal component analyses were conducted from the initial job criteria (Habeck et al., 2019b). The mean of these regions was calculated as the averaged volume between the two hemispheres. For the purpose of this study education and occupational complexity are the main proxy variables for CR. In terms of multitude of attributions or the multidimensionality of CR with its relation to variables such as brain health, education, sex, IQ, and age, the main focus will be sex differences in CR.

Education was self-reported based on years engaged in formal education. Educational data is based on (Steffener, 2021), whereby data was collected in the United States, and twelve years is considered the completion of a high school diploma, fourteen is an associate's degree, sixteen is a bachelor's degree, eighteen is a master's degree, and twenty is a PhD. The distribution of years of education in this sample is included in Figure 2. The figure details a histogram describing educational attainment in years stratified by sex, where education level peaks at bachelor's degree for men, while for women, the histogram has two peaks: bachelor's and master's degree (Steffener, 2021).

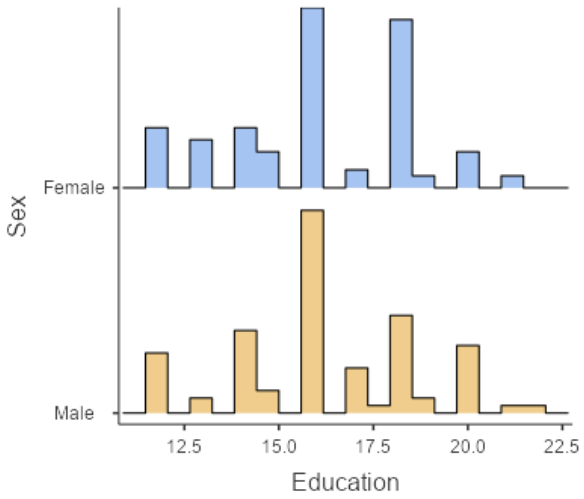

Figure 2: Histogram of years of education for participants split by sex

3.4 Cognitive Measures

Three cognitive composite scores were created for Memory, Speed/Attention, and Fluid ability (Reasoning) as derived from Z- normed average of scores on three different tests.

i. Memory

Memory was assessed using latent construct score of three sub-scores of the selective reminding task (SRT—total, delayed recall, and delayed recognition (Buschke & Fuld, 1974)).

In selective reminding, the participant is selectively reminded only of those items they fail to recall on the immediately preceding trial, prior to another attempt taken to recall all items in the list. This method of selective reminding is continued throughout learning of the words and it allows the patient to show that they have learned some of the items just recalled, by spontaneously retrieving them again without presentation in the next trial (Buschke & Fuld, 1974).

In the context of this study, participants were read a list of 12 words and were asked to recall the words following each of six trials. After each recall attempt is made, participants were then reminded of the words they failed to recall. SRT-total is the total number of recalled words

for all trials and has a maximum score of 72. SRT-delayed recall refers to the number of correctly recalled words after a 15-min delay. SRT-delayed recognition refers to the number of correctly recognized words when each of the 12 words is presented with three distracters (Steffener et al., 2013).

ii. Speed/Attention

Speed/attention was defined as a construct of the Wechsler adult intelligence scale-revised (WAIS-R; (Wechsler, 1981)) digit symbol subtest and the trail making test (J. C. Reed & Reed, 1997). The digit symbol test involves writing the symbol corresponding to each single-digit in a list of numbers using a key at the top of the test form as quickly as possible. The time to complete the Trails A section (numbers only) from the trail making test was used.

iii. Fluid Ability (Reasoning)

Fluid cognitive ability, which was measured using three different tests: Wisconsin Card Sorting Test (WCST), the Wechsler Adult Intelligence Scale- III (WAIS- III), and Selective Reminding Test (SRT), reflects an individual's capacity to process information, activities, and the ability to solve novel problems (Stawski et al., 2010). Fluid ability is related to general intelligence. Thus, fluid cognitive ability plays a key role in how individuals live their daily lives and how they experience daily stressors (Stawski et al., 2010). Fluid ability was found to have strong relationships to the WCST (Salthouse, 2005). Fluid ability or reasoning was defined as a construct comprising the WAIS- III (Wechsler, 1997) letter number sequencing subtest. The test involves participants repeating verbally presented lists of intermixed letters and numbers in alphabetical and numerical order (Wechsler, 1997).

3.5 MRI Data Acquisition

Magnetic Resonance Imaging (MRI) images were acquired in a 3.0T Philips Achieva Magnet using a standard quadrature head coil. A T1-weighted scout image was acquired to determine the subject position. One hundred and sixty-five contiguous 1 mm coronal T1-weighted images of the whole brain were acquired for each subject with an MPRAGE sequence using the following parameters: TR 6.5 ms, TE 3 ms; flip angle 8°, acquisition matrix 256 x 256 and 240 mm field of view. A neuroradiologist reviewed anatomical scans and any with potentially clinically significant findings, such as abnormal neural structure, were removed from the sample prior to the current analysis (Steffener, 2021). Each participant's structural T1 scans were analyzed using FreeSurfer v5.1 (Fischl, 2012)(http://surfer.nmr.mgh.harvard.edu/). The accuracy of FreeSurfer's subcortical segmentation and cortical parcellation (Fischl et al., 2002, 2004) has been reported to be comparable with manual labeling. Each participant's white and gray matter boundaries as well as gray matter and cerebrospinal fluid boundaries were visually inspected slice by slice by an experienced user; manual control points were added in the case of any visible discrepancy, and reconstruction was repeated until we reached satisfactory results within every participant (Eich et al., 2017) The subcortical structure borders were plotted by FreeView visualization tools and compared against the actual brain regions. In case of discrepancy, they were corrected manually. The regions of interest used in this analysis are Putamen, Caudate, and Hippocampus. The pathologic features of the selected subcortical structures have been related to cognitive and affective dysfunctions. However, men and women may have differential age trajectories regarding changes in these subcortical structures (Wang et al., 2019). Thus, investigation of these subcortical regions will aid in understanding the relationship between sociocultural and biological factors as preserves of CR and variations in brain volume .

3.6 Statistical Analysis

Jamovi (version 1.6) was used to conduct statistical analysis of the data. Comparisons were conducted for both sexes in the sample to assess differences in CR proxies, using independent sample t-tests.

Cognitive composite scores were assessed using a step-wise multiple linear regression model to test the influence of CR proxies and sex as moderators of the relationship between brain

volume and cognition. The first hypothesis was tested with CR proxy values of education and occupational complexity jointly and independently to predict cognitive measures. The second hypothesis was tested with an independent and interaction relationship between sex and CR proxies to predict cognitive measures.

The final model addresses the third hypothesis, which was tested using three different linear regressions for the different cognitive predictor variables (Memory, Speed/Attention, and Reasoning) against three brain regions (meanPutamen, meanHippocampus, and meanCaudate). All 9 linear regressions aided to identify how sex moderates the effect of CR proxies on neural measures. Differences in each of the different domains of cognition (Attention, Memory, and Reasoning) could be predictors of objective cognitive performance in both sexes.

A Pearson correlation was also utilized to examine the relationship between CR proxies with age, sex, and brain regions.

CHAPTER 4: RESULTS

Subject demographics, NART IQ, education, and job complexity age-scaled scores are summarized in Table 1. This cohort is well educated, where participants had an average of 16 years education (*SD*= 2.34), with a minimum of 12 years and a maximum of 16 years. In the overall sample, women were the same age as men, slightly more educated, and less likely to have occupations categorized as complex ($p < 0.05$). Pearson correlation analyses (Table 2) were run to investigate bivariate relationships between key variables. On the whole sample, there was a **positive** correlation between Education and Reasoning, r(**168**) = **.313**, *p*= **<0.001**. Education was highly correlated with the other cognition variables, **positive** correlation between Education and Speed/Attention, r(**168**) = **.247**, *p*= **<0.001,** and Memory r(**168**) = **.197**, *p*= **<0.05.** There was a **positive** correlation between Reasoning and meanPutamen r(**168**) = **.277**, *p*= **<0.05.** Volumes of the hippocampus and putamen, averaged across hemispheres, were **positively** correlated with Age r(**168**) = **.206** *p*= **<0.05 and r(168)= .286** *p*= **<0.001** respectively. Occupational complexity was found not to be significantly correlated with cognition variables, Education and Age.

Table 2: Whole Sample Two-tailed Pearson Correlations Between Criterion and Predictor Variables

Correlation Matrix

		Age - Remove mean	Education - Remove mean	occupational complexity - Remove mean	NPReasoning - Remove mean	NPMemory - Remove mean	NPSpeed_attention - Remove mean	meanCaudate-remove mean	meanHippocampus-remove mean	meanPutamen - Remove mean
Age - Remove mean	Pearson's r	—								
	p-value	—								
	N	—								
Education - Remove mean	Pearson's r	0.044	—							
	p-value	0.548	—							
	N	189	—							
occupational complexity - Remove mean	Pearson's r	-0.157	0.150	—						
	p-value	0.082	0.099	—						
	N	123	123	—						
NPReasoning - Remove mean	Pearson's r	-0.149 *	0.313 ***	0.108	—					
	p-value	0.042	< .001	0.236	—					
	N	186	186	121	—					
NPMemory - Remove mean	Pearson's r	-0.105	0.197 **	-0.025	0.290 ***	—				
	p-value	0.158	0.007	0.789	< .001	—				
	N	184	184	120	184	—				
NPSpeed_attention - Remove mean	Pearson's r	-0.188 *	0.247 ***	0.135	0.441 ***	0.273 ***	—			
	p-value	0.010	< .001	0.140	< .001	< .001	—			
	N	185	185	120	185	183	—			
meanCaudate-remove mean	Pearson's r	-0.052	0.089	-0.076	0.117	-0.014	0.072	—		
	p-value	0.503	0.250	0.433	0.132	0.861	0.354	—		
	N	168	168	110	167	165	166	—		
meanHippocampus-remove mean	Pearson's r	-0.206 **	0.157 *	0.065	0.176 *	-0.029	0.081	0.367 ***	—	
	p-value	0.007	0.043	0.497	0.023	0.708	0.298	< .001	—	
	N	168	168	110	167	165	166	168	—	
meanPutamen - Remove mean	Pearson's r	-0.286 ***	0.147	0.004	0.227 **	0.049	0.112	0.630 ***	0.426 ***	—
	p-value	< .001	0.057	0.968	0.003	0.535	0.151	< .001	< .001	—
	N	168	168	110	167	165	166	168	168	—

Note. * p < .05, ** p < .01, *** p < .001

Hypothesis 1

The first hypothesis, which analyzes the association of CR proxies independently and jointly on cognition measures, was tested with a regression equation using CR proxies (education and occupational complexity with their interaction) to predict cognition. The summary results of the regressions are found in Table 3, 4, and 5.

