Cognitive reserve: An investigation of construct validity and relationships with cognitive function in generally healthy older adults

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Declaration

I declare that this thesis has not been previously submitted as an exercise for a degree at this or any other university and it is entirely my own work.

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Summary

This thesis evaluated the construct validity of a multiple-indicator, latent variable model of cognitive reserve (CR), and investigated relationships between this construct and age-related cognitive outcomes in a cohort of generally healthy older adults. CR provides a framework to explain epidemiological and other findings of an association between intellectually enriching experiences across the lifespan and reduced risk of Alzheimer's disease, dementia, and age-related cognitive decline; measures of these intellectually enriching experiences are typically used as proxy indicators of the hypothetical construct CR. However, inconsistent measurement of CR using a range of proxy indicators has attracted criticism, limits comparability of study findings, and raises concerns about construct validity. Latent variable models of CR that combine multiple proxy indicators have been proposed as one potential solution to this problem, but to date these type of models have not been widely used or evaluated.

Chapter 1 introduces CR and related theoretical concepts, and provides an overview of the literature related to cognitive ageing, the effects of CR on cognitive function during normal, non-pathological ageing, and associated research issues. A systematic review of the measurement of CR in studies of investigating cognitive outcomes associated with normal, non-pathological ageing is presented in Chapter 2. This systematic review revealed considerable heterogeneity in proxy indicators used to measure CR across studies, and highlighted the need for theoretical and methodological work to promote a more standardised approach to measurement of the construct.

In Chapter 3, a series of structural equation models designed to provide progressively more demanding tests of convergent and discriminant validity were employed to evaluate the construct validity of a multiple-indicator, latent variable model of CR. These models provided consistent support for convergent validity of the latent CR construct and at least partial support for discriminant validity, although there was some overlap between CR and executive function constructs. In Chapter 4, cross-sectional models demonstrated significant direct effects of age and CR on executive function, but the interaction between age and CR had no significant effect on this outcome; there were also no significant relationships between these predictors and episodic memory. In

moderation analyses of the longitudinal dataset, there were no significant effects of the interaction between age and CR on decline in the cognitive outcome measures over two years.

Methods of neuropsychological assessment that focus on intra-individual differences in cognitive performance, rather than comparison with population norms, may be more sensitive for detecting subtle memory deficits in high-performing individuals with high CR; these individuals may continue to perform within the "normal range" while experiencing a decline for them relative to their premorbid function. In Chapter 5, participants were classified into subgroups using two alternative methods based on intra-individual differences, both of which attempt to "benchmark" memory performance relative to IQ. There were significant differences between subgroups for baseline memory performance; subgroups were not found to differ for baseline performance in other cognitive domains, for subjective memory measures, or for decline in cognitive performance over two years. A general discussion of the findings presented in this thesis, their implications in relation to the existing literature, limitations, and directions for future research is presented in Chapter 6.

This thesis is dedicated to my two glamorous grandmothers, Joan Murphy and Lily Hannigan, who embody the definition of positive ageing and who have taught me more about the value of intergenerational relationships, and the wisdom that comes with old age, than any textbook or journal article could every convey.

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List of Abbreviations

AAMI	Age-Associated Memory Impairment
AD	Alzheimer's disease
aMCI	Amnestic mild cognitive impairment
AMNART	American National Adult Reading Test
ApoE	Apolipoprotein E
BM	Brain maintenance
BR	Brain reserve
BRC	Brain reserve capacity
CAMDEX	Cambridge Mental Disorders of the Elderly Examination
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CES-D	Centre for Epidemiologic Studies Depression scale
CFI	Comparative fit index
CR	Cognitive reserve
CRIq	Cognitive Reserve Index questionnaire
CRQ	Cognitive Reserve Questionnaire
CRS	Cognitive Reserve Scale
CSF	Cerebrospinal fluid
CTT	Colour Trails Test
EEG	Electroencephalogram
ERP	Event-related potential
FCSRT	Free and Cued Selective Reminding Test
FDG-PET	Fluorodeoxyglucose-positron emission tomography
HADS-A	Hospital Anxiety and Depression Scale – Anxiety subscale
HAROLD	Hemispheric Asymmetry Reduction in Older Adults
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
LEQ	Lifetime of Experiences Questionnaire
LNS	Letter-Number Sequencing test
MAC-Q	Memory Assessment Clinics Questionnaire
MCI	Mild cognitive impairment
MIMIC	Multiple indicators, multiple causes variable

MLM	Maximum likelihood mean-adjusted (estimator)
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
NART	National Adult Reading Test
NIA-AA	National Institute on Aging and the Alzheimer Association
PASA	Posterior-Anterior Shift in Aging
PCAS	Premorbid Cognitive Abilities Scale
PET	Positron emission tomography
PFC	Prefrontal cortex
PiB-PET	C-Pittsburgh Compound B-positron emission tomography
PRMQ	Prospective and Retrospective Memory Questionnaire
rCBF	Resting regional cerebral blood flow
RMSEA	Root mean square of error approximation
SEM	Structural equation modelling
SES	Socioeconomic status
SMC	Squared multiple correlation
SPECT	Single-photon emission computed tomography
SRMR	Standardised root mean square residual
STAC	Scaffolding Theory of Ageing and Cognition
STACr	Scaffolding Theory of Ageing and Cognition – revised
TILDA	The Irish Longitudinal Study of Ageing
WAIS	Wechsler Adult Intelligence Scale
WMH	White matter hyper-intensities
WMS	Wechsler Memory Scale
WRAT	Wide Range Achievement Test

Chapter 1: General Introduction

> *One of the greatest success stories of modern times is the increasing number of people living into old age. However, this triumph of humanity is also one of our greatest challenges.*
>
> - Kofi Annan, Nobel Prize

The rapid expansion of the older population worldwide brings opportunities linked to the wealth of knowledge and experience possessed by older adults, but also brings significant challenges associated with increasing health, social, and financial support needs of elderly citizens. Perhaps one of the most formidable challenges associated with an ageing population is the potential for considerably increased incidence of age-related cognitive impairment. Advanced age is the single greatest risk factor for neurodegenerative diseases that cause dementia, and even in the absence of neurodegenerative pathology, the process of normal, non-pathological ageing is typically associated with subtle cognitive decline. A distinction can be drawn between disease-related and age-related cognitive decline; this thesis will focus on the latter. Considerable inter-individual variability is observed in the nature and severity of age-related cognitive decline. The majority of older adults considered to be "normally ageing" experience subtle declines in several cognitive domains, which are less severe than disease-related declines, but may have a range of negative consequences for their health, well-being, and quality of life. However, some older adults, who are sometimes described as "successfully ageing", show little or no decline in cognition and continue to perform at high levels in very old age. A range of risk and protective factors have been identified that may be associated with successful ageing, and may contribute to the minimisation of decline and the preservation of cognitive function across the lifespan. Cognitive reserve (CR) is a theoretical concept proposed to explain individual differences in risk for, and patterns of, cognitive impairment associated with advanced age, neurodegenerative disease, and/or brain damage; the concept of CR provides a framework for explaining how intellectually enriching experiences across the lifespan, along with innate abilities, might protect against cognitive decline associated with advancing age. This thesis investigates CR, and its relationship with cognitive outcomes

associated with normal, non-pathological ageing. This chapter introduces CR and related theoretical concepts, provides an overview of the literature related to normal cognitive ageing, discusses conceptual and measurement issues in CR research, and outlines the effects of CR on neuropsychological test performance.

1.1 What is reserve?

The concept of reserve emerged in response to repeated observations of significant discrepancies between brain pathology and its clinical manifestation in the form of cognitive deficits (Park & Reuter-Lorenz, 2009; Steffener & Stern, 2012). The clinical manifestation of Alzheimer's disease (AD) involves a dementia syndrome that is typically characterised by significant, progressive decline in memory and at least one other cognitive domain, and functional impairment that interferes with activities of daily living (Chertkow, Feldman, Jacova, & Massoud, 2013; Thomas, 2008). When cognitive decline is more severe than would be expected for normal ageing, but does not interfere with everyday function and does not meet clinical criteria for AD, individuals may be diagnosed with mild cognitive impairment (MCI) (Petersen, 2004); this level of impairment has also been described as prodromal AD, if accompanied by positive biomarkers, in more recent diagnostic criteria for research studies (Dubois et al., 2010; Dubois et al., 2007). Post-mortem examinations have revealed an apparent capacity for some adult brains to sustain AD pathology without manifesting clinical dementia symptoms, at a level of neuropathology that is sufficient to cause dementia in other patients (Starr & Lonie, 2008). A striking early study by Katzman et al. (1989) described 10 cases of cognitively normal older women who were discovered to have advanced AD pathology in the form of neuritic plaques at autopsy. Epidemiological studies have reported that between 25% and 67% of participants characterised as cognitively normal during repeated longitudinal assessments met pathological criteria for AD upon post-mortem examination (Crystal et al., 1988; Ince, 2001; Morris et al., 1996; Mortimer, Snowdon, & Markesbery, 2003; Price & Morris, 1999). For example, in a large epidemiological study that used a standard neuropathological protocol to study the brains of 456 elderly people, a mismatch was observed between burden of neuropathology post-mortem and cognitive performance prior to death; the degree of discrepancy increased with advancing age (Savva et al., 2009).

This pathology-cognition mismatch is not exclusive to AD, and has been observed across a range of conditions. For example, clinicians frequently note that a stroke of a certain magnitude can produce significant cognitive impairment in one patient, but have minimal impact on the cognitive function of another (Stern, 2002). Similarly, there have been repeated observations of individual differences in both the severity and duration of cognitive impairment resulting from comparable traumatic brain injuries (Kesler, Adams, Blasey, & Bigler, 2003; Ropacki & Elias, 2003). Considerable heterogeneity is also observed in cognitive changes associated with advancing age, suggesting that similar discrepancies may exist in the relationship between cognitive and neural manifestations of normal, non-pathological ageing.

These various lines of evidence have led researchers to hypothesise that, rather than being direct, the relationship between neural changes and their cognitive manifestation is modified by a third factor – a "reserve", that promotes resilience to age- and disease-related deteriorations in brain integrity, and that acts as a "buffer" between pathology and clinical outcome (J. Barnett & Sahakian, 2008; Satz, Cole, Hardy, & Rassovsky, 2011). A number of theoretical concepts have been proposed to account for this buffer; these include cognitive reserve (Stern, 2009), brain reserve (Satz, 1993), neurocognitive scaffolding (Park & Reuter-Lorenz, 2009) and brain maintenance (Nyberg, Lovdén, Riklund, Lindenberger, & Backman, 2012). These concepts vary in detail and in how they operationalise reserve, but share the assertion that higher levels of reserve are protective against either the development or expression of neuropathology, and that lower levels may infer an increased vulnerability for clinical symptoms and functional impairment associated with brain pathology (J. Barnett & Sahakian, 2008). This thesis focuses on cognitive reserve, and a detailed discussion of this concept and relations between the various theoretical perspectives mentioned above, is provided in Section 1.3.

1.2 The importance of reserve for an ageing population

The potential for a reserve factor to mitigate the impact of age- and disease-related neural changes on cognitive function is of considerable importance and interest to researchers, clinicians, and policy-makers working to address challenges associated with a rapidly ageing population.

1.2.1 Population ageing

Demographic ageing is a global phenomenon, with the percentage of the world's population made up by older persons expected to reach unprecedented levels over the next 50 years (United Nations Department of Economic and Social Affairs Population Division, 2009). The proportion of the Irish population aged over 65, which currently stands at approximately 12% (Central Statistics Office & Northern Ireland Statistics & Research Agency, 2011) is projected to rapidly increase to over 22% by 2041 (McGill, 2010). Current estimates suggest that the number of people aged over 75 years will reach almost one million in Ireland by 2041 (Centre for Ageing Research and Development in Ireland (CARDI), 2014). Among the over 60s, the oldest old (aged 80+) are the fastest growing group; at present almost one in every seven older people worldwide are aged over 80 years, and this figure is projected to increase to one in five by 2050 (United Nations Department of Economic and Social Affairs Population Division, 2009). On the island of Ireland, the number of people aged 85 and over increased by 40% between 2002 and 2011 (Central Statistics Office & Northern Ireland Statistics & Research Agency, 2011).

1.2.2 Ageing and cognition

While these increases in the quantity of life can be considered a triumph of modern medicine, failing mental function unfortunately impairs the quality of these extra years for many people. Among the growing number of individuals aged 65 and over, the prospect of experiencing cognitive decline that results in a loss of independence is reported as one of the most feared aspects of the ageing process; and neurocognitive frailty is currently considered to be the greatest obstacle to successful ageing (Daffner, 2010; Park & Reuter-Lorenz, 2009).