Table 3: Multiple Regression Model for Age, Education, and Occupational complexity, as Predictors of Speed/Attention cognition Scores for the Whole Sample

Model Fit Measures

			Overall Model Test			
Model	R	R^2	F	df1	df2	p
1	0.308	0.0947	3.01	4	115	0.021

Model Coefficients - NPSpeed_attention - Remove mean

Predictor	Estimate	SE	t	p
Intercept [a]	−0.0577	0.0629	−0.917	0.361
Age - Remove mean	−0.0364	0.0218	−1.670	0.098
Education - Remove mean	0.0535	0.0262	2.045	0.043
occupational complexity - Remove mean	0.0256	0.0702	0.364	0.716
Education - Remove mean ✻ occupational complexity - Remove mean	−0.0536	0.0284	−1.885	0.062

[a] Represents reference level

i. Speed/Attention

A multiple linear regression model (Table 3) was calculated to predict speed/attention based on age, education, occupation complexity, and the interaction between education and occupational complexity. A significant regression was found ($F(4,115) = 3.01$, $p = 0.021$ with an R^2 of 0.0947 and $R^2_{adjusted}$ of 0.0632).

Education main effects are significant, Education (B =0.0535, $t(115) = 2.045$, $p = 0.043$). The interactions between occupation complexity and education (B = -0.0536, $t(115) = -1.885$, $p = 0.062$) was not significant. No other main effects were significant, occupational complexity (B =0.0256, $t(115) = 0.364$, $p = 0.716$), age (B =-0.0364, $t(115) = -1.670$, $p = 0.098$).

ii. Reasoning

A multiple linear regression model (Table 4) was calculated to predict reasoning based on Age, education, occupation complexity, and the interaction between education, and occupational complexity. A significant regression was found ($F(4,116) = 6.32$, $p = <0.001$ with an R^2 of 0.179 and $R^2_{adjusted}$ of 0.151).

The interactions between occupation complexity and education ($B = -0.05793$, $t(116) = -2.0.28$, $p = 0.045$) was significant. Education main effects was significant, education ($B = 0.11552$, $t(116) = 4.448$, $p = <0.001$). No other main effects were significant, age ($B = -0.02146$, $t(116) = -0.985$, $p = 0.327$), occupational complexity ($B = -0.00994$, $t(116) = -0.141$, $p = 0.888$).

The significant interaction between occupational complexity and education (Figure 3) was driven by high reasoning marginal mean scores at high levels of education with high occupational complexity.

Table 4: Multiple Regression Model for Age, Education, and Occupational complexity, as Predictors of Reasoning cognition Scores for the Whole Sample

Model Fit Measures

				Overall Model Test			
Model	R	R^2	Adjusted R^2	F	df1	df2	p
1	0.423	0.179	0.151	6.32	4	116	< .001

Model Coefficients - NPReasoning - Remove mean

Predictor	Estimate	SE	t	p
Intercept	0.06440	0.0629	1.024	0.308
Age - Remove mean	−0.02146	0.0218	−0.985	0.327
Education - Remove mean	0.11552	0.0260	4.448	< .001
occupational complexity - Remove mean	−0.00994	0.0704	−0.141	0.888
occupational complexity - Remove mean ✻ Education - Remove mean	−0.05793	0.0286	−2.028	0.045

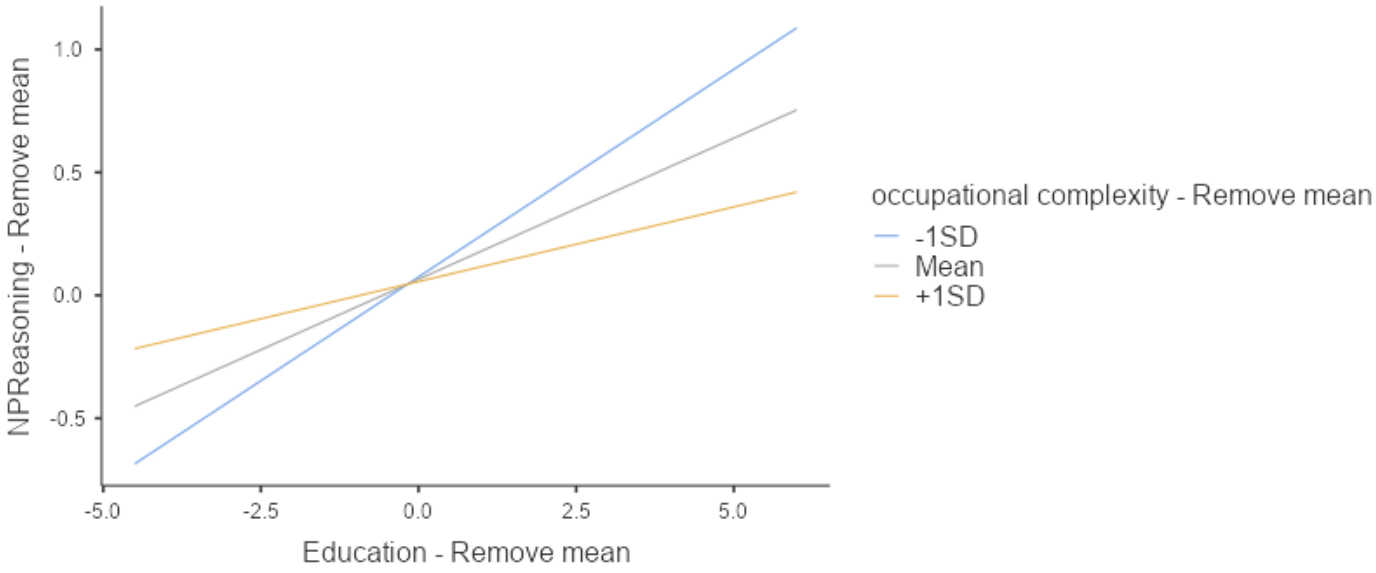

Figure 3: Interaction between education and occupational complexity predicting reasoning

iii. ***Memory***:

A multiple linear regression model (Table 5) was calculated to predict memory based on age, education, occupation complexity, and the interaction between education, and occupational complexity. A significant regression was found ($F(4,115) = 3.69$, $p = 0.007$ with an R^2 of 0.114 and $R^2_{adjusted}$ of 0.114).

Education and age main effects were significant, education (B =0.09497, $t(115) = 2.7884$, $p = 0.006$), age (B =-0.07664, $t(115) = -2.6836$, $p = 0.008$). There was no significant interaction between occupation complexity and education (B = -0.04703, $t(115) = -1.2579$, $p = 0.211$). No other main effects were significant, occupational complexity (B =-0.04703, $t(115) = -1.2579$, $p = 0.211$).

Table 5: Multiple Regression Model for Age, Education, and Occupational complexity, as Predictors of Memory cognition Scores for the Whole Sample

Model Fit Measures

			Overall Model Test			
Model	R	R^2	F	df1	df2	p
1	0.337	0.114	3.69	4	115	0.007

Model Coefficients - NPMemory - Remove mean

Predictor	Estimate	SE	t	p
Intercept	0.00715	0.0815	0.0877	0.930
Age - Remove mean	−0.07664	0.0286	−2.6836	0.008
Education - Remove mean	0.09497	0.0341	2.7884	0.006
occupational complexity - Remove mean	−0.12634	0.0912	−1.3861	0.168
Education - Remove mean ✻ occupational complexity - Remove mean	−0.04703	0.0374	−1.2579	0.211

Hypothesis 2

To ascertain whether the influence of sex was moderating CR proxy variables and influencing cognition, linear regression analysis was built from Hypothesis (1). Hypothesis (2) introduces the moderating effects of sex into the regression. Hypothesis (2) considers cognition as the dependent variable and sex, years of education, and occupational complexity as independent covariates.

i. Speed/Attention

A multiple linear regression model (Table 6) was calculated to predict speed/attention based on age, education, occupation complexity, sex, education, and the interactions between sex, education, and occupational complexity. A significant regression was found ($F(8,111) = 2.285$, $p = 0.0265$ with an R^2 of 0.141 and $R^2_{adjusted}$ of 0.0795).

The interactions between sex, occupation complexity, and education ($B = 0.1244$, $t(111) = 1.993$, $p = 0.0487$), as well as education and occupational complexity ($B = -0.0948$, $t(111) = -2.606$, $p = 0.0104$) were both significant. No other interaction effects were significant: sex and occupational complexity ($B = -0.0313$, $t(111) = -0.210$, $p = 0.834$), sex and education ($B = -0.0127$,

t(111) = -0.241, p = 0.810). No main effects were significant, Age (B =-0.0351, t(111) = -1.619, p = 0.108), Education (B =-0.0351, t(111) = 1.456, p = 0.148), occupational complexity (B =0.0135, t(111) = 0.146, p = 0.884), and sex (B =0.1002, t(111) = 0.771, p = 0.443).

The significant interaction between sex, occupational complexity, and education (Figure 4) was driven by higher speed/attention marginal mean scores for males than females at high levels of education with high occupational complexity, no difference between sexes at low education and occupational complexity levels.

Table 6: Multiple Regression Model for Age, Education, Occupational complexity, and Sex as Predictors of Speed/Attention cognition Scores for the Whole Sample

Model Fit Measures

			Overall Model Test			
Model	R	R^2	F	df1	df2	p
1	0.376	0.141	2.28	8	111	0.027

Model Coefficients - NPSpeed_attention - Remove mean

Predictor	Estimate	SE	t	p
Intercept [a]	−0.1287	0.0895	−1.438	0.153
Age - Remove mean	−0.0351	0.0217	−1.619	0.108
Education - Remove mean	0.0540	0.0371	1.456	0.148
occupational complexity - Remove mean	0.0135	0.0924	0.146	0.884
Sex:				
Male – Female	0.1002	0.1300	0.771	0.443
Education - Remove mean ✻ occupational complexity - Remove mean	−0.0948	0.0364	−2.606	0.010
Education - Remove mean ✻ Sex:				
Education - Remove mean ✻ (Male – Female)	−0.0127	0.0527	−0.241	0.810
occupational complexity - Remove mean ✻ Sex:				
occupational complexity - Remove mean ✻ (Male – Female)	−0.0313	0.1485	−0.210	0.834
Education - Remove mean ✻ occupational complexity - Remove mean ✻ Sex:				
Education - Remove mean ✻ occupational complexity - Remove mean ✻ (Male – Female)	0.1244	0.0624	1.993	0.049

[a] Represents reference level

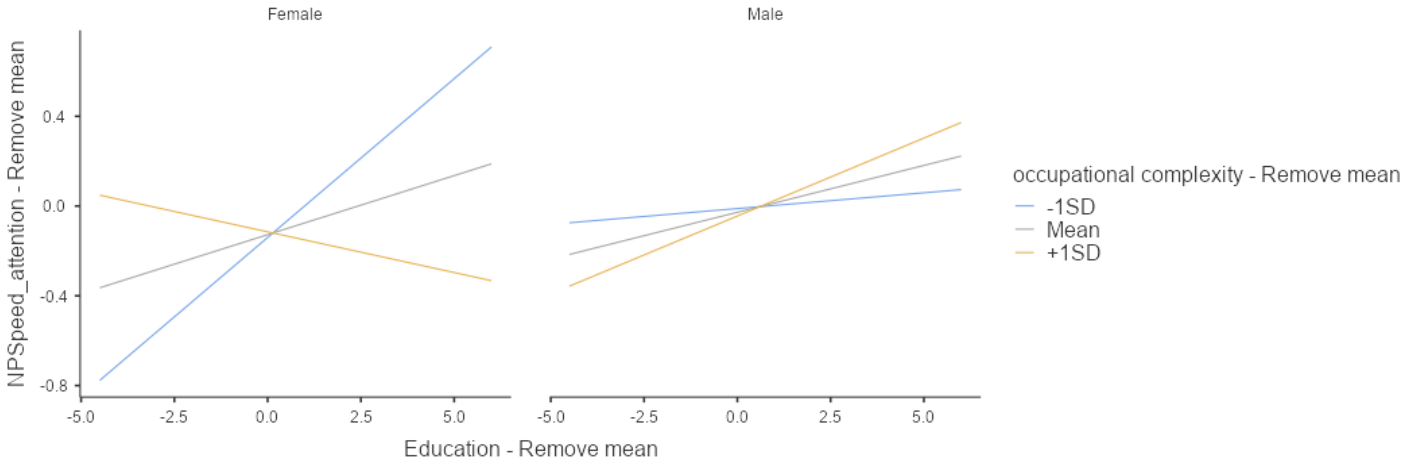

Figure 4: The interaction between education and occupational complexity predicting speed/attention split by sex

ii. Reasoning

A multiple linear regression model (Table 7) was calculated to predict reasoning based on age, education, occupation complexity, sex, education, and the interactions between sex, education, and occupational complexity. A significant regression was found ($F(8,112) = 3.73$, $p = <0.001$ with an R^2 of 0.210 and $R^2_{adjusted}$ of 0.154)

Education ($B = 0.0990$, $t(112) = 2.7155$, $p = 0.008$), sex ($B = 0.26243$, $t(112) = 2.0107$, $p = 0.047$) were found significant. No interaction effects were significant. The interactions between occupation complexity, and education ($B = -0.06715$, $t(112) =$, $p = 0.071$) were not significant. Sex, education, and occupational complexity ($B = 0.00543$, $t(112) = 0.0860$, $p = 0.932$), sex and occupational complexity ($B = 0.03949$, $t(112) = 0.2627$, $p = 0.793$), sex and education ($B = 0.01530$, $t(112) = 0.2904$, $p = 0.722$). No main effects were significant, age ($B = -0.01913$, $t(112) = -0.8775$, $p = 0.382$), occupational complexity ($B = -0.00925$, $t(112) = -0.0994$, $p = 0.921$).

Table 7: Multiple Regression Model for Age, Education, Occupational complexity, and sex as Predictors of Reasoning cognition Scores for the Whole Sample

Model Fit Measures

			Overall Model Test			
Model	R	R^2	F	df1	df2	p
1	0.458	0.210	4.29	7	113	< .001

Model Coefficients - NPReasoning - Remove mean

Predictor	Estimate	SE	t	p
Intercept [a]	−0.06583	0.0882	−0.7467	0.457
Age - Remove mean	−0.01938	0.0217	−0.8935	0.373
Education - Remove mean	0.09865	0.0363	2.7189	0.008
Sex:				
Male – Female	0.26092	0.1299	2.0093	0.047
occupational complexity - Remove mean	0.00560	0.0736	0.0761	0.939
Education - Remove mean ✻ Sex:				
Education - Remove mean ✻ (Male – Female)	0.01815	0.0513	0.3535	0.724
occupational complexity - Remove mean ✻ Education - Remove mean	−0.06462	0.0354	−1.8276	0.070
Sex ✻ occupational complexity - Remove mean ✻ Education - Remove mean:				
(Male – Female) ✻ occupational complexity - Remove mean ✻ Education - Remove mean	0.00459	0.0628	0.0730	0.942

[a] Represents reference level

iii. Memory

A multiple linear regression model (Table 8) was calculated to predict memory based on age, education, occupation complexity, sex, education, and the interactions between sex, education, and occupational complexity. A significant regression was found ($F(8,111) = 2.63$, $p = 0.01$ with an R^2 of 0.159 and $R^2_{adjusted}$ of 0.098.

There are no interaction effects significant in the model. Main effects from Age (B =-0.0794, t(111) = -2.798, p = 0.006) were significant. No other interaction effects were significant: sex, education, and occupational complexity (B = 0.00910, t(111) = -0.107, p = 0.915), sex and occupational complexity (B =0.207, t(111) = 1.066, p = 0.289), sex and education (B=0.077, t(111) = 1.134, p = 0.259), and education and occupational complexity (B = -0.0593, t(111) = -1.253, p = 0.213). No main effects were significant, education (B =-0.06348, t(111) = 1.354, p = 0.179), sex (B =-0.26189, t(111) = -1.560, p = 0.122), and occupational complexity (B =-0.234, t(111) = -1.958, p = 0.053).

Table 8: Multiple Regression Model for Age, Education, Occupational complexity, and sex as Predictors of Memory cognition Scores for the Whole Sample

Model Fit Measures

			Overall Model Test			
Model	R	R^2	F	df1	df2	p
1	0.399	0.159	2.63	8	111	0.011

Model Coefficients - NPMemory - Remove mean

Predictor	Estimate	SE	t	p
Intercept [a]	0.13940	0.1145	1.218	0.226
occupational complexity - Remove mean	−0.23436	0.1197	−1.958	0.053
Age - Remove mean	−0.07949	0.0284	−2.798	0.006
Education - Remove mean	0.06348	0.0469	1.354	0.179
Sex:				
Male – Female	−0.26189	0.1679	−1.560	0.122
Education - Remove mean ✻ occupational complexity - Remove mean	−0.05930	0.0473	−1.253	0.213
Education - Remove mean ✻ Sex:				
Education - Remove mean ✻ (Male – Female)	0.07779	0.0686	1.134	0.259
occupational complexity - Remove mean ✻ Sex:				
occupational complexity - Remove mean ✻ (Male – Female)	0.20742	0.1945	1.066	0.289
Education - Remove mean ✻ occupational complexity - Remove mean ✻ Sex:				
Education - Remove mean ✻ occupational complexity - Remove mean ✻ (Male – Female)	−0.00910	0.0847	−0.107	0.915

[a] Represents reference level

Hypothesis 3

To demonstrate if sex moderates CR proxies influencing the relationship brain volume and cognitive score, hypothesis (3) addresses the relationship between brain measures and cognitive performance differing by sex and its interaction with reserve proxies. Hypothesis (3) builds upon previous hypotheses and investigates the influence of sex on the brain volume-cognition score relationship and how CR proxies moderate the relationship between brain and cognition.

i. Speed/Attention

i. Mean Putamen

A multiple linear regression model (Table 9) was calculated to predict speed/attention based on age, education, occupation complexity, sex, mean Putamen volume, and their interactions. A non-significant regression was found ($F(15,92) = 1.11$, $p = 0.359$ with an R^2 of 0.153 and $R^2_{adjusted}$ of 0.0152).