Considerable heterogeneity is observed in cognitive outcomes associated with advancing age, which range from essentially preserved functioning among individuals sometimes referred to as "successfully ageing" or "super-elderly", to severe impairments associated with dementing disorders such as AD (Anderson, 2008; Daffner, 2010). The varying levels of cognitive decline observed in older adults are not thought to be related to one common process of "brain ageing", but instead are thought to result from distinct trajectories involved in normal ageing and pathological disease

states (Anderson, 2008). Advanced age is the single biggest risk factor for neurodegenerative conditions that result in dementia, of which the most common is AD, a progressive neurodegenerative disorder that causes loss of function and neuronal cell death in several brain areas (Buckner, 2004; Keller, 2006; Reitz, Brayne, & Mayeux, 2011). The clinical presentation of dementia may initially vary depending on the underlying cause, but ultimately involves a severe and widespread decline in cognitive abilities, that interferes with a person's everyday functioning and their ability to live independently (Henderson, 2014). Brain diseases such as AD are emerging as leading causes of mortality, as advances in medicine continue to delay onset and reduce incidence of other conditions such as heart disease, cancer, and stroke (Depp, Harmell, & Vahia, 2012).

While risk for dementia increases dramatically with age, current evidence does not support the idea that dementia is an inevitable consequence of ageing, or that all individuals would go on to develop dementia if they were to live for long enough (Anderson, 2008). Studies investigating cognitive function among centenarians have reported that between 15% and 25% of individuals who live to the age of 100 do not exhibit clinical signs of dementia (Kliegel, Moor, & Rott, 2004; Perls, 2004). It is generally accepted that almost all older adults experience some decline in cognitive abilities, in the same way that physical abilities such as muscle strength or lung function are somewhat diminished during normal ageing. However, this type of non-pathological, age-related cognitive decline is subtle, and has minimal impact on everyday functioning (Anderson, 2008; Salthouse, 2012). The term "non-pathological" is used to reflect the fact that the changes occurring are age-related, but less severe that those associated with diagnosable conditions such as AD or MCI (Deary & Gow, 2008). In the absence of specific dementia pathologies, this non-pathological cognitive ageing would not be expected to progress to dementia across the lifespan (Henderson, 2014). This thesis focuses on the cognitive changes associated with normal, non-pathological ageing, as opposed to pathological declines associated with neurodegenerative conditions.

Cognition plays a critical role in mental and physical health, and social and emotional well-being. Cognitive ability is "one of the most valued human characteristics" (Salthouse, 2012, p.203); it is fundamental to our sense of self, to the access we have to

our past, and to our interactions with the world around us (Deary & Gow, 2008). Age-related declines in cognitive function are not so severe as to interfere with day-to-day function, but for some older adults they cause frustration, may lead to reduced engagement in some activities, and can have a negative impact on quality of life (Anderson, 2008; Sartori, Vance, Slater, & Crowe, 2012). Cognitive impairment that does not reach the threshold for dementia diagnosis is associated with increased disability, increased risk for depression and social withdrawal, increased healthcare costs and increased likelihood of progression to dementia (S. M. Albert, Glied, Andrews, Stern, & Mayeux, 2002; Petersen, 2004; Plassman et al., 2008; Sartori et al., 2012). Therefore, the minimisation of age-related decline, and the maintenance of brain health and optimal cognitive function across the lifespan are of crucial importance for the health and well-being of older adults.

1.2.2.1 Factors contributing to heterogeneity of cognitive ageing

It is likely that a multitude of genetic and environmental factors contribute to inter-individual variability in late-life cognitive outcomes. Identification of these factors is an important topic of research, because risk or protective factors that are modifiable could be manipulated, promoted, or discouraged in interventions aimed at optimising cognitive function across the lifespan and preventing decline in old age (Deary & Gow, 2008). Twin studies have demonstrated significant genetic influences on cognitive function; however the proportion of variance attributable to heritability appears to be much larger in midlife than in late life. For example, one longitudinal study found that heritability estimates for general cognitive ability dropped from ~80% in midlife to less than 60% in late life, suggesting that the relative influence of environmental factors increases with age (Finkel, Pedersen, Plomin, & McClearn, 1998). A range of environmental and health-related factors have been identified that contribute to optimal cognitive function. These factors influence cognition throughout life, but may become increasingly important in late life, when age- and disease-related brain changes have the potential to cause cognitive impairment (Anstey, 2014). There is considerable evidence that psychological factors such as depression and chronic stress are associated with damage to various brain structures, and may infer an increased risk for cognitive impairment in old age (Anstey, 2014). A number of large longitudinal studies have found that vascular risk factors in midlife, such as obesity, hypertension, and hypercholesterolemia, are associated with increased risk of subsequent dementia, and

these factors may also impact on risk for cognitive decline during normal, non-pathological ageing (Daffner, 2010; Mangialasche, Kivipelto, Solomon, & Fratiglioni, 2012). Lifestyle factors such as physical activity, smoking, alcohol use, and nutrition may also influence brain health and cognitive outcomes for older adults, although the exact mechanisms involved in these relationships are not yet fully understood (Depp et al., 2012; Kirkwood et al., 2008). There is evidence for a reciprocal positive relationship between social engagement and cognitive function in late life (Lövdén, Ghisletta, & Lindenberger, 2005; Small, Dixon, McArdle, & Grimm, 2012). In addition to childhood cognitive ability, which appears to account for a significant proportion of variance in late-life cognitive function (Richards, Shipley, Fuhrer, & Wadsworth, 2004; Whalley et al., 2000), continued cognitive development across the lifespan through intellectually enriching exposures (e.g. education, complex occupations, mentally stimulating leisure activities) appears to buffer against cognitive impairment or decline in old age (Anstey, 2014; J. Barnett & Sahakian, 2008). One potential explanation for the protective effects of lifelong intellectual enrichment is the hypothesis that these exposures build CR, by facilitating development of cognitive skills and neural processes that can be invoked to maintain cognitive function in the face of neural damage (Stern, 2002, 2009, 2012).

1.2.2.2 Cognitive changes associated with normal, non-pathological ageing

In order to understand the influence of CR on age-related changes in cognition, it is necessary to first outline the "typical" features of normal, non-pathological cognitive ageing, while acknowledging that older adults vary widely in the extent to which they are affected by these changes. A considerable number of cross-sectional and longitudinal studies, many involving large cohorts of participants, have consistently documented changes in cognition associated with normal ageing (e.g. Hultsch, Hertzog, Small, McDonald-Miszczak, & Dixon, 1992; Lindenberger & Baltes, 1997; Schaie, 1996; Zelinski & Burnight, 1997). The exact trajectories of the declines observed differ as a function of study design (Salthouse, 2009). Cross-sectional studies suggest a pattern of decline in several cognitive domains that begins early in adulthood, with a relatively linear gradient throughout the lifespan, and similar slopes of decline observed across the affected domains (Hedden & Gabrieli, 2004; Schaie & Willis, 2010). On the other hand, longitudinal evidence paints a more complex picture, with little decline in the majority of domains until mid- to late-life, at which point the slope of decline

observed differs across the affected domains (see Figure 1.1) (Hedden & Gabrieli, 2004; Schaie & Willis, 2010).

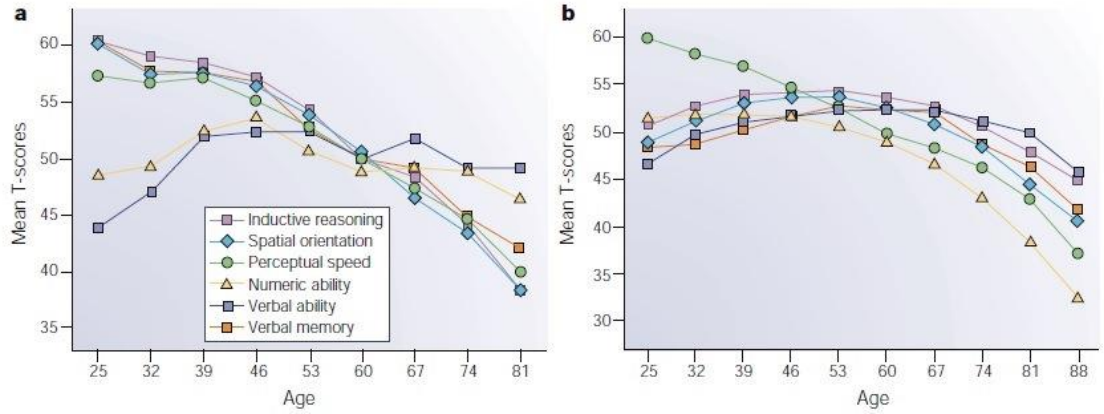

Figure 1.1: Cross-sectional versus longitudinal patterns of age-related cognitive change

Note: Reproduced from (Schaie, 1996). The graphs above document the patterns of age-related cognitive decline observed in (a) cross-sectional data and (b) seven-year longitudinal data, from the Seattle Longitudinal Study. The cross-sectional data (a) shows lifelong declines in all domains with the exception of verbal and numeric ability, whereas the longitudinal data (b) shows declines only after age 55 for all domains apart from processing speed, which shows a pattern of lifelong decline.

Cohort effects on cognitive performance in cross-sectional designs (group differences due to historical factors such as systematic variance in educational opportunity and attainment between generations), or both practice and attrition effects during repeated longitudinal assessments, may explain these conflicting findings (Hedden & Gabrieli, 2004; Zelinski & Burnight, 1997). The accelerated late-life declines observed in some longitudinal studies may also be due to the influence of undiagnosed neurodegenerative disease processes among some study participants (Hedden & Gabrieli, 2004).

Despite the differences between longitudinal and cross-sectional findings, the available evidence provides support for the occurrence of age-related declines in cognitive function. However, overall cognitive performance is the outcome of dynamic interactions between multiple domains of cognition, and age does not affect all of these domains equally (Keller, 2006). Some cognitive domains show relative stability or even improvement in later years, while significant age-related decline occurs in other domains (Anderson, 2008; Buckner, 2004; Salthouse, 2004).

Horn and Catell's (1967) distinction between "fluid" and "crystallised" abilities is useful in delineating functions that are differentially affected by non-pathological

ageing. Crystallised abilities such as vocabulary, storage of general knowledge, and implicit memory remain relatively preserved, whereas decline is well-documented in fluid abilities including processing speed, episodic memory, executive functions, reasoning, and working memory (Deary et al., 2009; Rog & Fink, 2013). While research suggests different trajectories of age-related change for fluid and crystallised abilities, it is important to note that these cannot be considered as two completely independent aspects of cognition. For example, a person's level of crystallised intelligence may influence the effectiveness of their fluid abilities, and fluid abilities also play a significant role in the acquisition of accumulated crystallised knowledge (Raz, 2000).

In the absence of dementia pathologies, the greatest effects of cognitive ageing can be seen in tasks that rely on executive function and attention, as distinct from impairments in declarative memory that are the hallmarks of the early stages of AD (Buckner, 2004). Slowing of processing speed, which occurs gradually throughout life and begins as early as age 30, is also a fundamental characteristic of cognitive ageing (Anderson, 2008). The impact of slowed processing speed on many higher-order functions raises the possibility that this general decline is responsible for a significant proportion of age-associated cognitive change across the affected domains (Salthouse, 1996). Declines in attentional processes, such as reduced inhibitory mechanisms of selective attention, may contribute to age-related deterioration in working memory and may also interfere with various aspects of executive performance (Anderson, 2008). Normal ageing is also typically associated with some decline in memory for recent events and delayed recall of verbal information (Anderson, 2008; Yankner, Lu, & Loerch, 2008). These changes in memory are significantly milder than those associated with neurodegenerative disease, and may result, at least in part, from age-related decline of executive processes required for efficient encoding and retrieval (Buckner, 2004). Changes in language function are also observed with age in the absence of identifiable disease. These changes include decreased efficiency of phonological retrieval, resulting in word finding difficulties reported by some older adults, which are often referred to as the "tip of the tongue" phenomenon (Burke & Shafto, 2004).

In contrast to age-related decline in memory for recent information or events, autobiographical memory and knowledge accumulated earlier in life remain relatively

stable across the lifespan – although older adults may experience some slowing in the retrieval of this information from long-term memory (Anderson, 2008). Measures of vocabulary, verbal ability, attention span, and implicit memory are also relatively preserved, exhibiting only slight declines until very old age (Hedden & Gabrieli, 2004; Yankner et al., 2008). Older adults exhibit little, if any, decline in emotional processing and control; mood regulation improves after around age 60, and while overall memory for contextual details of events declines with age, this decline is less evident in memory for emotionally relevant details (Kensinger & Corkin, 2009).

1.2.2.3 Inter-individual variability in cognitive ageing

Cognitive ageing could be described as a process characterised by variability, and in addition to *intra*-individual variability observed in contrasting patterns of stability and decline across cognitive domains, there is considerable variability at the *inter*-individual level in terms of the magnitude of age-related changes experienced (Hedden & Gabrieli, 2004). For example, in a longitudinal study of 2,509 adults who were aged 70 and over and were cognitively normal at baseline, Yaffe et al. (2009) found that the majority of participants exhibited a pattern of minor age-associated decline in global cognition, but a significant proportion (30%) showed no decline, or even improvement, over an eight year period. While individuals differ in terms of their level of cognitive function throughout life, these inter-individual differences increase with age, due to greater variance in cognitive change among older groups (H. Christensen, 2001; de Frias, Lövdén, Lindenberger, & Nilsson, 2007). An illustration of this can be seen in data from the Betula longitudinal study, which shows increased heterogeneity in memory performance as a function of age, with an overall negative age trend, but a significant proportion of the sample continuing to perform at high levels at advanced ages (see Figure 1.2) (Habib, Nyberg, & Nilsson, 2007; Nyberg et al., 2012). As inter-individual variability in cognitive function increases, older adults who experience little age-related decline and continue to function at levels similar to their younger counterparts can be classified as exhibiting "successful" as opposed to "normal" ageing (Rowe & Kahn, 1997).

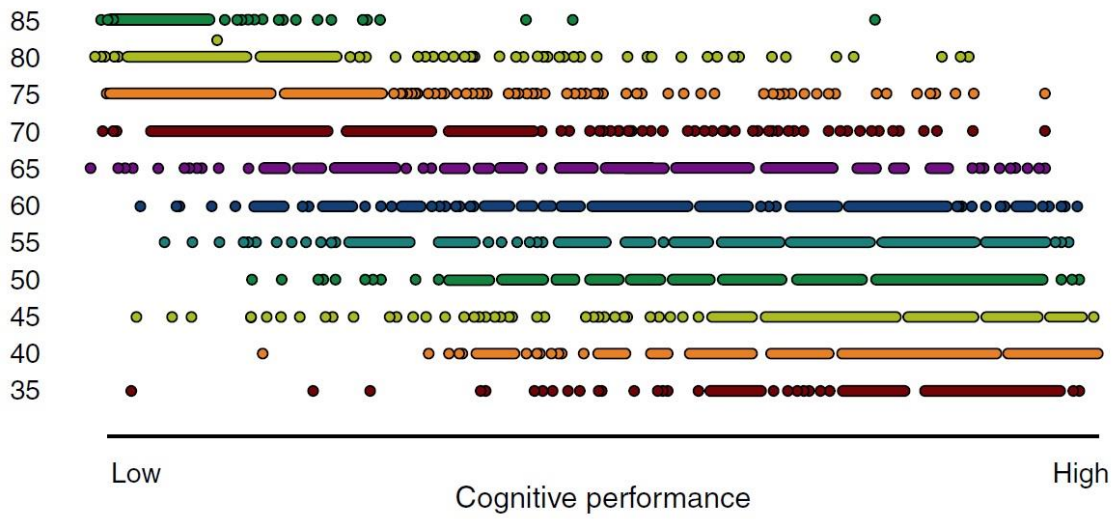

Figure 1.2: Inter-individual variability in cognitive performance increases with age

Note: Reproduced from (Nyberg et al., 2012). This graph depicts results of a Q-mode factor analysis using data from the Betula longitudinal study (Habib et al., 2007) that classified individuals as exhibiting successful or usual ageing, and found considerable heterogeneity in cognitive performance (each circle denotes the average score of an individual). Although these is a clear negative age trend for cognitive performance, several individuals continued to perform at high levels in very old age, and increased variability in performance as a function of age is also evident.

1.2.2.4 Neural correlates of age-related cognitive declines

Increased availability of more sophisticated neuroimaging techniques have allowed researchers to investigate structural, functional, and neurochemical brain changes that are associated with ageing, and may underlie the well-established age-related cognitive changes discussed above. A series of deleterious brain changes have been found to occur during the process of normal ageing in the absence of neurodegenerative disease. These include synaptic degeneration and volumetric reductions in both grey and white matter, although decreases in white matter volume may be most prominent among the oldest old (after the age of 70) (Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; Hedden & Gabrieli, 2004). Increases in white matter abnormalities referred to as "white matter hyper-intensities" (WMH) (due to their bright appearance on MRI scans) are another well-established feature of non-pathological ageing (Buckner, 2004); the severity of these WMH is strongly linked with chronological age along with vascular risk factors (Gunning-Dixon et al., 2009). Changes in neurotransmitter systems, including loss of receptors and reduced connectivity between neurochemical pathways, are also evident, particularly within the dopaminergic system (Bäckman, Lindenberger,

Li, & Nyberg, 2010; Cabeza, Anderson, Locantore, & McIntosh, 2002; Hedden & Gabrieli, 2004). Age-related changes in functional brain activity, particularly in frontal regions, have also been documented. Neuroimaging studies comparing young and older adult groups have demonstrated age-related decreases in task-related activation of certain brain regions, along with over-recruitment of other regions by older adults, including some areas not activated by younger controls (e.g. Cabeza et al., 1997; Grady, Randy McIntosh, Horwitz, & Rapoport, 2000; Reuter-Lorenz et al., 2000).

Just as ageing has a disproportionate effect on some cognitive domains, neural changes associated with advancing age do not impact all brain areas equally, and anterior regions appear particularly susceptible to age-related degradation (Raz & Rodrigue, 2006). The current literature supports a two-component view of neurobiological ageing, with structural and functional declines in frontal-striatal regions most prominent during normal, non-pathological ageing, and changes in medial-temporal structures, beginning with volumetric loss in the entorhinal cortex that progressively spreads to the hippocampus and other regions, occurring in the presence of pathology related to AD (Buckner, 2004; Hedden & Gabrieli, 2004).

The exact nature of relationships between these various forms of brain deterioration, and their association with age-related cognitive changes, is not yet fully understood. There is some evidence that prefrontal cortex (PFC) volume is positively correlated with performance on executive functioning tasks (Raz, Gunning-Dixon, Head, Dupuis, & Acker, 1998). Reduced white matter integrity and WMH severity are associated with age-related deficits in multiple cognitive domains, including memory, executive function, and processing speed (Brickman, Habeck, Zarahn, Flynn, & Stern, 2007; Brickman et al., 2006; Gunning-Dixon et al., 2009). Age-related declines in dopaminergic function have been found to explain a significant proportion of variance in measures of executive function, speed, and episodic memory (Bäckman et al., 2010; Rieckmann et al., 2011). The influence of genetic and environmental factors associated with heterogeneity in cognitive ageing may complicate attempts to map age-related neural changes to cognitive function (Deary & Gow, 2008). Further research is required to link these neural changes to cognitive outcomes, and to investigate whether these relationships are modified by reserve.

1.3 Theoretical perspectives: Cognitive reserve, brain reserve, brain maintenance, and neurocognitive scaffolding

A number of theoretical concepts have been proposed to explain preservation of cognitive function in the face of advanced age or neuropathological disease; these concepts may be useful for understanding differential risk for age-related cognitive decline (Barulli & Stern, 2013). The majority of papers draw a broad distinction between separate but related concepts of brain reserve and cognitive reserve (Stern, 2009). More recently, additional concepts of brain maintenance (Nyberg et al., 2012) and neurocognitive scaffolding (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014) have emerged in the literature. The sections that follow will outline each of these in turn, before discussing both overlap and distinctions between these complementary concepts.

1.3.1 Brain reserve

Brain reserve (BR) refers to structural attributes of the brain that allow it to cope to varying degrees with pathologic changes, and is typically quantified with measures such as brain size or neuronal count (Satz et al., 2011; Stern, 2002). BR employs a threshold model, whereby a certain level of brain reserve capacity (BRC) is required to maintain cognitive function, with clinical deficits becoming apparent once pathology reduces BRC beyond this threshold (Stern, 2009; Tucker & Stern, 2011). This model proposes that individuals with a higher level of BR will withstand a greater degree of pathology before reaching the threshold for clinical and functional deficits (Stern, 2003; Tucker & Stern, 2011). Studies employing general indicators of brain size such as head circumference or total intracranial volume have found an inverse association with risk for dementia (Graves et al., 1996; Mortimer et al., 2003); the strength of the relationship is reduced when genetic factors such as the apolipoprotein E (ApoE) gene are controlled for (Graves et al., 2001). In an important theoretical paper, Stern (2009) defines brain reserve as a "passive" model, based on assumptions that the threshold for clinical manifestation of pathology is fixed and applies to all individuals; that specific types of brain damage result in the same outcome for everyone; that repeated incidences of brain damage have an additive effect; and that pathology is either sufficient or insufficient to deplete BRC past a critical threshold. This model therefore does not account for individual differences in how the brain processes tasks (Stern, 2009).

1.3.2 Cognitive reserve

In contrast to the "passive" model implied by BR, cognitive reserve (CR) represents an "active" model of individual differences in age- and disease-related cognitive outcomes, proposing that these differences are determined by brain function rather than structure (Stern, 2012). CR represents the brain's dynamic attempts to cope with pathology or depletion of neural resources, by employing active cognitive processes to support maintenance of cognitive function. Specific mechanisms underlying this active form of reserve remain poorly understood. At a behavioural level, it has been suggested that variance in the selection, use, and adaptation of cognitive strategies may be an important aspect of CR, although this hypothesis has been the subject of relatively little research to date (Barulli, Rakitin, Lemaire, & Stern, 2013). At a neural level, CR is hypothesised to operate via greater efficiency and capacity of primary networks used to perform cognitive tasks (termed "neural reserve"); to be associated with greater ability to recruit compensatory networks to maintain performance when the primary network is compromised (termed "neural compensation"); or to be mediated by general CR networks that support cognitive performance across multiple domains (Robertson, 2014; Steffener, Barulli, Habeck, & Stern, 2014; Steffener & Stern, 2012).

The individual differences in cognitive efficiency, capacity, and flexibility thought to constitute CR are conceptualised as being shaped by both innate differences (e.g. intelligence) and by activities and experiences that provide complex mental stimulation across the lifespan (e.g. educational attainment; complex occupations; engagement in mentally stimulating leisure and social activities) (Barulli & Stern, 2013). Variables that represent these innate abilities and intellectually enriching exposures are typically used as proxy variables to estimate CR (Jones, Manly, Glymour, Rentz, & Stern, 2011). The model therefore proposes that greater exposure to cognitively stimulating experiences across the lifespan allows individuals with higher CR to tolerate a greater degree of brain pathology without cognitive or functional impairment, resulting in more successful cognitive ageing and a reduced risk of incident dementia (Stern, 2002, 2009, 2012)

The metaphor of computer hardware versus software is frequently employed in the literature when discussing differences between BR and CR (e.g. Corral, Rodriguez,

Amenedo, Sanchez, & Diaz, 2006; Mehta et al., 2009). The "hardware" of BR refers to structural factors such as brain size, brain volumes, synaptic density, or neuronal count – this model assumes that there is a fixed threshold of brain "hardware" required in order to avoid cognitive impairment or decline. The "software" of CR, on the other hand, refers to active cognitive processing – an individual who can process cognitive tasks with greater efficiency, or has greater ability to use alternative processes in a compensatory manner, can be viewed as having more effective "software" that allows them to maintain function in the presence of more substantial damage to their "hardware" (BR) than someone with lower CR.