Table 9: Multiple Regression Model for Age, Education, Occupational complexity, sex, and meanPutamen as Predictors of Speed/Attention cognition Scores for the Whole Sample

Model Fit Measures

				Overall Model Test			
Model	R	R^2	Adjusted R^2	F	df1	df2	p
1	0.391	0.153	0.0152	1.11	15	92	0.359

Model Coefficients - NPSpeed_attention - Remove mean

Predictor	Estimate	SE	t	p
Intercept *	−0.10618	0.1095	−0.9698	0.335
Education - Remove mean	0.04763	0.0439	1.0838	0.281
occupational complexity - Remove mean	0.02145	0.1052	0.2040	0.839
Sex:				
Male – Female	−0.00695	0.1633	−0.0426	0.966
meanPutamen - Remove mean	7.61e−5	1.50e−4	0.5066	0.614
Education - Remove mean ✻ occupational complexity - Remove mean	−0.09342	0.0437	−2.1374	0.035
Education - Remove mean ✻ Sex:				
Education - Remove mean ✻ (Male – Female)	0.00782	0.0785	0.0996	0.921
occupational complexity - Remove mean ✻ Sex:				
occupational complexity - Remove mean ✻ (Male – Female)	0.01300	0.1891	0.0688	0.945
Education - Remove mean ✻ meanPutamen - Remove mean	−1.50e−5	6.07e−5	−0.2462	0.806
occupational complexity - Remove mean ✻ meanPutamen - Remove mean	1.35e−5	1.56e−4	0.0869	0.931
meanPutamen - Remove mean ✻ Sex:				
meanPutamen - Remove mean ✻ (Male – Female)	1.86e−4	2.35e−4	0.7925	0.430
Education - Remove mean ✻ occupational complexity - Remove mean ✻ Sex:				
Education - Remove mean ✻ occupational complexity - Remove mean ✻ (Male – Female)	0.18575	0.0845	2.1991	0.030
Education - Remove mean ✻ occupational complexity - Remove mean ✻ meanPutamen - Remove mean	4.51e−5	7.45e−5	0.6050	0.547
Education - Remove mean ✻ meanPutamen - Remove mean ✻ Sex:				
Education - Remove mean ✻ meanPutamen - Remove mean ✻ (Male – Female)	−4.34e−5	1.08e−4	−0.4001	0.690
occupational complexity - Remove mean ✻ meanPutamen - Remove mean ✻ Sex:				
occupational complexity - Remove mean ✻ meanPutamen - Remove mean ✻ (Male – Female)	−1.80e−4	2.68e−4	−0.6704	0.504
Education - Remove mean ✻ occupational complexity - Remove mean ✻ meanPutamen - Remove mean ✻ Sex:				
Education - Remove mean ✻ occupational complexity - Remove mean ✻ meanPutamen - Remove mean ✻ (Male – Female)	−1.53e−4	1.31e−4	−1.1698	0.245

* Represents reference level

ii. Mean Caudate

A multiple linear regression model (Table 10) was calculated to predict speed/attention based on age, education, occupation complexity, sex, mean Caudate volume, and their interactions. A non-significant regression was found ($F(15,92) = 1.18$, $p = 0.298$ with an R^2 of 0.162 and $R^2_{adjusted}$ of 0.0252.

Table 10: Multiple Regression Model for Age, Education, Occupational complexity, sex, and meanCaudate as Predictors of Speed/Attention cognition Scores for the Whole Sample

Model Fit Measures

				Overall Model Test			
Model	R	R^2	Adjusted R^2	F	df1	df2	p
1	0.402	0.162	0.0252	1.18	15	92	0.298

Model Coefficients - NPSpeed_attention - Remove mean

Predictor	Estimate	SE	t	p
Intercept *	−0.04837	0.1103	−0.43869	0.662
Education - Remove mean	0.02795	0.0474	0.58936	0.557
occupational complexity - Remove mean	0.05927	0.1091	0.54316	0.588
meanCaudate-remove mean	2.21e−4	1.93e−4	1.14483	0.255
Sex:				
Male – Female	0.00152	0.1535	0.00993	0.992
Education - Remove mean ✻ occupational complexity - Remove mean	−0.14735	0.0605	−2.43712	0.017
Education - Remove mean ✻ meanCaudate-remove mean	−4.01e−5	9.34e−5	−0.42954	0.669
occupational complexity - Remove mean ✻ meanCaudate-remove mean	2.18e−4	2.55e−4	0.85462	0.395
Education - Remove mean ✻ Sex:				
Education - Remove mean ✻ (Male – Female)	−0.00114	0.0759	−0.01504	0.988
occupational complexity - Remove mean ✻ Sex:				
occupational complexity - Remove mean ✻ (Male – Female)	−0.09644	0.1732	−0.55689	0.579
meanCaudate-remove mean ✻ Sex:				
meanCaudate-remove mean ✻ (Male – Female)	−6.90e−5	2.80e−4	−0.24639	0.806
Education - Remove mean ✻ occupational complexity - Remove mean ✻ meanCaudate-remove mean	−9.61e−5	1.43e−4	−0.67334	0.502
Education - Remove mean ✻ occupational complexity - Remove mean ✻ Sex:				
Education - Remove mean ✻ occupational complexity - Remove mean ✻ (Male – Female)	0.14227	0.0989	1.43862	0.154
Education - Remove mean ✻ meanCaudate-remove mean ✻ Sex:				
Education - Remove mean ✻ meanCaudate-remove mean ✻ (Male – Female)	3.34e−5	1.32e−4	0.25336	0.801
occupational complexity - Remove mean ✻ meanCaudate-remove mean ✻ Sex:				
occupational complexity - Remove mean ✻ meanCaudate-remove mean ✻ (Male – Female)	5.40e−5	3.89e−4	0.13875	0.890
Education - Remove mean ✻ occupational complexity - Remove mean ✻ meanCaudate-remove mean ✻ Sex:				
Education - Remove mean ✻ occupational complexity - Remove mean ✻ meanCaudate-remove mean ✻ (Male – Female)	1.20e−4	1.96e−4	0.61333	0.541

* Represents reference level

iii. Mean Hippocampus

A multiple linear regression model (Table 11) was calculated to predict speed/attention based on age, education, occupation complexity, sex, mean Hippocampus volume, and their interactions. A non-significant regression was found ($F(15,92) = 1.53$, $p = 0.110$ with an R^2 of 0.200 and $R^2_{adjusted}$ of 0.0649.

Table 11: Multiple Regression Model for Age, Education, Occupational complexity, sex, and meanHippocampus as Predictors of Speed/Attention cognition Scores for the Whole Sample

Model Fit Measures

				Overall Model Test			
Model	R	R^2	Adjusted R^2	F	df1	df2	p
1	0.447	0.200	0.0694	1.53	15	92	0.110

Model Coefficients - NPSpeed_attention - Remove mean

Predictor	Estimate	SE	t	p
Intercept *	−0.0601	0.1075	−0.559	0.577
Education - Remove mean	0.0171	0.0476	0.358	0.721
occupational complexity - Remove mean	0.0274	0.1026	0.267	0.790
meanHippocampus-remove mean	4.29e−4	2.24e−4	1.910	0.059
Sex:				
Male – Female	0.0276	0.1514	0.182	0.856
Education - Remove mean ✻ occupational complexity - Remove mean	−0.1185	0.0519	−2.282	0.025
Education - Remove mean ✻ meanHippocampus-remove mean	−7.70e−5	9.10e−5	−0.847	0.399
occupational complexity - Remove mean ✻ meanHippocampus-remove mean	3.96e−4	2.62e−4	1.513	0.134
Education - Remove mean ✻ Sex:				
Education - Remove mean ✻ (Male – Female)	0.0162	0.0653	0.248	0.805
occupational complexity - Remove mean ✻ Sex:				
occupational complexity - Remove mean ✻ (Male – Female)	0.0676	0.1753	0.385	0.701
meanHippocampus-remove mean ✻ Sex:				
meanHippocampus-remove mean ✻ (Male – Female)	−4.11e−4	3.34e−4	−1.230	0.222
Education - Remove mean ✻ occupational complexity - Remove mean ✻ meanHippocampus-remove mean	1.40e−5	1.30e−4	0.107	0.915
Education - Remove mean ✻ occupational complexity - Remove mean ✻ Sex:				
Education - Remove mean ✻ occupational complexity - Remove mean ✻ (Male – Female)	0.1648	0.0833	1.978	0.051
Education - Remove mean ✻ meanHippocampus-remove mean ✻ Sex:				
Education - Remove mean ✻ meanHippocampus-remove mean ✻ (Male – Female)	1.21e−4	1.37e−4	0.879	0.382
occupational complexity - Remove mean ✻ meanHippocampus-remove mean ✻ Sex:				
occupational complexity - Remove mean ✻ meanHippocampus-remove mean ✻ (Male – Female)	−7.83e−4	4.15e−4	−1.889	0.062
Education - Remove mean ✻ occupational complexity - Remove mean ✻ meanHippocampus-remove mean ✻ Sex:				
Education - Remove mean ✻ occupational complexity - Remove mean ✻ meanHippocampus-remove mean ✻ (Male – Female)	−8.82e−5	1.78e−4	−0.495	0.622

* Represents reference level

iv. Reasoning

i. Mean Putamen:

A multiple linear regression model (Table 12) was calculated to predict reasoning based on age, education, occupation complexity, sex, mean Hippocampus volume, and their interactions. A significant regression was found ($F(15,93) = 2.62$, $p = 0.002$ with an R^2 of 0.297 and $R^2_{adjusted}$ of 0.184.