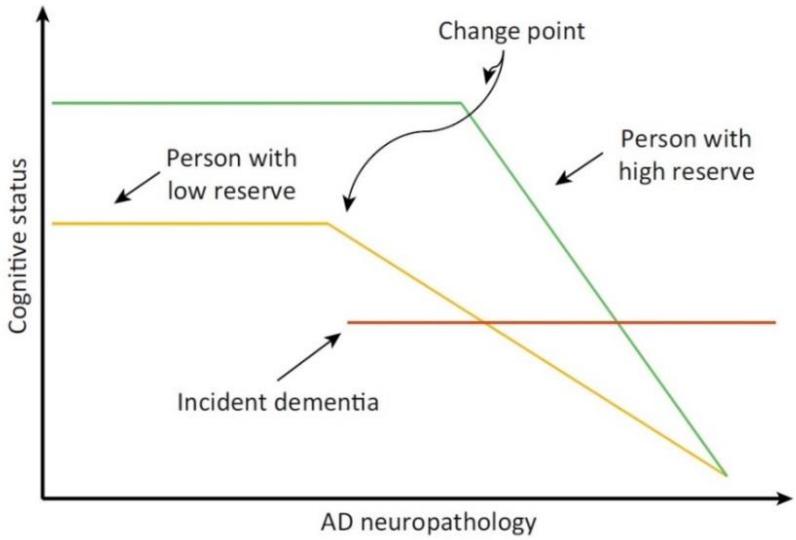

Figure 1.3: Impact of cognitive reserve on rate of decline in Alzheimer's disease

Note: Reproduced from Barulli and Stern (2013). Theoretical illustration of the mediating effect of CR on the relationship between AD pathology and cognitive decline. AD pathology (represented on the X axis) begins to accumulate many years before any changes in cognitive function are observed. The CR model assumes that AD pathology accumulates at the same rate in individuals with high and low CR, but that individuals with higher CR can tolerate a greater degree of this neuropathology before exhibiting any decline in cognitive function, resulting in a later "change point" for the beginning of cognitive decline among patients in this group (Stern, 2012). It follows that high CR individuals will have accumulated a greater degree of neuropathology at the point where their cognitive symptoms are sufficiently severe to meet clinical diagnostic criteria for AD. At any level of cognitive performance, AD pathology will be more severe among the high CR group (Stern, Alexander, Prohovnik, & Mayeux, 1992). A more rapid decline is therefore observed in high CR individuals after the "change point" when decline begins, and after dementia diagnosis (Hall et al., 2007; Stern, Albert, Tang, & Tsai, 1999)

CR implies a pathological threshold for clinical expression that is not fixed, and varies across individuals; more flexible and efficient management of available BR raises this threshold among individuals with higher CR (Henderson, 2014; Stern, 2012). This is supported by findings from the Nun Study, demonstrating that smaller head

circumference (i.e. lower BR) was associated with greater risk of AD in the sample as a whole, but not for individuals with more years of education (i.e. higher CR) (Mortimer et al., 2003). In progressive neurodegenerative disorders such as AD, this raised pathological threshold for clinical symptoms will delay diagnosis to a later stage of the disease process, and may explain repeated observations of a more rapid decline in cognitive function and progression to death after diagnosis for individuals with greater educational and occupational attainment (see Figure 1.3) (Stern, 2012). This phenomenon cannot be easily understood under the BR model, which would propose a similar rate of decline for all individuals once they have reached the threshold for clinical diagnosis (Tucker & Stern, 2011).

1.3.3 Brain maintenance

While some individuals appear better equipped to cope with neuropathology through both structural attributes (i.e. BR) and functional differences in the processing of tasks (i.e. CR), it is important to also acknowledge that the absence or minimisation of neural change itself may be an important determinant of successful cognitive ageing (Nyberg et al., 2012). Nyberg et al (2012) propose the concept of brain maintenance (BM), based on evidence for considerable heterogeneity not only in the magnitude of cognitive decline associated with ageing, but also in the degree of senescent structural, functional, and neurochemical brain changes observed among older adults. Proponents of BM argue that postponement or avoidance of neural changes associated with ageing plays a key role in preservation of cognitive function in late life (Nyberg et al., 2012). BM is therefore proposed as a complementary construct to earlier models of brain and cognitive reserve, and attempts to explain the conditions that allow individuals to more successfully evade, rather than tolerate or adapt to, reductions in brain integrity (Barulli & Stern, 2013). This model postulates that both genetic factors and favourable life experiences contribute to BM, and may exert their influence via avoidance or reduced risk of negative influences on brain integrity (such as cerebrovascular conditions or occupational exposure to toxins), but also by directly promoting positive brain plasticity (Lövdén et al., 2010; Nyberg et al., 2012).

Neuroimaging studies have demonstrated considerable variability in the degree to which older adults' structural and functional brain integrity deviates from that of young adults; and have found that older participants' cognitive performance is inversely

related to the magnitude of these age-related changes in brain integrity (Nyberg et al., 2012). In studies comparing older adults to younger controls, age-related reductions in several markers of brain integrity, including connectivity between dopamine pathways (Rieckmann et al., 2011) and patterns of functional recruitment in response to increased task demand (Nagel et al., 2009, 2011), were evident at a group level, but participants within the older groups varied considerably in the extent of brain changes they exhibited. Higher levels of cognitive performance were observed among the older participants whose brain integrity showed the least deviation from that of younger controls (Nyberg et al., 2012; Rieckmann et al., 2011). These findings support the notion that some older adults do not experience significant brain changes with age, and that maintenance of a youthful brain is an important contributor to the preservation of cognitive function in later life (Nyberg et al., 2012). However, the BM model cannot account for variability in the level of maintained function when neuropathology is present, or for evidence that CR proxies can operate in a compensatory rather than neuroprotective manner (Barulli & Stern, 2013).

1.3.4 Neurocognitive scaffolding

The concept of neurocognitive scaffolding forms part of the wider Scaffolding Theory of Ageing and Cognition (STAC), originally published by Park and Reuter-Lorenz (2009) and subsequently extended in the STAC-revised model (STACr) (Reuter-Lorenz & Park, 2014). The revised theory incorporates a life-course perspective, proposing that structural and functional brain integrity are determined by biological ageing along with a complex set of life-course influences that either enhance, preserve, or deplete neural resources; these influences also affect our ability to engage in a process of "neurocognitive scaffolding" as an attempt to maintain homeostasis in cognitive function when increased demands are placed on our available neural resources (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014). There are many conceptual similarities between neurocognitive scaffolding and CR. Neurocognitive scaffolding is described as a process of functional reorganisation that involves recruitment of alternative or additional neural circuitry as "scaffold" to support task performance when the efficiency of primary structures or networks involved in that task is reduced or compromised (Barulli & Stern, 2013; Park & Reuter-Lorenz, 2009). Neurocognitive scaffolding is not specific to ageing, but is a normal adaptive response that occurs across the lifespan in the face of both extrinsic challenges, such as unanticipated or

increased levels of task demand (for example during novel skill acquisition), and intrinsic challenges, such as metabolic or structural neural changes (for example due to ageing or neuropathology) (Park & Reuter-Lorenz, 2009). It is suggested that the effectiveness of scaffolding may vary between individuals, and that physical fitness, cognitive stimulation, and other environmental factors may be associated with greater ability to use neurocognitive scaffolding to support cognitive performance (Park & Reuter-Lorenz, 2009). The authors consider the PFC to be a primary location for scaffolding processes, and cite established models of age-related changes in brain activation (e.g. Hemispheric Asymmetry Reduction in Older Adults (HAROLD) (Cabeza, 2002); Posterior-Anterior Shift in Aging (PASA) (Dennis & Cabeza, 2008)) as examples of compensatory scaffolding. This scaffolding model suggests that recruitment of additional neural circuitry (for example increased bilateral activation or over-activation of frontal areas) supports basic cognitive processes that are challenged due to structural deterioration of existing neural circuitry (Park & Reuter-Lorenz, 2009; Scheller, Minkova, Leitner, & Kloppel, 2014).

1.3.5 Complementary concepts

The concepts of brain reserve, cognitive reserve, brain maintenance, and neurocognitive scaffolding can be considered as complementary rather than conflicting (Barulli & Stern, 2013). The proposed mechanisms underlying each concept are likely to overlap and interact to some degree. While BR was initially described as "passive" and considered to be fixed, more recent scientific developments demonstrating the structural plasticity of the human brain in response to enriching experiences (for a review see Lövdén, Wenger, Mårtensson, Lindenberger, and Bäckman (2013)) have led researchers to acknowledge that the concepts of CR and BR may interact to a greater extent than originally conceived (Barulli & Stern, 2013; Stern, 2012). For example, intervention studies involving exposure to enriching experiences including aerobic exercise (e.g. Erickson et al., 2011) or intense language study (e.g. Mårtensson et al., 2012) report small but significant increases in hippocampal volume (in the range of 2-4%) and cortical thickness (2-5%) among the experimental group, with no such effects among controls (Lövdén et al., 2013). BR and CR may therefore make both independent and synergistic contributions to maintenance of cognitive function in the face of pathology (Steffener & Stern, 2012; Tucker & Stern, 2011). BR, CR and neurocognitive scaffolding (NS) all fit within the wider theory of plasticity –

cognitively stimulating activities across the lifespan foster development of functional (CR, NS) and structural (BR, NS) plasticity that supports clinical resistance to pathologic lesions (Petrosini et al., 2009). The scaffolding model bears many similarities to CR, and it could be argued that neurocognitive scaffolding is essentially analogous to the neural compensation aspect of CR proposed by Stern (2009). These similarities are acknowledged by the authors of the STAC theory, who claim that the concepts are distinct because neural compensation in the CR model is a process specific to old age, whereas neurocognitive scaffolding is considered to be an adaptive response to challenge across the lifespan (Park & Reuter-Lorenz, 2009). However, as noted by Barulli and Stern (2013), CR is related to enriching experiences throughout life and has been shown to operate in response to a range of neural challenges and forms of brain damage. The CR and scaffolding models therefore both incorporate compensatory activity across the lifespan, and share a number of conceptual features. There is some evidence to suggest that engagement in mentally stimulating activities is associated with a reduced rate of hippocampal atrophy during normal ageing (Valenzuela, Sachdev, Wen, Chen, & Brodaty, 2008). Lifelong cognitive stimulation has also been linked with less deposition of amyloid-beta, a pathological marker of AD (Jagust & Mormino, 2011). Therefore, while intellectually enriching exposures may impart CR that moderates the relationship between neuropathology and cognitive outcome, they may also have a direct neuroprotective effect on the brain and, as such, contribute to enhanced BM.

In summary, it is likely that successful cognitive ageing is determined by a complex range of genetic and environmental factors that influence the capacity, efficiency, and flexibility of our neural networks throughout life. Inter-individual variability in this capacity, efficiency, or flexibility of neural networks may account for lifelong variance in cognitive abilities. This variability may also influence the degree to which our brains are protected from deleterious changes associated with age or pathological disease (BM); and may also account for varying ability to cope with these deleterious changes should they occur (CR, BR, NS). Further research is required to understand the neuroprotective, neuroregenerative, neurotrophic, and compensatory mechanisms that underlie the influence of each concept on preservation of optimal function among older adults. General theories such as the STAC-r model provide a useful framework for generating hypotheses about how these various concepts may interact and contribute to

successful cognitive ageing; a great deal of empirical work is required to disentangle the positive and negative influences of genetic and environmental factors, and to determine whether the various concepts may be refined or combined to create a more coherent account of mechanisms that protect against age- and disease-related cognitive decline. This thesis aims to contribute to this literature by investigating the construct validity of CR, and by investigating relationships between factors hypothesised to contribute to CR and cognitive outcomes associated with normal, non-pathological ageing.

1.4 Intellectual enrichment and late-life cognitive function: evidence for cognitive reserve

Epidemiological studies investigating environmental factors associated with risk of dementia and AD provided the initial foundations upon which the CR concept was built (Jones et al., 2011; Petrosini et al., 2009). An early study by Stern et al. (1994) found that risk for incident dementia among participants with less than eight years of education was 2.2 times greater than those with higher education levels. In the same study, participants with low occupational attainment were found to have a similarly increased risk for dementia, and the highest risk was associated with a combination of both low educational and low occupational attainment (Stern et al., 1994). Comparable findings emerged in respect of leisure activities, with individuals classified as having high levels of activity participation found to have a 38% reduced risk of developing dementia (Scarmeas, Levy, Tang, Manly, & Stern, 2001). A large body of similar epidemiological findings have since emerged. In a meta-analysis of 22 cohort studies, the combined effects of education, occupation, IQ, and mental activities were found to be associated with a 46% reduction in risk of incident dementia (Valenzuela & Sachdev, 2006b).

Further epidemiological evidence for CR is derived from studies demonstrating more rapid cognitive decline and progression to death after AD diagnosis in individuals with higher levels of education and occupational attainment, supporting the assumption that these individuals are at a more advanced pathological disease stage when they reach the level of cognitive impairment required for diagnosis (e.g. Stern et al., 1999; Stern et al., 1995). AD patients who engaged in a greater number of leisure activities prior to

dementia onset were shown to experience a more rapid decline in cognitive function following diagnosis (Helzner, Scarmeas, Cosentino, Portet, & Stern, 2007).

In addition to this epidemiological evidence, advances in neuroimaging techniques and identification of pathological markers of AD have allowed researchers to investigate the moderating effects of CR proxies in relationships between pathology and cognitive function. A number of studies employing measures of resting regional cerebral blood flow (rCBF) as a surrogate for AD pathology in participants matched for cognitive performance (i.e. clinical severity) have found that higher educational and occupational attainment (i.e. higher CR) was associated with greater decreases in rCBF (indicating more advanced AD pathology) (e.g. Stern et al., 1992; Stern et al., 1995). Similar associations have been shown for mentally stimulating activity, suggesting that this proxy for CR moderated the relationship between AD pathology (rCBF) and neuropsychological performance (Scarmeas et al., 2003).

While initial evidence for CR was primarily derived from studies of AD and dementia, the reserve concept can be applied to any situation involving a balance between neural change and a person's current level of functioning (Stern, 2007). CR has since been investigated in a range of clinical conditions, and has also been studied in relation to cognitive changes associated with normal, non-pathological ageing.

A large number of epidemiological studies have demonstrated a positive relationship between CR and level of cognitive function in late life. Cohort studies of generally healthy, normally ageing older adults have found that, after controlling for other socioeconomic and demographic variables, higher levels of cognitive performance were exhibited by participants with higher educational attainment (e.g. Le Carret et al., 2003), greater complexity of occupation (e.g. Correa-Ribeiro, Lopes, & Lourenco, 2013), and more frequent of engagement in mentally stimulating activities (e.g. Wilson et al., 2005). A recent meta-analysis of 135 cross-sectional studies found modest positive associations between CR (measured by education level, occupational status and participation in cognitively stimulating activities) and late-life cognitive function in several domains, including memory, executive function, visuospatial ability, and language (Opdebeeck, Martyr, & Clare, 2015).

There is relatively consistent evidence for a relationship between CR and *level* of cognitive function in old age, but findings related to the effects of CR on age-related *change* in cognitive function are less clear. Several longitudinal studies have demonstrated an inverse relationship between CR and rate of age-related cognitive decline (e.g. Hultsch, Hertzog, Small, & Dixon, 1999; Marioni et al., 2012; Wilson et al., 2013), but other studies have failed to replicate this association (e.g. Gonzalez, Tarraf, Bowen, Johnson-Jennings, & Fisher, 2013; Tucker-Drob, Johnson, & Jones, 2009; Van Gerven, Willemien, & Jolles, 2007).

Studies investigating the potential moderating role of CR in relationships between age-related brain changes such as WMH, and cognitive function, have also produced mixed findings to date. In a study of 141 community-dwelling older adults, Nebes et al. (2006) found a significant effect for the interaction between education and total WMH volume on processing speed, such that older adults with low education (CR) displayed greater decrements in processing speed as WMH severity increased, compared to those in the highly educated group. Brickman et al. (2006) demonstrated a similar moderating role for two CR indicators (education and occupation) in the relationship between WMH and cognitive performance in a sample of 704 dementia-free older adults. However, a similar study by Christensen et al. (2009) found no significant effects of brain atrophy, WMH severity, or interactions between education and atrophy/WMH on rate of cognitive decline over four years. Another study using bilingualism as an indicator of CR found that when matched for level of cognitive function, bilingual older adults had greater declines in white matter integrity than their monolingual counterparts, suggesting that bilinguals were better able to tolerate age-related neuropathology (B. T. Gold, Johnson, & Powell, 2013). In a structural MRI study, smaller hippocampal volume was related to lower episodic memory performance in midlife, but only for individuals with low CR, indexed by IQ (Vuoksimaa et al., 2013). Rentz et al. (2010) found evidence of amyloid deposition among clinically normal older adults using PiB PET imaging, but the relationship between amyloid deposition and cognitive performance was significantly modified by CR, with a systematically weaker association between pathology and performance in the high CR group.

1.5 Challenges associated with investigating cognitive reserve

The concept of CR provides a useful framework for exploring the influence of intellectually enriching exposures on risk for cognitive impairment, but it is not without its limitations. Conceptual and methodological difficulties have been highlighted by several authors, who note that inconsistent measurement of CR limits comparability of study findings and raises concerns about construct validity (Harrison et al., 2015; Jones et al., 2011; Satz et al., 2011). Since CR is a hypothetical construct, it cannot be measured directly, and it is instead typically quantified using proxy indicator variables that reflect innate abilities and intellectually enriching exposures hypothesised to develop CR across the lifespan (Harrison et al., 2015). However, a wide range of variables have been investigated as proxies for CR, either in isolation or in various combinations, and these inconsistencies in definition and measurement of the construct may limit the conclusions that can be drawn from empirical findings claiming to support the CR hypothesis (Jones et al., 2011). Furthermore, it has been noted that any single indicator used to measure CR may be linked to cognitive performance via alternative pathways, rather than via hypothesised CR mechanisms (Jones et al., 2011).

One proposed solution to problems associated with inconsistent use of single proxy indicators is to use latent variable modelling techniques to create multiple-indicator models of CR that combine several proxy measures (Jones et al., 2011; Satz et al., 2011). The theoretical rationale for using such multiple-indicator models is clear. Given that commonly used proxy indicators reflect exposures proposed to contribute to CR at different points throughout one's life, they may modulate the active processes of CR in different ways (Foubert-Samier et al., 2012; Opdebeeck et al., 2015). Accumulating evidence for independent and synergistic contributions of various proxy indicators to CR (e.g. Dekhtyar et al., 2015; Richards & Sacker, 2003) provides empirical support for use of a combination of indicators to estimate the construct. Multiple-indicator measures may also reduce potential bias from non-reserve pathways between any CR indicator and cognitive function, since these alternative mechanisms may only be relevant for one or a subset of the indicators used (Jones et al., 2011; Watson & Joyce, 2015). Measures that combine indicators shown to independently contribute to CR may therefore provide a more accurate representation of reserve than could be obtained with any one indicator, and lead to greater understanding of the theoretical concept of CR

(Jones et al., 2011; Ward, Summers, Saunders, & Vickers, 2014). This thesis will employ a multiple-indicator approach to measurement of CR, using structural equation modelling techniques to test the construct validity of a model combining several CR proxy indicators, and to investigate the relationship of this latent CR construct to cognitive outcomes associated with normal, non-pathological ageing.

1.6 Implications of cognitive reserve for neuropsychological assessment

The cognitive manifestation of neurodegeneration is typically slow and progressive, and subtle cognitive changes associated with early pathological decline can be difficult to distinguish from normal age-related decline on neuropsychological measures, particularly in high-functioning individuals with high levels of CR (Knopman & Caselli, 2012; Rentz et al., 2007; Sperling et al., 2011). For individuals with high levels of premorbid function, performance on neuropsychological tests that represents a decline for them, relative to their previous ability, may continue to fall within the "normal range" for the population (Petersen, 2004; Stern, 2013). Researchers and clinicians must therefore give careful consideration to an individual's CR when interpreting their neuropsychological test performance in comparison to normative data. Subtle disease-related cognitive changes associated with early stages of neurodegeneration may be more difficult to detect among individuals with high levels of CR, because these deficits may be masked by their neuropsychological test performance relative to population norms (Sperling et al., 2011; Stern, 2013).

Several authors have suggested that measures focused on intra-individual differences in cognitive performance, rather than comparison with group norms, may be a more sensitive approach for the detection of subtle cognitive changes in high-performing older adults (Benke, 2011; Jacobson, Delis, Bondi, & Salmon, 2002). One potential approach is to identify distinct subgroups among elderly cohorts by defining asymmetric cognitive profiles based on dissociations between two abilities or domains (Jacobson, McEvoy, Dale, & Fennema-Notestine, 2009). Another suggested approach is to use IQ-adjusted norms to identify individuals whose neuropsychological test performance is within the normal range for the population, but would be considered impaired relative to their premorbid function (Rentz et al., 2004; Rentz et al., 2007). This thesis aims to test the utility of these two suggested methods for "'unmasking" the

effects of CR on neuropsychological test performance, by investigating whether these methods distinguish between normally ageing participants in terms of baseline cognitive performance, subjective memory ratings, or change in cognitive function over two years.

1.7 Research issues

A wide range of age-extrinsic factors, including but not limited to vascular conditions, drug and alcohol abuse, hypertension, blood pressure variability, endocrine fluctuations, diabetes mellitus, and mild sensory impairment have been associated with cognitive performance among older adults (K. J. Christensen, Moye, Armson, & Kern, 1992). The influence of these factors should therefore be considered, where possible, when interpreting empirical findings related to ageing and cognitive function. The exclusion criteria used for this thesis were carefully chosen to limit, in as far as possible, the impact of age-extrinsic factors known to affect cognitive performance.

Pathological neural changes associated with AD may begin to develop a decade or more before cognitive symptoms emerge (Sperling et al., 2011). The cognitive manifestation of this neurodegenerative pathology is typically slow and progressive, and at an early stage is difficult to distinguish from normal age-related decline on neuropsychological measures (Rentz et al., 2007; Sperling et al., 2011). This accumulation of pathology without clinical symptoms results in potential inadvertent inclusion of individuals with preclinical or prodromal AD in apparently normally ageing samples (Hedden & Gabrieli, 2004). Autopsy studies have identified AD pathology in a significant proportion of cognitively normal samples, with up to 12% having accumulated sufficient pathology to meet NIA-Reagan neuropathologic guidelines for intermediate likelihood of AD, and as many as 25% meeting CERAD pathologic criteria for possible AD (Schmitt et al., 2000). It is important to both interpret and present research findings attempting to describe normal, non-pathological cognitive ageing with the caveat that these studies potentially include participants with early pathological decline caused by undiagnosed neurodegenerative disease (Deary et al., 2009). That caveat applies to this thesis, which focuses on cognitive changes associated with normal ageing as opposed to pathological declines associated with neurodegenerative conditions.

1.8 Thesis outline

This thesis aims to address issues related to measurement of CR, using structural equation modelling techniques to combine several proxy indicators in a multiple-indicator model of CR; to evaluate the construct validity of this model; and to investigate the relationship of this latent CR construct to cognitive performance and age-related declines in cognitive function among a cohort of normally ageing, generally healthy older adults. Methods that attempt to unmask the effects of CR on neuropsychological test performance, by focusing on intra-individual differences in cognitive performance, will also be investigated. Chapter 2 reviews the measurement of CR in studies investigating relationships between the construct and cognitive outcomes associated with normal, non-pathological ageing. Chapter 3 demonstrates the construct validity of a multiple-indicator, latent variable model of CR. In Chapter 4, this multiple-indicator model of CR is used to investigate cross-sectional relationships between CR and age-related cognitive performance, and to investigate whether CR moderates longitudinal relationships between age and cognitive decline over two years. Chapter 5 describes a study investigating use of cognitive asymmetry scores and IQ-adjusted norms as potential methods for unmasking the effects of CR on neuropsychological test performance. A general discussion of these findings, their interpretation, implications, and associated issues and limitations is presented in Chapter 6.

Chapter 2: Proxy indicators of cognitive reserve in studies of normally ageing populations: a systematic review

2.1 Introduction

Cognitive reserve (CR) is a hypothetical construct, and therefore cannot be measured directly (Stern, 2012; Ward et al., 2014). Instead, a set of variables that reflect innate differences in neural efficiency and processing (i.e. intelligence), and exposure to intellectually enriching experiences across the lifespan (e.g. education, complex occupations, mentally stimulating leisure activities) are typically used as proxy indicator measures (Harrison et al., 2015; Ward et al., 2014). Education is the most commonly used proxy for CR, perhaps because it is relatively easy to measure and quantify (Farias et al., 2012). Other proxy indicators of CR include occupational complexity (Correa-Ribeiro et al., 2013) or attainment (Stern et al., 1994); participation in mentally stimulating activities (Wilson et al., 2013); leisure activities in general (Scarmeas et al., 2001); literacy (Manly, Jacobs, Touradji, Small, & Stern, 2002; Manly, Touradji, Tang, & Stern, 2003); vocabulary or reading-based estimates of premorbid function (Sole-Padulles et al., 2009; Vemuri et al., 2011); social engagement (Bennett, Schneider, Tang, Arnold, & Wilson, 2006); and bilingualism (Craik, Bialystok, & Freedman, 2010). A number of authors have criticised this proxy indicator approach, stating that inconsistency and heterogeneity in the indicators used to represent CR limits comparability of study findings and raises concerns about construct validity (Harrison et al., 2015; Jones et al., 2011; Satz et al., 2011). Furthermore, as noted in Chapter 1, any single indicator used to measure CR may be linked to cognitive function via alternative pathways, rather than via hypothesised reserve mechanisms (Jones et al., 2011). For example, education and occupation, commonly used as CR indicators, are also key indicators of socioeconomic status (SES) (Adler & Newman, 2002; Jones et al., 2011). SES is proposed to affect health-related outcomes through a range of mechanisms including access to information and resources to promote health, exposure to toxins and environmental hazards, healthcare quality and utilisation, engagement in health behaviours, and ability to manage chronic conditions (Adler & Newman, 2002; Link & Phelan, 1995). Therefore, the influence of these hypothesised CR indicators on cognitive outcomes may instead be explained, at least in part, by SES-related mechanisms (Jones et al., 2011). Similarly, low levels of education are

associated with lifestyle choices that increase risk of high blood pressure and type 2 diabetes, which in turn increase risk for cerebrovascular disease and dementia (Mangialasche et al., 2012; Watson & Joyce, 2015). Therefore, empirical findings of an increased risk of dementia among those with low levels of education that are attributed to the effects of CR may in fact be mediated by these other risk factors (Watson & Joyce, 2015).