The interactions between occupation complexity and education (B = -0.08836, t(92) = -2.1223, p = 0.036) was significant. Education main effects was significant, education (B =0.09016, t(92) = 2.2297, p = 0.028). No other interaction or main effects were significant.

Table 12: Multiple Regression Model for Age, Education, Occupational complexity, sex, and meanPutamen as Predictors of Reasoning cognition Scores for the Whole Sample.

Model Fit Measures

				Overall Model Test			
Model	R	R^2	Adjusted R^2	F	df1	df2	p
1	0.545	0.297	0.184	2.62	15	93	0.002

Model Coefficients - NPReasoning - Remove mean

Predictor	Estimate	SE	t	p
Intercept *	0.01639	0.1021	0.1605	0.873
Education - Remove mean	0.09016	0.0404	2.2297	0.028
occupational complexity - Remove mean	−0.00113	0.0999	−0.0113	0.991
meanPutamen - Remove mean	1.93e−4	1.44e−4	1.3404	0.183
Sex:				
Male – Female	0.18499	0.1548	1.1950	0.235
Education - Remove mean ✻ occupational complexity - Remove mean	−0.08836	0.0416	−2.1223	0.036
Education - Remove mean ✻ meanPutamen - Remove mean	−9.57e−5	5.79e−5	−1.6511	0.102
occupational complexity - Remove mean ✻ meanPutamen - Remove mean	−6.84e−5	1.49e−4	−0.4582	0.648
Education - Remove mean ✻ Sex:				
Education - Remove mean ✻ (Male – Female)	−0.02632	0.0744	−0.3538	0.724
occupational complexity - Remove mean ✻ Sex:				
occupational complexity - Remove mean ✻ (Male – Female)	0.24622	0.1810	1.3603	0.177
meanPutamen - Remove mean ✻ Sex:				
meanPutamen - Remove mean ✻ (Male – Female)	−1.08e−4	2.25e−4	−0.4772	0.634
Education - Remove mean ✻ occupational complexity - Remove mean ✻ meanPutamen - Remove mean	−5.24e−5	7.13e−5	−0.7345	0.464
Education - Remove mean ✻ occupational complexity - Remove mean ✻ Sex:				
Education - Remove mean ✻ occupational complexity - Remove mean ✻ (Male – Female)	0.07561	0.0810	0.9340	0.353
Education - Remove mean ✻ meanPutamen - Remove mean ✻ Sex:				
Education - Remove mean ✻ meanPutamen - Remove mean ✻ (Male – Female)	1.87e−4	1.04e−4	1.7983	0.075
occupational complexity - Remove mean ✻ meanPutamen - Remove mean ✻ Sex:				
occupational complexity - Remove mean ✻ meanPutamen - Remove mean ✻ (Male – Female)	−3.68e−4	2.58e−4	−1.4278	0.157
Education - Remove mean ✻ occupational complexity - Remove mean ✻ meanPutamen - Remove mean ✻ Sex:				
Education - Remove mean ✻ occupational complexity - Remove mean ✻ meanPutamen - Remove mean ✻ (Male – Female)	−7.85e−5	1.25e−4	−0.6263	0.533

* Represents reference level

ii. Mean Caudate:

A multiple linear regression model (Table 13) was calculated to predict reasoning based on age, education, occupation complexity, sex, mean Caudate volume, and their interactions. A significant regression was found ($F(15,93) = 2.09$, $p = 0.017$ with an R^2 of 0.252 and $R^2_{adjusted}$ of 0.131. No interaction or main effects were found significant.

Table 13: Multiple Regression Model for Age, Education, Occupational complexity, sex, and meanCaudate as Predictors of Reasoning cognition Scores for the Whole Sample

Model Fit Measures

				Overall Model Test			
Model	R	R^2	Adjusted R^2	F	df1	df2	p
1	0.502	0.252	0.131	2.09	15	93	0.017

Model Coefficients - NPReasoning - Remove mean

Predictor	Estimate	SE	t	p
Intercept *	−4.09e−4	0.1066	−0.00384	0.997
Education - Remove mean	0.08405	0.0452	1.85944	0.066
occupational complexity - Remove mean	−0.02173	0.1077	−0.20181	0.841
meanCaudate-remove mean	2.15e−4	1.92e−4	1.11675	0.267
Sex:				
Male – Female	0.25101	0.1505	1.66736	0.099
Education - Remove mean ✻ occupational complexity - Remove mean	−0.07561	0.0597	−1.26742	0.208
Education - Remove mean ✻ meanCaudate-remove mean	−1.12e−4	9.20e−5	−1.21974	0.226
occupational complexity - Remove mean ✻ meanCaudate-remove mean	−2.18e−4	2.53e−4	−0.85959	0.392
Education - Remove mean ✻ Sex:				
Education - Remove mean ✻ (Male – Female)	0.01423	0.0743	0.19152	0.849
occupational complexity - Remove mean ✻ Sex:				
occupational complexity - Remove mean ✻ (Male – Female)	0.03217	0.1718	0.18724	0.852
meanCaudate-remove mean ✻ Sex:				
meanCaudate-remove mean ✻ (Male – Female)	−2.72e−4	2.79e−4	−0.97559	0.332
Education - Remove mean ✻ occupational complexity - Remove mean ✻ meanCaudate-remove mean	−1.33e−5	1.41e−4	−0.09394	0.925
Education - Remove mean ✻ occupational complexity - Remove mean ✻ Sex:				
Education - Remove mean ✻ occupational complexity - Remove mean ✻ (Male – Female)	−0.00411	0.0981	−0.04184	0.967
Education - Remove mean ✻ meanCaudate-remove mean ✻ Sex:				
Education - Remove mean ✻ meanCaudate-remove mean ✻ (Male – Female)	1.42e−4	1.31e−4	1.08673	0.280
occupational complexity - Remove mean ✻ meanCaudate-remove mean ✻ Sex:				
occupational complexity - Remove mean ✻ meanCaudate-remove mean ✻ (Male – Female)	4.35e−4	3.87e−4	1.12251	0.265
Education - Remove mean ✻ occupational complexity - Remove mean ✻ meanCaudate-remove mean ✻ Sex:				
Education - Remove mean ✻ occupational complexity - Remove mean ✻ meanCaudate-remove mean ✻ (Male – Female)	2.81e−5	1.94e−4	0.14474	0.885

* Represents reference level

iii. Mean Hippocampus

A multiple linear regression model (Table 14) was calculated to predict reasoning based on age, education, occupation complexity, sex, mean Hippocampal volume, and their interactions. A significant regression was found ($F(15,93) = 2.20$, $p = 0.011$ with an R^2 of 0.262 and $R^2_{adjusted}$ of 0.143). No interaction or main effects were found significant.

Table 14: Multiple Regression Model for Age, Education, Occupational complexity, sex, and meanHippocampus as Predictors of Reasoning cognition Scores for the Whole Sample.

Model Fit Measures

				Overall Model Test			
Model	R	R^2	Adjusted R^2	F	df1	df2	p
1	0.512	0.262	0.143	2.20	15	93	0.011

Model Coefficients - NPReasoning - Remove mean

Predictor	Estimate	SE	t	p
Intercept *	−0.0170	0.1044	−0.1628	0.871
Education - Remove mean	0.0828	0.0446	1.8578	0.066
meanHippocampus-remove mean	1.92e−4	2.21e−4	0.8669	0.388
occupational complexity - Remove mean	−0.0130	0.1020	−0.1275	0.899
Sex:				
Male – Female	0.2439	0.1502	1.6237	0.108
Education - Remove mean ✻ meanHippocampus-remove mean	−7.25e−5	8.71e−5	−0.8323	0.407
Education - Remove mean ✻ occupational complexity - Remove mean	−0.0511	0.0522	−0.9795	0.330
meanHippocampus-remove mean ✻ occupational complexity - Remove mean	9.48e−6	2.64e−4	0.0359	0.971
Education - Remove mean ✻ Sex:				
Education - Remove mean ✻ (Male – Female)	0.0229	0.0635	0.3608	0.719
meanHippocampus-remove mean ✻ Sex:				
meanHippocampus-remove mean ✻ (Male – Female)	−5.64e−5	3.34e−4	−0.1688	0.866
occupational complexity - Remove mean ✻ Sex:				
occupational complexity - Remove mean ✻ (Male – Female)	0.1633	0.1764	0.9258	0.357
Education - Remove mean ✻ meanHippocampus-remove mean ✻ occupational complexity - Remove mean	8.86e−5	1.32e−4	0.6737	0.502
Education - Remove mean ✻ meanHippocampus-remove mean ✻ Sex:				
Education - Remove mean ✻ meanHippocampus-remove mean ✻ (Male – Female)	1.55e−4	1.36e−4	1.1381	0.258
Education - Remove mean ✻ occupational complexity - Remove mean ✻ Sex:				
Education - Remove mean ✻ occupational complexity - Remove mean ✻ (Male – Female)	0.0129	0.0841	0.1535	0.878
meanHippocampus-remove mean ✻ occupational complexity - Remove mean ✻ Sex:				
meanHippocampus-remove mean ✻ occupational complexity - Remove mean ✻ (Male – Female)	−4.38e−4	4.19e−4	−1.0447	0.299
Education - Remove mean ✻ meanHippocampus-remove mean ✻ occupational complexity - Remove mean ✻ Sex:				
Education - Remove mean ✻ meanHippocampus-remove mean ✻ occupational complexity - Remove mean ✻ (Male – Female)	−1.93e−4	1.80e−4	−1.0739	0.286

* Represents reference level

iv. Memory

i. Mean Putamen

A multiple linear regression model (Table 15) was calculated to predict memory based on age, education, occupation complexity, sex, mean Putamen volume, and their interactions. A significant regression was found ($F(15,92) = 1.73$, $p = 0.05$ with an R^2 of 0.220 and $R^2_{adjusted}$ of 0.0933).