It is also important to note that each of the variables commonly used as proxy indicators of the construct are thought to make independent and synergistic contributions to CR across the lifespan (Stern, 2009). An important prospective study found that childhood intelligence, educational attainment, and adult occupation each separately influenced cognitive ability in midlife (measured by the National Adult Reading Test [NART]); this showed that CR is not fixed, but rather is determined at any one time point by a combination of intellectually enriching exposures (Richards & Sacker, 2003). Therefore, the use of any single proxy indicator as a measure of CR may not adequately reflect its theoretical conceptualisation as a dynamic construct influenced by a range of experiences across the lifespan (Pettigrew et al., 2013).

A number of approaches have been proposed to address the problems associated with single indicator proxy measures of CR. One potential solution is the use of latent variable analytic techniques to combine several proxy indicators in a multiple-indicator model of CR (Jones et al., 2011; Lojo-Seoane, Facal, Guardia-Olmos, & Juncos-Rabadán, 2014), an approach that will be discussed in detail in Chapter 3. A second approach has been the development of a number of standardised scales or questionnaires to measure CR, containing items relating to several common proxy indicators. The most widely cited of these instruments is the Lifetime of Experiences Questionnaire (LEQ), developed and validated by Valenzuela and Sachdev (2007), which consists of 42 questions about frequency and intensity of participation in activities related to education, complex occupations, and cognitively-stimulating leisure pursuits across three different life stages. Rami et al (2011) developed an 8-item, Spanish-language, Cognitive Reserve Questionnaire (CRQ) containing items related to education, occupation, and cognitively stimulating leisure activities, which has been used to measure CR in a number of subsequent studies (Arenaza-Urquijo et al., 2013; Kehoe et al., 2015; Molinuevo et al., 2014; Sobral, Pestana, & Paúl, 2014). The

Cognitive Reserve Scale (CRS) (Leon, García-García, & Roldan-Tapia, 2014; Leon, Garcia, & Roldan-Tapia, 2011), also developed in Spanish, provides a CR score based on participation in 24 cognitively stimulating activities at different points across the lifespan. The Cognitive Reserve Index questionnaire (CRIq) (Nucci, Mapelli, & Mondini, 2012) creates a composite CR score based on demographic data and sub-scores related to education, working activity, and leisure time. The CRIq was developed and validated in Italian (Nucci et al., 2012), and although English and French versions are available, to date it has been primarily used in studies of Italian-speaking populations (e.g. Giordano et al., 2012; Puccioni & Vallesi, 2012b). The Premorbid Cognitive Abilities Scale (PCAS) is an informant questionnaire for estimating premorbid ability, containing items addressing education, principal lifetime occupation, reading, writing, calculation, and technology use, which the authors suggest may also serve to provide an estimate of CR (Apolinario et al., 2013). These scales, although not yet extensively used, may be useful in standardising the measurement of CR across studies to aid comparability of results.

Other authors have suggested a move away from the use of proxy indicators altogether, and have proposed alternative measures of CR. Reed and colleagues (2010) proposed a novel measure based on decomposition of cognitive function scores, defining CR as the variance in episodic memory not accounted for by magnetic resonance imaging (MRI) measures of brain structure/pathology and demographic factors. Replication and extension of the original analyses in a large community-based sample provided further support for this measure of reserve (Zahodne et al., 2013). This innovative use of sophisticated imaging methodologies is a promising approach that may provide more direct operational measures of CR. This type of measure also avoids the problems of confounding associated with traditional CR proxies such as education or occupation, which may be related to risk for dementia through alternative, non-reserve pathways (Watson & Joyce, 2015). However, for the majority of research studies, practical and cost considerations are likely to preclude collection of imaging data required for these measures from anything more than small samples (Giogkaraki, Michaelides, & Constantinidou, 2013). Furthermore, while measurement of CR as the variance in cognitive performance not accounted for by pathology is intuitively appealing, the neuropathology of some neurodegenerative conditions is not yet fully understood, and well-validated pathologic markers may not be available (Jones et al., 2010). Therefore

the use of proxy indicators, while not a perfect method, is likely to remain prominent in the literature, at least for large scale and population-based studies.

This thesis focuses on a proxy indicator approach to measurement of CR, in order to evaluate the construct validity of a latent variable model combining multiple proxy indicators, and to investigate the relationship of this latent CR construct to cognitive function in a normally ageing population. This chapter presents a systematic review of the literature related to CR and cognitive function in normal ageing, which was conducted in order to inform the development of a multiple-indicator model of CR for Chapter 3. The primary purpose of this review was to establish what proxy indicators have been used to measure CR when investigating its effects on cognitive outcomes associated with normal ageing. The secondary aim was to review the current evidence for a relationship between CR, as measured by proxy indicators, and cognitive function during normal, non-pathological ageing.

Brain changes that occur during normal ageing are associated with a decline in cognitive function for some individuals, although individual trajectories of cognitive change among older adults are highly heterogeneous (Buckner, 2004). CR may play an important role in the relationship between normal, non-pathological ageing and cognitive function, by allowing some individuals to cope better with typical age-related brain changes (Stern, 2009); as a consequence, this review focuses on studies of generally healthy adults who are considered to be normally ageing.

2.2 Methods

2.2.1 Search strategy

In order to collate articles for this review, searches of the PubMed database were performed to identify studies investigating the influence of CR indicators on age-related cognitive outcomes. These searches were conducted using indexed search terms, which included "cognitive reserve" and "neural reserve" in combination with "education", "occupation", "intelligence", "IQ", "leisure", "socioeconomic status", "social network", "activity", "cognitive decline", "ageing", "aging" and "risk factors". The selection of search terms was informed by the aims and purpose of this review, and a reading of review papers and key literature related to CR and ageing. All searches were conducted during the period of December 2013 - January 2014. Searches were restricted to articles published within 10 years of the search date (i.e. articles published after January 2004). Database searches were supplemented with reference lists in key review papers and journal articles, the author's own files, and searches on Google Scholar.

Articles were selected for inclusion in the review using a two-stage process. For the first stage, titles and abstracts were screened to exclude duplications and articles that did not meet inclusion criteria. Full texts of the remaining studies were then screened for eligibility. All search results were managed in an excel database which documented decisions regarding inclusion/exclusion, and the criteria used to determine exclusion of an article. All references and full text articles were managed using the EndNote database. A flowchart illustrating study selection process is provided in Figure 2.1 (page 35).

2.2.2 Selection criteria

A set of inclusion and exclusion criteria were developed in order to select papers to be reviewed. These criteria were informed by the review question, the aims of the study, and a reading of key review papers on the topic.

For the purposes of this review, only original studies, published in English-language articles within the past 10 years were included. Studies were included that examined the relationship between a proxy indicator (or multiple proxy indicators) of CR and cognitive outcomes associated with normal ageing in older (age > 50 years) adults. In

order to aid the selection process, a table detailing inclusion and exclusion criteria for this review was created as a reference point (see Table 2.1).

Articles were included that met the following criteria: (i) at least one independent variable was a proxy indicator of CR, or a variable combining several proxy indicators of CR; (ii) the population were normally ageing, and aged 50 and over; (iii) the sample were initially healthy and free from any health conditions that could significantly impact cognitive function; (iv) a cognitive outcome associated with normal, non-pathological ageing was measured. Articles were excluded if (i) no CR proxy indicator was included as an independent variable; (ii) the primary outcome was dementia, mild cognitive impairment (MCI) or Alzheimer's disease (AD); (iii) the population was not aged 50 and over; (iv) the sample included participants with dementia or cognitive impairment (including MCI) at baseline; (v) the sample included participants with clinical conditions that could significantly impact cognitive function; or (vi) the study investigated a non-cognitive outcome or a cognitive outcome not associated with normal, non-pathological ageing. Studies using both cross-sectional and longitudinal observational or quasi-experimental designs were included, and intervention studies or randomised controlled trials were excluded.

Since the aim of this chapter was to review studies investigating CR proxies in relation to outcomes associated with normal ageing, studies were excluded if they had a clinical population (e.g. AD patients), or studied outcomes associated with a clinical condition such as Alzheimer's disease, multiple sclerosis, Parkinson's disease etc. For studies that included a mixed population, including normally ageing and clinical groups (e.g. normal controls versus AD patients), papers were included that reported separate results for each group (i.e. results for population meeting the inclusion criteria could be extracted from the paper). Papers that included normal controls and patient groups, but investigated outcomes associated with the clinical condition, were not included.

For the purposes of this review, a "normally ageing population" was defined as adults aged 50 and over, without cognitive impairment at baseline, and free of clinical conditions that could significantly impact cognitive function. Papers investigating cognitive outcomes among a group of adults both within and outside of this age range (e.g. adults ranging from 18-80 years) were not included if the results were analysed for

the group as a whole. Studies that included younger participants as a separate group (e.g. young adult control group and an older adult group that met the inclusion criteria), and used comparisons between the groups to investigate age-associated cognitive outcomes, were included in the review.

Table 2.1: Study Selection Guidelines

INCLUDE IF:	EXCLUDE IF:
Language	
English language	Not in English
Publication date	
Within past 10 years	Not within past 10 years
Article type	
Original research study	Not original study (i.e. review, meta-analysis, comment, letter etc.)
Sample/Population	
- Normally ageing: dementia free, aged 50+ - Older adult and young control group – if separate results for old/young group; and older group meet other inclusion criteria - Normal ageing group along with clinical group (AD/dementia/MCI) – if results can be extracted for normal group	- Clinical population/condition (e.g. AD patients, Parkinson's, MS etc.) - Population not aged 50+ - Animal study - Non-normally ageing population
CR measure	
- CR proxy indicator, or multiple proxy indicators as independent variable	- Imaging measure
Outcome	
- Cognitive outcome measure associated with normal cognitive ageing - Cognitive performance/function among normally ageing older adults - Changes in cognition associated with normal ageing - Rate of age-related cognitive decline - Cognitive function/change associated with age-related brain changes	- Dementia/AD/MCI as primary outcome - Non-cognitive outcome measure (e.g. IADL, neuropathology) - Cognitive outcome associated with any dependent variable that is not normal ageing process – e.g. any condition/disease process (e.g. AD symptom progression in patient group) - Brain structure/function measured using neuroimaging
Neuroimaging Markers	
- Use of a neuroimaging marker to represent burden of age-related pathology, examined in correlation with a CR proxy indicator such as education to investigate a cognitive outcome	- Use of a neuroimaging marker as a proxy measure of brain or cognitive reserve - Use of neuroimaging markers of neurodegenerative pathology associated with clinical condition (e.g. AD) - Use of neuroimaging marker of pathology as primary outcome measure
Study design	
- Cross-sectional - Longitudinal - Case control - Observational studies - Prospective cohort studies - Retrospective cohort studies	- Intervention studies - RCTs

The primary outcomes of interest were any cognitive outcomes associated with normal ageing. Specifically, these included cognitive function or performance among older adults (without dementia); rate of age-related cognitive decline; and cognitive impairment associated with age-related brain changes. Studies investigating the relationship of CR to non-cognitive outcomes (e.g. IADL, motor function, neuropathology only) were excluded. Studies in which the primary outcome was brain structure or function measured using neuroimaging techniques were not included in this review.

Articles were included that investigated relationships between one of the specified outcomes and one proxy indicator or multiple indicators of CR. Indicators selected for inclusion in this review were variables related to complex mental activity across the lifespan that are commonly used as proxies for CR in the current literature, including education, occupation, literacy, vocabulary, IQ, multilingualism or bilingualism, and variables associated with leisure or cognitively stimulating activity participation.

Neuroimaging markers have served a dual purpose in the literature to date, having been used both as proxy measures for brain and cognitive reserve, and as a measure of neuropathology. Following the approach employed by Jones et al. (2010), studies that used a neuroimaging marker as a proxy measure of CR were excluded. Studies that examined a CR indicator (such as education) in correlation with an imaging measure, with the imaging measure being used as an indicator of age-related neuropathological burden, were included in this review, provided that these indicators were analysed in relation to a cognitive outcome.

2.2.3 Data extraction and analysis

The results of each study were assessed qualitatively, with key details from each article tabulated (see Table 2.3) to facilitate the review process. Data related to the study design, sample size, sampling method, participant characteristics, CR indicators, cognitive outcome measures, covariates, analytic method, and key findings were extracted and tabulated. Study findings are discussed with reference to the method used to measure CR, the characteristics of the sample studied, and the cognitive outcomes investigated. A meta-analysis was not attempted due to the wide range of CR indicators, cognitive tests, and statistical techniques adopted within the various studies.

2.3 Results

2.3.1 Included studies

Initial searches of the PubMed database yielded 801 articles, with an additional 16 articles identified through supplementary searches of reference lists of review papers, the author's own files, and Google Scholar. Four-hundred and seven records were duplicated between searches, resulting in a total of 410 unique publications to be screened. Upon initial screening of titles and abstracts, 87 review articles were identified and removed, leaving 324 original articles to be considered for inclusion. Titles and abstracts were screened for articles that did not meet the inclusion criteria, and a further 244 papers were excluded on this basis. The full texts of the remaining 79 articles were then screened for eligibility (see Study Selection Flowchart – Figure 2.1). A total of 35 articles were deemed to meet the inclusion criteria and retained for this review. Summary data and characteristics of the included studies are detailed in Table 2.3 (page 45). Excluded studies tables are provided in Appendix A.

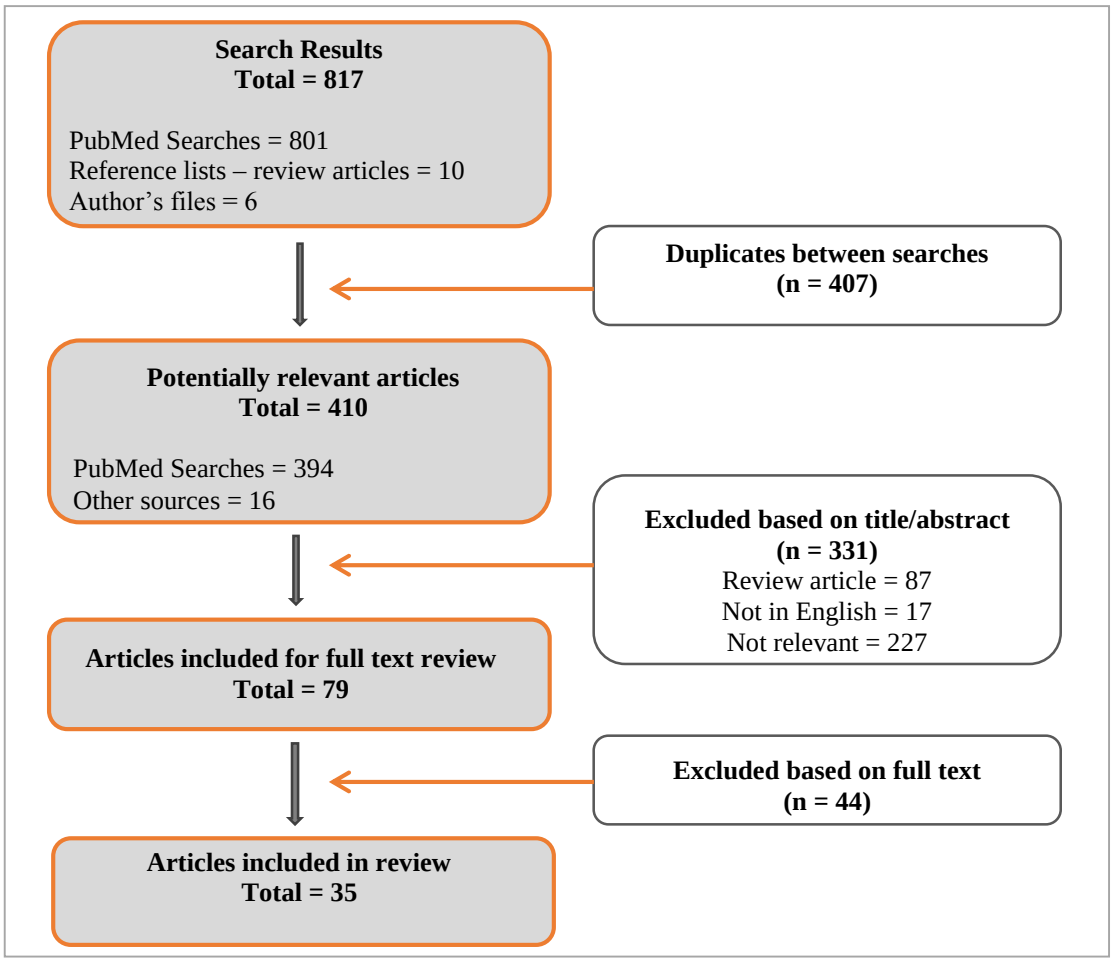

Figure 2.1: Study Selection Flowchart

2.3.2 Proxy indicators used to measure cognitive reserve

The proxy measures used to index CR, summarised in Table 2.2, varied widely across the articles included in this review. Of the 35 articles reviewed, 18 studies used a single proxy indicator to measure CR. The most commonly used single proxy indicator was education, which was investigated in seven studies (H. Christensen et al., 2009; Kaplan et al., 2009; Nebes et al., 2006; Ritchie, Bates, Der, Starr, & Deary, 2013; Van Gerven, Van Boxtel, Ausems, Bekers, & Jolles, 2012; Van Gerven et al., 2007; Zahodne et al., 2011). Three studies investigated measures of cognitively stimulating leisure activities (Gooding, Abner, Jicha, Kryscio, & Schmitt, 2014; Wilson et al., 2005; Wilson et al., 2013). The protective effect of multilingualism or bilingualism on late-life cognition was investigated in three studies (Crane et al., 2010; Kavé, Eyal, Shorek, & Cohen-Mansfield, 2008; Zahodne, Schofield, Farrell, Stern, & Manly, 2014). A measure of IQ or premorbid function was used as the sole indicator of CR in two studies (Fritsch, Larsen, & Smyth, 2007; Vuoksimaa et al., 2013). The final three studies with a single proxy indicator of CR used measures of occupation (Correa-Ribeiro et al., 2013), literacy (Manly, Schupf, Tang, & Stern, 2005), and SES (based on education and occupation) (Czernochowski, Fabiani, & Friedman, 2008) respectively.

A further eight of the reviewed articles used several proxy indicators of CR, but considered them in parallel rather than in combination, reporting separate results for the relationship between each indicator and the cognitive outcome(s) of interest. Education was again the most common proxy indicator among this group of articles, and was included as an indicator in seven studies. The effects of education on the outcome of interest were studied in parallel with reading-based measures of premorbid function (Barulli et al., 2013; Tucker-Drob et al., 2009), measures of occupation (Murray et al., 2011; Singh-Manoux et al., 2011; Staff, Murray, Deary, & Whalley, 2004), leisure activity (Murphy & O'Leary, 2010), and both occupation and leisure activity (Foubert-Samier et al., 2012). The final paper in this group investigated the effects of occupation and cognitively stimulating leisure activities as separate indicators of CR (Adam, Bonsang, Grotz, & Perelman, 2013).

Table 2.2: Proxy indicators used to measure CR

Proxy Indicator	N
Single indicator	**18**
Education	7
Occupation	1
IQ	2
Bilingualism/Multilingualism	3
Cognitively-stimulating activity	3
Literacy	1
SES	1
Multiple indicators in parallel	**8**
Education, reading (premorbid ability)	2
Education, occupation	3
Education, leisure activity	1
Education, occupation, leisure activity	1
Occupation, leisure activity	1
Published CR scale	**2**
CRIq	2
Composite score	**2**
Education, NART IQ, WAIS vocab	1
Education, occupation, social engagement	1
Latent variable	**5**
Education, vocabulary/reading	3
Education, SES	1
Boredom-proneness, loneliness, leisure, marital status	1

Notes: CRIq = Cognitive Reserve Index questionnaire; NART = National Adult Reading Test; WAIS – Wechsler Adult Intelligence Scale

A number of studies employed more sophisticated multiple-indicator approaches to measurement of CR, by investigating the combined effect of a number of proxy indicators on an age-related cognitive outcome. Two of the included studies (Puccioni & Vallesi, 2012a, 2012b) used a published CR scale – the CRIq (Nucci et al., 2012) – which contains items related to a number of proxy indicators and provides a formula for the calculation of a total CR score. Two studies calculated a composite CR score by combining scores for several proxy indicators. Marioni et al (2012) classified participants into high-, medium- or low-CR groups based on tertiles for a cognitive lifestyle score that combined information related to education, occupation and social engagement using a weighted formula. Gordon et al (2012) created a composite CR score by averaging z-scores for years of education, NART-IQ and the WAIS vocabulary subtest. Following the methodological approach discussed by Jones and colleagues (2011), the remaining five articles in this group used statistical modelling procedures to create a latent CR construct with a number of proxy measures as observed indicators. McGinnis (2012) used principal components analysis to create a CR factor

score that represented the shared variance between years of education and a vocabulary score. Using structural equation modelling, Brickman et al. (2011) defined CR as a latent construct with reading performance and years of education as reflective indicators; and a study by Giogkaraki et al (2013) defined CR as a multiple indicators, multiple causes (MIMIC) latent construct, with measures of vocabulary, reading performance, and years of education as observed indicators. In a study using latent growth curve analysis to test the relationship of CR to baseline cognitive function and rate of cognitive decline, CR was defined as an "adult intellectual achievement" latent construct, with years of education and two SES measures (household income and household wealth) as observed indicators (Gonzalez et al., 2013). A study by Conroy, Golden, Jeffares, O'Neill, and McGee (2010) examined the effects of two latent CR variables, using clustering around latent variables analysis to identify one cluster of variables they termed "cognitive reserve – personal" comprising social activity, leisure exercise, marital status, loneliness, and boredom proneness and a second cluster termed "cognitive reserve – sociodemographic" comprising education and rural/urban domicile.

In addition to the diverse range of variables used as proxy indicators of CR across studies, a further source of variability was observed in studies using the same proxy indicator variable (e.g. education), but different methods of measuring or operationalising that variable (e.g. total years of education, highest level of education, high versus low education etc.). Education was the most consistently used proxy indicator (included in 22 of the 35 reviewed studies), and it was also operationalised using a relatively consistent approach, with the majority of studies using years of full-time education as a continuous variable (15 of 22 studies) (e.g. Barulli et al., 2013; Kaplan et al., 2009; Ritchie et al., 2013; Staff et al., 2004). The remaining studies compared high- versus low-education groups, dichotomised based on years of full-time education (Zahodne et al., 2011) or highest level of education completed (Foubert-Samier et al., 2012; Nebes et al., 2006; Van Gerven et al., 2012; Van Gerven et al., 2007); or used a categorical variable to describe different levels of educational attainment (Murray et al., 2011; Singh-Manoux et al., 2011). Occupation variables used as CR indicators typically represented occupational status/attainment (e.g. unskilled, semi-skilled, administrative, professional, managerial etc.) (Foubert-Samier et al., 2012; Marioni et al., 2012; Murray et al., 2011; Puccioni & Vallesi, 2012a, 2012b; Singh-

Manoux et al., 2011; Staff et al., 2004), although occupational complexity (Correa-Ribeiro et al., 2013) and a variable representing current occupational activity/inactivity (Adam et al., 2013) were also considered.

Measures used to represent leisure/cognitively stimulating activities varied widely, and included measures related to one specific activity (musical training) (Gooding et al., 2014), simple counts of the number of activities (from a list or scale) that the participant engaged in currently or over a specified time frame (Adam et al., 2013; Foubert-Samier et al., 2012), intensity of engagement in social activity (Marioni et al., 2012), and scales designed to measure frequency of participation in a range of physical, social, and cognitive activities (Murphy & O'Leary, 2010; Puccioni & Vallesi, 2012a, 2012b; Wilson et al., 2005; Wilson et al., 2013). Studies using leisure/cognitive activity participation as a CR indicator included measures of both current activity (Murphy & O'Leary, 2010; Puccioni & Vallesi, 2012b; Wilson et al., 2013) and past or lifelong activity engagement (Wilson et al., 2005; Wilson et al., 2013). Reading ability/vocabulary was used as a CR indicator in six of the included studies, with a fairly consistent approach to measurement of this variable using standardised and well-validated word reading and vocabulary tests that mainly differed in terms of the language they were administered in.

The remaining CR indicators were used in relatively few of the included studies (bilingualism/multilingualism = 3 studies; IQ = 4 studies; SES = 2 studies), and it is therefore not considered meaningful to comment on the consistency of measures used for these variables within the current review.