The interaction between mean Putamen and sex was found significant (B= 0.00724, t(92) = 2.5058, p = 0.014). Sex (B= -0.4153, t(92) = -2.1046, p = 0.038) was significant. No interaction was found significant. No additional main effects were found significant.

Table 15: Multiple Regression Model for Age, Education, Occupational complexity, sex, and meanPutamen as Predictors of Memory cognition Scores for the Whole Sample

Model Fit Measures

				Overall Model Test			
Model	R	R^2	Adjusted R^2	F	df1	df2	p
1	0.469	0.220	0.0933	1.73	15	92	0.058

Model Coefficients - NPMemory - Remove mean

Predictor	Estimate	SE	t	p
Intercept *	0.1533	0.1302	1.1777	0.242
occupational complexity - Remove mean	−0.2169	0.1274	−1.7029	0.092
Education - Remove mean	0.0953	0.0515	1.8488	0.068
meanPutamen - Remove mean	−1.01e−4	1.83e−4	−0.5524	0.582
Sex:				
Male – Female	−0.4153	0.1973	−2.1046	0.038
occupational complexity - Remove mean ✻ Education - Remove mean	−0.0488	0.0531	−0.9188	0.361
occupational complexity - Remove mean ✻ meanPutamen - Remove mean	5.65e−6	1.90e−4	0.0297	0.976
Education - Remove mean ✻ meanPutamen - Remove mean	9.26e−5	7.39e−5	1.2540	0.213
occupational complexity - Remove mean ✻ Sex:				
occupational complexity - Remove mean ✻ (Male – Female)	0.2639	0.2317	1.1391	0.258
Education - Remove mean ✻ Sex:				
Education - Remove mean ✻ (Male – Female)	0.0389	0.0964	0.4035	0.688
meanPutamen - Remove mean ✻ Sex:				
meanPutamen - Remove mean ✻ (Male – Female)	7.24e−4	2.89e−4	2.5058	0.014
occupational complexity - Remove mean ✻ Education - Remove mean ✻ meanPutamen - Remove mean	8.45e−5	9.09e−5	0.9297	0.355
occupational complexity - Remove mean ✻ Education - Remove mean ✻ Sex:				
occupational complexity - Remove mean ✻ Education - Remove mean ✻ (Male – Female)	0.0690	0.1082	0.6376	0.525
occupational complexity - Remove mean ✻ meanPutamen - Remove mean ✻ Sex:				
occupational complexity - Remove mean ✻ meanPutamen - Remove mean ✻ (Male – Female)	−1.18e−4	3.30e−4	−0.3591	0.720
Education - Remove mean ✻ meanPutamen - Remove mean ✻ Sex:				
Education - Remove mean ✻ meanPutamen - Remove mean ✻ (Male – Female)	−1.68e−4	1.33e−4	−1.2645	0.209
occupational complexity - Remove mean ✻ Education - Remove mean ✻ meanPutamen - Remove mean ✻ Sex:				
occupational complexity - Remove mean ✻ Education - Remove mean ✻ meanPutamen - Remove mean ✻ (Male – Female)	−1.39e−4	1.60e−4	−0.8717	0.386

* Represents reference level

ii. Mean Caudate

A multiple linear regression model (Table 16) was calculated to predict reasoning based on age, education, occupation complexity, sex, mean Caudate volume, and their interactions. A non-significant regression was found ($F(15,92) = 1.36$, $p = 0.182$ with an R^2 of 0.182 and $R^2_{adjusted}$ of 0.0487). No interaction or main effects were found significant in the model.

Table 16: Multiple Regression Model for Age, Education, Occupational complexity, sex, and meanCaudate as Predictors of Memory cognition Scores for the Whole Sample

Model Fit Measures

				Overall Model Test			
Model	R	R^2	Adjusted R^2	F	df1	df2	p
1	0.427	0.182	0.0487	1.36	15	92	0.182

Model Coefficients - NPMemory - Remove mean

Predictor	Estimate	SE	t	p
Intercept [a]	0.1373	0.1349	1.0174	0.312
Education - Remove mean	0.1041	0.0572	1.8185	0.072
meanCaudate-remove mean	−1.98e−4	2.43e−4	−0.8120	0.419
occupational complexity - Remove mean	−0.2235	0.1363	−1.6396	0.104
Sex:				
Male – Female	−0.2365	0.1908	−1.2397	0.218
Education - Remove mean ✻ meanCaudate-remove mean	7.15e−5	1.16e−4	0.6138	0.541
Education - Remove mean ✻ occupational complexity - Remove mean	−0.0177	0.0755	−0.2349	0.815
meanCaudate-remove mean ✻ occupational complexity - Remove mean	−2.54e−5	3.21e−4	−0.0792	0.937
Education - Remove mean ✻ Sex:				
Education - Remove mean ✻ (Male – Female)	0.0721	0.0941	0.7660	0.446
meanCaudate-remove mean ✻ Sex:				
meanCaudate-remove mean ✻ (Male – Female)	5.65e−4	3.55e−4	1.5903	0.115
occupational complexity - Remove mean ✻ Sex:				
occupational complexity - Remove mean ✻ (Male – Female)	0.3070	0.2181	1.4078	0.163
Education - Remove mean ✻ meanCaudate-remove mean ✻ occupational complexity - Remove mean	1.37e−4	1.79e−4	0.7640	0.447
Education - Remove mean ✻ meanCaudate-remove mean ✻ Sex:				
Education - Remove mean ✻ meanCaudate-remove mean ✻ (Male – Female)	−2.17e−4	1.71e−4	−1.2678	0.208
Education - Remove mean ✻ occupational complexity - Remove mean ✻ Sex:				
Education - Remove mean ✻ occupational complexity - Remove mean ✻ (Male – Female)	−0.1167	0.1243	−0.9392	0.350
meanCaudate-remove mean ✻ occupational complexity - Remove mean ✻ Sex:				
meanCaudate-remove mean ✻ occupational complexity - Remove mean ✻ (Male – Female)	−9.57e−5	5.06e−4	−0.1893	0.850
Education - Remove mean ✻ meanCaudate-remove mean ✻ occupational complexity - Remove mean ✻ Sex:				
Education - Remove mean ✻ meanCaudate-remove mean ✻ occupational complexity - Remove mean ✻ (Male – Female)	7.31e−5	2.61e−4	0.2797	0.780

[a] Represents reference level

iii. Mean Hippocampus

A multiple linear regression model (Table 17) was calculated to predict reasoning based on age, education, occupation complexity, sex, mean Hippocampal volume, and their interactions. A non-significant regression was found ($F(15,92) = 1.53$, $p = 0.111$ with an R^2 of 0.200 and $R^2_{adjusted}$ of 0.0691).

Table 17: Multiple Regression Model for Age, Education, Occupational complexity, sex, and meanHippocampus as Predictors of Memory cognition Scores for the Whole Sample

Model Fit Measures

				Overall Model Test			
Model	R	R^2	Adjusted R^2	F	df1	df2	p
1	0.447	0.200	0.0691	1.53	15	92	0.111

Model Coefficients - NPMemory - Remove mean

Predictor	Estimate	SE	t	p
Intercept *	0.2119	0.1317	1.609	0.111
Education - Remove mean	0.0892	0.0562	1.587	0.116
occupational complexity - Remove mean	−0.2332	0.1286	−1.814	0.073
meanHippocampus-remove mean	1.65e−4	2.79e−4	0.592	0.555
Sex:				
Male – Female	−0.2793	0.1895	−1.474	0.144
Education - Remove mean ✻ occupational complexity - Remove mean	−0.0216	0.0658	−0.328	0.744
Education - Remove mean ✻ meanHippocampus-remove mean	5.57e−5	1.10e−4	0.507	0.614
occupational complexity - Remove mean ✻ meanHippocampus-remove mean	−2.47e−4	3.33e−4	−0.742	0.460
Education - Remove mean ✻ Sex:				
Education - Remove mean ✻ (Male – Female)	0.0455	0.0812	0.560	0.577
occupational complexity - Remove mean ✻ Sex:				
occupational complexity - Remove mean ✻ (Male – Female)	0.4868	0.2232	2.182	0.032
meanHippocampus-remove mean ✻ Sex:				
meanHippocampus-remove mean ✻ (Male – Female)	−3.31e−4	4.22e−4	−0.784	0.435
Education - Remove mean ✻ occupational complexity - Remove mean ✻ meanHippocampus-remove mean	1.57e−4	1.66e−4	0.948	0.345
Education - Remove mean ✻ occupational complexity - Remove mean ✻ Sex:				
Education - Remove mean ✻ occupational complexity - Remove mean ✻ (Male – Female)	−0.0203	0.1112	−0.182	0.856
Education - Remove mean ✻ meanHippocampus-remove mean ✻ Sex:				
Education - Remove mean ✻ meanHippocampus-remove mean ✻ (Male – Female)	1.69e−4	1.71e−4	0.989	0.325
occupational complexity - Remove mean ✻ meanHippocampus-remove mean ✻ Sex:				
occupational complexity - Remove mean ✻ meanHippocampus-remove mean ✻ (Male – Female)	−4.27e−4	5.29e−4	−0.808	0.421
Education - Remove mean ✻ occupational complexity - Remove mean ✻ meanHippocampus-remove mean ✻ Sex:				
Education - Remove mean ✻ occupational complexity - Remove mean ✻ meanHippocampus-remove mean ✻ (Male – Female)	−2.94e−4	2.28e−4	−1.288	0.201

* Represents reference level

CHAPTER 5: DISCUSSION

Cognitive Reserve (CR) is a theoretical construct that is used to inform models of cognitive aging and is presumed to be indicative of life experiences which help manage brain pathology (Yaakov Stern, 2010). Essentially, the concept of CR has been proposed to explain the difference between observed cognitive performance and the cognitive performance expected in an individual with a given degree of neuropathology (Yaakov Stern, 2010). The purpose of this study was to investigate how sex influences the accumulation of proxies of reserve (e.g. education and occupational attainment) and whether these differences are a result of sex differences in the relationships between neural, cognitive, and reserve proxies. This study is the first to add empirical evidence regarding sex differences in cognitive function among older adults using later life experiences and MRI data to link life-course factors with brain volume variations.

The results of this research provide supporting evidence that: (1) cognition is highly influenced independently and jointly by CR proxies, (2) speed/ attention is influenced by the relationship between sociocultural preservers of CR and sex, and (3) It is not clear about the association between sociocultural and biological preservers of CR and brain volume variation.

Life-course factors were expected to increase CR based on the principles of the scaffolding theory of aging and cognition-revised model (STAC-r) (Reuter-Lorenz & Park, 2014). This prediction was based on the new STAC-r constructs that parallel the concepts of CR and Brain Reserve (BR), which refer to the brain's ability for reserve enhancement through reserve enriching factors (Reuter-Lorenz & Park, 2014). The results of the present study support the hypothesis that life-course experiences have a direct effect on both neural resource enrichment and depletion. However, the STAC-r model fails to consider gender and sex differences in reserve, despite some of the contributors to reserve being influenced by sex and gender (Figure 2) (Reuter-Lorenz & Park, 2014). CR literature suggests that reserve enriching variables such as high educational attainment and occupational complexity provide older adults cognitive protection as a result of CR proxies which allow the brain to cope longer before the clinical manifestations of AD emerge. Revising the model further to include factors such as sex and gender would highlight their influence on the core construct of compensatory scaffolding.

It was hypothesized that older adults with higher education and occupational complexity scores would exhibit higher cognitive composite scores as outlined in compensation theories (Reuter-Lorenz & Park, 2014). Similarly, it was hypothesized that sex plays a role in moderating the compensatory relationship between CR proxies and cognitive performance, where women were expected to have poorer cognitive score in comparison to men due to educational and occupational complexity differences. Lastly, it was hypothesized that sex influences the brain-cognition relationship and moderates CR proxies in the brain-cognition relationship.

Hypothesis 1

Past researchers have found men had higher education attainment levels than women when both sexes formative years were between ~1915-1955 (Giacomucci et al., 2022; Malpetti et al., 2017; Subramaniapillai et al., 2021), while the present study shows both men and women having equal mean years of education (16 years). This finding may be explained by the notion that New York is a progressive metropolitan city and has a diverse population consisting of immigrant and non-immigrant individuals. Many women by the 1940s pursued higher levels of education and there was an enormous variety in the kinds of jobs occupied by female immigrants. Many women have professional and managerial positions while others end up in low-level service and factory work (ELY, 1974). This high demand for work led to increased education of young women, decreased fertility, an increase of job opportunities for women, and a change in gendered roles predominantly held by women. Despite this transition from what was defined as home-maker role to active participants in the labor force, occupational complexity was higher in men than women. Higher education is related to higher cognitive scores, but high occupational complexity negatively moderates the relationship between education and cognition. This pattern of results is not consistent with the previous literature, where occupational and leisure activities have markedly significant protective effects on cognitive decline and dementia, especially for individuals whose jobs involve social interaction (Subramaniapillai et al., 2021).

With respect to occupational activity, cognitively demanding work conditions are associated with a decreased risk of cognitive decline in older adults, where engagement in mentally stimulating activity/work may promote neural connectivity (Boots et al., 2015). A possible explanation is some occupational demands serve as cognitive training that can aid in better brain

health, while some job aspects (ex. environmental exposures) could be detrimental to brain health (Habeck et al., 2019a). The results of the analyses with education and occupational complexity entered are displayed in Tables 3, 4, and 5. Examination of the models including interaction terms revealed one significant interaction between any occupational complexity and education when predicting Reasoning; the results were separated by sex, and interactions were included in subsequent analyses.

Hypothesis 2

The second hypothesis addressed the influence of sex differences in CR proxies across different cognitive domains. Examination of the models including interaction terms revealed one significant interaction between sex, occupational complexity, and education when predicting Speed/Attention: the results strongly imply that occupational complexity benefits men and not women. One interpretation of these findings is men might benefit more from college education in terms of earnings, employment opportunities, and career development than women. These advantages may then translate into higher SES and more extensive social networks, factors that serve as protection for cognition and lead to accumulation of reserve (Hout, 2012). Future studies will contribute to existing knowledge of the link between multidimensional reserve proxies and cognition when considering both sex and gender (Mielke et al., 2014).

Characteristic differences in generations, including societal changes in economic, political, environmental, and social landscapes, may have an impact on the understanding of differences in sociocultural and biological preserves of cognitive reserve. In the past century in Canada and the United States, education has exponentially increased for women, where more women are obtaining higher educational degrees than men (Subramaniapillai Sivaniya , Almey Anne , Rajah M. Natasha, 2001). As a consequence, education plays a different role according to gender, where generally higher education provides greater resistance against cognitive decline in women than in men (Launer et al., 1999; Letenneur et al., 2000). This idea is further supported by the finding that, although women have been engaging in more reserve contributors as societies modernize, some gender-typical factors still disadvantage women to a greater extent than men. For example, exposure to constant negative psychosocial conditions, which could be a result of

socioeconomic and gender inequality, could contribute to women having twice the risk of depression than men. This increased risk emerges as early as puberty and could potentially worsen during menopause (Mielke et al., 2014).

The different effect of education between women and men is a controversial topic and may be explained by a multifactorial approach. Hence, social factors should be considered. Many cognitive reserve contributors are highly gendered, specifically differences in education, occupation, physical activity, and social support (Giacomucci et al., 2022). Few studies have focused on the differences between sexes in a group of older adults, especially cognitive function. A study conducted by (Herlitz et al., 1997), investigated memory function in a sample of men and women aged 35 to 80 years of age; this study was able to identify sex differences in episodic memory in favour in women. Our study found no significant sex differences in memory or executive functioning or reasoning amongst men and women. Among individuals aged 85 years and older, women were observed to have higher and better scores for cognitive speed and memory than men, despite factors hindering their cognitive function such as lower educational attainment (Herlitz et al., 1997). Our sample consisted of participants aging from 55 to 71 years, with the majority being between 60 to 65 years. We found significant sex differences in favour of men than women in speed and attention tasks. This is consistent with The Midlife in the United States (MIDUS) study, where women, across middle and old age, performed better on tasks of memory while men performed significantly better on a test of executive function and speed tasks (Hughes et al., 2018).

A previous study found gender differences in rate of cognitive decline is almost the same for both men and women between 60 and 80 years-of-age, but this difference changes for women, where until the 80s they have a steeper cognitive decline. This could be attributed to women having longer life expectancy or to hormonal differences; where as a result of increased age, cognitive deterioration was also found to be faster in women due to the declined buffering effects of CR The same study found also observed women having greater performance on measures of episodic memory while men had better spatial abilities (Ferreira et al., 2014). Differences in test characteristics between different studies could serve as an explanation between variance in study findings. Furthermore, this data was collected in New York City, while other studies showing sex differences in memory may come from regions with different “levels of progressiveness” with

respect to women. Another reason could be the subtle gender differences that occur at different stages of adulthood. Additionally, variance in study results could be due to gender differences in cognition emerging later in life closer to old age. If this is the case, the same study hypotheses need to be used to evaluate participants at various age cohorts in later life or even where a large proportion of the sample is deceased (Anstey et al., 2021). Gender differences in cognitive abilities, particularly at older ages, could be explained by a combination of gender differences in chronic disease, lifestyle, and environmental exposures. It has also been suggested that sex differences may be due to task demands that differentially engage male or female interest, familiarity, or motivation (Mckelvie et al., 1993), while other researchers suggested these differences may be explained by biological differences between men and women, such as brain asymmetry (Howieson & Lezak, 2010).

As a consequence, education can be hypothesized to play a different role according to gender, probably acting as a minor contributor of CR in women alongside other social contributors, or there are underlying factors that may need to be addressed to get the full picture of why these distinctions occur.

Hypothesis 3

For the third hypothesis, the relationship between brain measures and cognitive performance differs by the influence of sex on CR proxies, whereas past researchers have found evidence to suggest cognitively normal participants show positive correlations between contributors of reserve (e.g.: years of education and occupation) and cerebral glucose metabolism in a variety of brain regions. In women, this association was noted in anterior limbic-affective and executive network regions; in men, for the posterior associative cortices (Mielke et al., 2014). Mielke et al.(2003), also found sex differences in the patterns of association between proxy measures of cognitive reserve and brain activity, again highlighting the need to segregate data by sex when investigating the effects of reserve in protecting against Alzheimer's Disease (AD) (Mielke et al., 2014). The present study has shown no evidence for a sex effect for memory and speed/attention, yet from a biological point of view, sex-specific differences should be explained, at least in part, by the role of sex hormones on brain function. Estrogen is thought to have a neuroprotective effect, and estrogen loss due to menopause might have a significant effect on

cognitive decline and AD. This study has only found significant sex differences in reasoning cognitive domain. This differs from previous studies, with a sample of adults between 35-80 years of age found higher average performance in women on tests of episodic memory, verbal recognition and fluency tasks, whereas men demonstrated the expected advantage for visuospatial ability (de Frias et al., 2006). The Seattle Longitudinal Study of Aging observed women to have significantly slower rates of decline than men on tests of spatial reasoning and verbal meaning. The Swedish Twin Study of Aging initially reported no significant sex differences in rates of cognitive decline (Finkel et al., 2003), but later during follow-up observed differential rates of decline for two tests: faster quadratic decline for women on a test of crystallized ability, and faster linear decline for men on a test of fluid ability (Finkel et al., 2006). Alternatively, other longitudinal studies observing older adults (70 -100 years of age) found men and women showed similar rates of cognitive change over time (Gerstorf et al., 2006). Given that a number of studies suggest risk of AD is greater in older women than older men, the results demonstrating lower performance or no difference in performance between men and women in the three cognitive domains may seem contradictory. However, when taking into consideration second half of the 20th century, unprecedented historical changes in the socio-economic standing of women in developed nations, labelled as the 'gender revolution' (England, 2010), could have created protective measures for cognition across adulthood in women. Accordingly, the risk of AD increases with age for both sexes, but a decline in estrogen is related to increased risk of the disease in post-menopausal women (Tang et al., 1996). In the Baltimore longitudinal study of aging, it was found that woman taking estrogen replacement therapy (ERT) were less likely to develop AD compared to those who did not have hormonal replacement (Kawas et al., 1997). Additionally, women taking replacement therapy showed improved performance in psychometric tests. Gonadotropins, which are increased in the postmenopausal period are capable of crossing the blood–brain barrier and are proposed to play a crucial role in AD pathogenesis (Rocca et al., 2009). The mechanism for steroid hormones in AD is hypothesized to influence the inflammatory reaction, which is extremely crucial in AD pathology. Findings of sex differences in baseline cognitive performance independent of these factors suggest additional contributors and biological pathways play a role (Levine et al., 2021b). Thus, maintaining health during middle age and across the menopause transition might buffer against cognitive decline during this critical period in a woman's life when there is elevated risk of progressing to AD. The role of brain pathology in the CR-dementia link has been investigated,

where proposed hypotheses suggest that CR might be directly associated with neuropathology, such as reducing the deposition of β-amyloid in aging (Li et al., 2021a). Another potential explanation for our pattern of results relates to changing societal conditions disproportionately improving for women more than men. With women's increased access to higher education and opportunities to pursue complex occupations, increased exposure to cognitive stimulation, economic prosperity, health improvements and changes in average family size has particularly advantaged women over time. It is possible that changing societal conditions may lead to greater resilience to age-related cognitive change to highly educated women (Weber et al., 2014). Taken together, influences of biological and environmental factors operate interdependently to impact women's susceptibility to cognitive decline.

In sum, studies should focus on inclusion of the multiplicity of biological and psychosocial factors implicated in cognition. Exploration of socio-cultural factors and social determinants of health, even in the context of studying biological measures, is crucial in providing the full view of the implications involved in cognitive function. Using an interdisciplinary approach allows for an examination of the brain, cognition, and socio-cultural factors that surround cognitive sex differences. Societal expectations and views on women shape inequalities that impact trajectories of healthy cognitive aging. The intersecting power dynamic that white men have in society usually disadvantages women relative to age and gender inequalities. Women have a greater risk of poverty and workplace discrimination; this creates a disadvantage in factors that influence cognition such as depression (Barrett & Toothman, 2018). Traditional gender-role attitudes vary not only across different countries, but also across regions in the same country. Traditional gender-role attitudes were linked with diminished cognitive performance for women, where women in countries with less traditional attitudes were more likely to have better cognitive performance in later life relative to those in more traditional countries (Bonsang et al., 2017). These findings can also be expanded for people of colour and visible minorities. Black men continue to have a disadvantage in comparison to White men, in lower employment rates across all education levels; this suggests for people of colour, education is a poor indicator of experiences related to CR. Exploration of racial/ethnic differences provides a more accurate understanding of life-course factors that contribute to CR and may allow for the identification of factors affected by inequalities in the onset and progression of AD (Bonsang et al., 2017). It is also crucial to consider the influence of cultural attitudes and values when trying to understand what mitigates cognitive aging.

Variation in CR measures and proxy indicators can vary, not only across countries, but also across geographical areas in the same country. In the United States, cognition can vary across state level as well as urban/rural districts. Cross-sectional analyses of urban/rural differences showed better cognitive ability in central cities in comparison to rural areas; this could be a result of social capital or educational attainment opportunities in urban areas (Grossmann & Varnum, 2011). The geographical distribution of people and their characteristics has important implications for regional demographics and economic development. Thus, the complex link between the sociodemographic context of one's environment and the trajectory of cognitive health in older life needs to be addressed when understanding the implications of socio-economic factors in CR (Jokela, 2014).

CHAPTER 6: CONCLUSION

In conclusion, the understanding of the mechanisms involved with successful aging is far from straightforward, where the relationship between CR proxies and the maintenance of cognitive efficiency regarding age-related changes/brain pathology is dynamic in nature. CR proxies involving learning, social involvement, and complexity of occupation develop throughout an individual's lifetime have a mediating role in improving neural connections and maintaining cognitive health and performance. These improved neural networks mitigate and protect against impairments in later life, causing increased functional connectivity that may delay or even prevent the onset of AD (Pietzuch et al., 2019). The use of the STAC-r model have provided this study with the roadmap for hypothesis development and testing. However, the impact of CR considering demographic characteristics of the population or discrepancies in measuring CR measures or outcomes (i.e., cognitive, or functional) must be addressed, preferably with the use of longitudinal methodology. Future work should focus on implementing factors involving both biological as well as psychosocial variables that will help to clarify the relationship between CR proxies and brain reserve, as well as improve their measurement.

Strengths

This study has some remarkable strengths such the inclusion of a great number of variables, among which brain measures (MRI data), several cognitive score, and two CR proxies.

An additional strength of this study is it builds off from previously conducted research; this allows for consistent knowledge dissemination due to the use of the same definition of Cognitive Reserve.

Limitations

There are at least three potential limitations concerning the results of this study. The first limitation concerns biological sex or gender not explicitly tested. Consequently, biological sex is difficult to disentangle from sociocultural gender. Future work should explicitly test participants' biological sex, as a measure of genes and hormones, and their gender identity by assessing self-perceptions, social attitudes, and expectations. For example, the effect of education on cognition is likely to arise through expectations of gender roles rather than effects of biological sex, but absence of data on gender leads us to refer to sex rather than gender differences.

A second potential limitation is this study did not collect sex hormone levels, which are important for future studies to test, because these differences could help clarify how age-related hormonal changes within sex might influence our interpretation of the results. For example, previous studies have shown changes in estradiol and progesterone can contribute to different AD incidences in women (Rahman et al., 2019). The "estrogen hypothesis" postulates estrogen plays a protective role against AD-dementia, while estrogen dysfunction seems to exacerbate, or perhaps precipitate the AD process in women (Rahman et al., 2019). Sex differences in aging are understood to have significant relevance during distinct hormonal transition periods, such as menopause in women and andropause in men.

A third limitation is since the sampling was conducted in New York City; external validity excludes generalizability between suburban vs rural community dwellers.

Clinical Implication and Future Directions

Despite these limitations, results suggest several theoretical and practical implications. The results of this study help contribute to further understanding of sex differences and gender implications on cognition in healthy older adults. These data have potential research implications. For example, preferably longitudinal studies will allow a better understanding of the neural mechanisms underlying CR and BR. In addition, people from gender diverse communities (e.g., transgender, gender queer, gender non-binary) should be included in forthcoming studies which will allow for the investigation of gender identity on cognition. This has significant empirical potential since there is still much to learn about the implications of biological and hormonal mechanisms underlying cognitive processes in synergy with socio-cultural and psychosocial factors. Additionally, the social ecological model provides a perspective on the role of multiple interacting social ecological levels for individual health and is explicit about the potential impact of intervening on a given risk factor (Peterson et al., 2021). Multilevel interaction between society and environmental influences result in broader human ecology (Peterson et al., 2021). The incorporation of more explicit biopsychosocial perspectives allows for in-depth understanding of the implications that the environment has on cognitive aging and dementia outcome; this would clarify the best opportunity and methods for early intervention options (Peterson et al., 2021).

The developments provided by previous studies together with the results of this study are evidence supporting that education is a powerful tool and as little as elementary education can aid in the reduction of dementia prevalence in illiterate populations. Thus, equal access to education for both men and women, especially in developing countries, is crucial due to the high prevalence of illiteracy and dementia burden (Farfel et al., 2013).

Interdisciplinarity of the Study

The central focus of this study involved the interplay between cognition and gendered psychosocial contributors to reserve in older healthy adults. The knowledge gained from neural and cognitive performance measures will help to inform psychology, health science and cognitive science fields.

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