2.3.3 Relationship of cognitive reserve to cognitive outcomes during normal, non-pathological ageing

2.3.3.1 CR and level of cognitive function

Twenty-one of the included studies investigated the relationship between CR and level of cognitive performance in old age, using either a global measure of cognition or measures of specific cognitive domains as outcome variables. The findings of all of these studies provide at least partial support for the CR hypothesis, based on evidence of a positive relationship between the CR indicator(s) and level of cognitive function

among older adults. Regardless of the proxy indicator used, higher CR was associated with superior performance on global measures of cognition measured either in a cross-sectional design, at baseline assessment in longitudinal studies (Adam et al., 2013; Conroy et al., 2010; Correa-Ribeiro et al., 2013; Gonzalez et al., 2013; Murray et al., 2011; Ritchie et al., 2013; Singh-Manoux et al., 2011), or at each of a number of assessment time points in a longitudinal study (Kavé et al., 2008). Greater levels of CR (as measured by various proxy indicators) were also found to be associated with better performance on measures of memory (Fritsch et al., 2007; Giogkaraki et al., 2013; Gooding et al., 2014; Kaplan et al., 2009; Manly et al., 2005; Murphy & O'Leary, 2010; Singh-Manoux et al., 2011; Staff et al., 2004; Vuoksimaa et al., 2013; Wilson et al., 2005; Zahodne et al., 2011; Zahodne et al., 2014); processing speed/executive function (Foubert-Samier et al., 2012; Giogkaraki et al., 2013; Gooding et al., 2014; Kaplan et al., 2009; Manly et al., 2005; Tucker-Drob et al., 2009; Wilson et al., 2005; Zahodne et al., 2011; Zahodne et al., 2014); visual-spatial ability (Kaplan et al., 2009; Wilson et al., 2005); reasoning (Singh-Manoux et al., 2011; Staff et al., 2004; Tucker-Drob et al., 2009); and language (Manly et al., 2005; Singh-Manoux et al., 2011; Zahodne et al., 2014). One study found that there was no significant relationship between CR (measured by education) and late-life processing speed, although a significant effect of CR was found for late-life IQ in the same sample (Ritchie et al., 2013).

While these results generally support a positive relationship between CR indicators and level of cognitive function in late life, the findings in some studies differed according to the indicator used to measure CR, the cognitive outcome studied, and participant characteristics. In a number of studies that conducted separate analyses for several proxy indicators of CR, the effects found differed by proxy indicator. For example, Murphy and O'Leary (2010) found a significant relationship between CR and memory scores when CR was measured using education, but no significant relationship when CR was measured using leisure activity. In another study, a significant positive effect on global cognition was found for occupational complexity with data and things, but not for complexity of work with people (Correa-Ribeiro et al., 2013). Murray et al. (2011) found that education, but not occupation, had a significant positive effect on general cognitive ability in late life using a model that controlled for childhood IQ and markers of age-related neuropathology. A study investigating the effects of education and

occupation found that occupation accounted for a significant proportion of variance in verbal reasoning, but not verbal memory; and found an inverse pattern of results when education was used to indicate CR, with a significant positive effect on verbal memory but not reasoning (Staff et al., 2004). One study also found effects that differed by gender, finding that higher adolescent IQ was associated with better memory performance and with increased benefit from use of cognitive support in a memory task for males only, with no significant effects for females (Fritsch et al., 2007).

In summary, the cross-sectional studies reviewed generally supported a positive relationship between CR and level of cognitive function in late life, although the strength of this relationship varied across cognitive domains, and also varied depending on the indicator used to measure CR.

2.3.3.2 Moderating effect of CR on relationship between age and performance on a particular cognitive task/paradigm

A second group of included studies used quasi-experimental designs to compare the performance of older adult and younger control groups on a cognitive task, in order to first determine whether the specific ability or task measured was negatively affected by ageing, and to then investigate whether CR influenced the relationship between age and this cognitive measure. Czernochowski et al (2008) compared low-CR older adults', high-CR older adults', and young controls' performance on a recency memory task, and found that the low-CR older group performed significantly worse than the other two groups, but the high-CR older group performed at a similar level to young controls; the authors suggested that this demonstrated a moderating role for CR in the negative relationship between age and recency memory. Another study using this design found that older adults had significantly lower scores for a strategy selection task, but that higher CR was associated with better strategy selection ability among the older group (Barulli et al., 2013). However, the effect of CR on strategy selection among the older adults in this study was significant only when NART-IQ was used as a CR indicator, and did not remain significant when education was used to index CR (Barulli et al., 2013). In two experimental studies (Puccioni & Vallesi, 2012a, 2012b) conflict resolution performance on a Stroop task was significantly lower for older adults compared to young controls, and higher CR was associated with better task performance among the older adult group, suggesting that those with higher CR showed

less of an age-related deficit in conflict resolution. Using a reading distraction task, older adults were found to have greater susceptibility to distraction by semantically-related text than young controls, and in analyses that controlled for age, a latent CR construct comprising education and vocabulary accounted for a significant proportion of the variance in distraction susceptibility scores (McGinnis, 2012). Using a repetition priming task that was shown to be negatively affected by age, a significant correlation between CR and task performance was found in older adults, but not in young controls, suggesting that high CR may be protective against age-associated reductions in priming (Gordon et al., 2012). Van Gerven et al (2007) found a significant negative age effect on switching focal attention using the N-back paradigm, but found no significant age group by education interaction effect, suggesting that education (as proxy for CR) had no significant influence on the negative relationship between age and task performance. Therefore, the findings of all but one of these studies suggest that CR may mitigate the negative impact of age on cognitive tasks for which older adults are found to perform at a significantly lower level than young controls.

2.3.3.3 CR and decline in cognitive function

Eleven of the included studies used longitudinal observational designs to investigate the relationship between CR and rate of cognitive decline, with follow-up intervals ranging from 3 to 23 years. Older adults classified into a low-CR group, according to literacy scores, experienced significantly steeper declines in memory, executive function, and language over mean 3.4 years of follow-up, compared to those in the high-CR group (Manly et al., 2005). Wilson et al (2013) found that higher CR (indicated by more frequent participation in cognitively stimulating activity) was associated with a slower rate of cognitive decline not attributable to pathologic burden. Marioni (2012) demonstrated a significant relationship between CR and change in cognitive function over 16 years, such that high CR was associated with decreased risk of moving from a non-impaired to slightly-impaired state based on cut-off scores for the Mini Mental State Examination (MMSE); high CR was also associated with a greater likelihood of recovering from a slightly-impaired to non-impaired cognitive state. In a longitudinal prospective cohort study, education was found to be inversely associated with decline in immediate and delayed recall over four years, but had no significant effect on decline in mental speed (H. Christensen et al., 2009). Singh-Manoux et al (2011) found a significant inverse relationship between occupational attainment and rate of decline in

reasoning, memory, executive function, and global cognition, but found no significant effects when education was used as a CR indicator. A number of the included studies failed to demonstrate any protective effects of CR against age-related decline, finding no significant relationship between the CR indicators measured and rate of decline in global cognitive function (Crane et al., 2010; Gonzalez et al., 2013) or in domains including memory, executive function, reasoning, and speed (Tucker-Drob et al., 2009; Van Gerven et al., 2012; Zahodne et al., 2011; Zahodne et al., 2014). In several of these studies, CR indicators were positively related to cognitive measures at baseline, but had no significant effect on change in cognitive measures over the follow-up period, leading the authors to suggest that CR may be related to level of cognitive function among older adults, but not to rate of cognitive decline associated with normal, non-pathological ageing (Gonzalez et al., 2013; Tucker-Drob et al., 2009; Zahodne et al., 2011; Zahodne et al., 2014). The longitudinal studies reviewed therefore provide further support for a positive relationship between CR and level of cognitive function in late life, but the evidence is less clear in terms of the relationship of CR to rate of age-related cognitive decline.

2.3.3.4 Moderating effect of CR on relationship between neuropathology and cognition

A number of studies provided a more direct test of the CR hypothesis by investigating whether CR moderated the relationship between measures of age-related neural damage, such as white matter hyper-intensities (WMH) or hippocampal atrophy/volume, and cognitive function. Brickman et al (2011) found a positive relationship between CR and WMH severity when cognitive function was controlled for, suggesting that for a given level of cognitive function, individuals with higher CR can tolerate a greater degree of age-related neuropathology. Nebes et al (2006) found a significant negative relationship between WMH severity and processing speed that was moderated by education, such that the less educated group showed a greater decrement in processing speed for increasing WMH severity than the highly educated group. The same authors found that age-associated decrements in working memory and inhibitory efficiency were not significantly associated with WMH severity, and therefore did not test whether CR moderated the relationship between WMH and performance on these measures (Nebes et al., 2006). Vuokismaa et al (2013) demonstrated a significant interaction effect for hippocampal volume and CR, such that the relationship between

hippocampal volume and verbal learning was significant only at low levels of CR, but these results were not replicated when free recall was used as the cognitive outcome measure. A study of a large sample of community-dwelling older adults failed to support a moderation hypothesis for CR, finding a significant negative relationship between education and decline in memory, but no significant effects for the interaction between education and either WMH or brain atrophy, although this was perhaps unsurprising since the authors also found no main effects of either of the neuropathological measures on cognitive decline (H. Christensen et al., 2009). Findings from a number of studies demonstrating a positive relationship between CR and cognitive function while controlling for neuropathology in analyses also provide some support for a moderating role of CR. Two studies found that CR (measured by education and occupation) was positively associated with late-life cognitive function in analyses that controlled for childhood ability and common, subclinical neuropathological burden associated with ageing (WMH and hippocampal atrophy) (Murray et al., 2011; Staff et al., 2004), although in one of these studies (Murray et al., 2011) significant effects were only found when education, but not occupation, was used as a CR indicator. In a clinicopathologic study by Wilson et al (2013), frequency of participation in cognitively stimulating activity accounted for a significant proportion of residual variance in cognitive decline not accounted for by burden of neuropathology along with age at death, sex, and years of education. The studies reviewed in this section therefore provide some support for a moderating role of CR in relationships between age-related neuropathology and cognitive function, although the strength and significance of these relationships again varied depending on the cognitive outcome and CR indicator studied.

Table 2.3: Characteristics of included studies

Ref: Author (Year)	Participants	Sample and sampling method	CR Indicator(s)	Cognitive outcome measures	Study design and Analysis	Summary of findings
Adam et al. (2013)	N: 25,152	SHARE cohort Nationally representative population-based samples aged 50+ across Europe	***Occupation; Leisure activity*** Occupation activity status (active, inactive 0-4 yrs., inactive 4-9 yrs., inactive 10-14 yrs., inactive >15 yrs., never active) Frequency of participation in non-professional activities during past month	Global measure of cognitive function summarising episodic memory (word list learning) and semantic fluency (animal fluency) (average of standardised scores)	Cross-sectional – analysis of wave 1 data from longitudinal study Stochastic frontier analysis	Used stochastic frontier analysis to create a 'frontier' corresponding to optimum expected cognitive performance for each individual given age and education level. Both professional and non-professional activities were positively associated with cognitive function. Higher activity participation associated with higher cognitive performance (closer to level expected for age and education).
Barulli et al. (2013)	N: 38 (18 older, 20 young) Young M 24.7 yrs. (SD3.6) 60% Female Older M 68.2 yrs. (SD4.5) 55.56% Female English-speaking; normal/corrected-to-normal vision; free from dementia and current psychiatric disorder	Convenience sample recruited from existing participant pools	***Education, IQ*** Years of education NART-IQ	Strategy selection during computational estimation task – mean % use of best strategy and RT	Cross-sectional, experimental General linear models	Significant effect of age group on accurate strategy selection – older group were significantly worse at using appropriate strategy than younger adults. Significant strategy type x age group x NART IQ interaction (F(1,36)=5.521; MSE=1143.438; P=.025) – CR moderated the relationship between age group and strategy use – older adults with high NART IQ (CR) selected best strategy more often than those with low NART IQ; no significant association between NART IQ and strategy selection in young group. No significant interaction found for education.
Brickman et al. (2011)	N: 704 M 80.2 yrs. SD 5.56 67.05% female Dementia free at MRI scan	Subset of WHICAP cohort with MRI data available	***CR Composite*** Latent variable combining years of education; WRAT-3 reading score	Latent constructs representing Episodic memory (SRT); Visual-spatial ability (BVRT recognition and matching; RDT,	Cross-sectional Structural equation modelling (path analysis)	Significant negative relationship between WMH and cognitive performance. Significant positive relationship between CR and cognitive performance. No significant direct relationship between CR and WMH.

		Overall cohort is stratified random sample of Medicare recipients aged 65+ in selected census tracts	Note also measured BR indicators (height, total cranial volume, cranial length)	Identities and Oddities); Executive function/speed (CTT); Language (modified BNT; letter and category fluency; WAIS-R similarities; Boston Diagnostic Aphasia Examination repetition and comprehension)		In models testing relationship between CR and WMH while controlling for cognitive function, higher CR associated with more severe WMH at any given level of cognitive function (suggesting that CR moderates the relationship between WMH and cognitive function) – strongest associations for executive function/speed and language.
H. Christensen et al. (2009)	N: 416 M: 62.6 yrs. (SD1.4) at baseline 48% female Community-dwelling	Subsample of 60+ cohort from PATH Through Life Project with MRI and longitudinal cognitive data available Random sample from electoral roles Canberra, Australia	***Education*** Years of education (estimated based on highest level attained) *Note:* Also measured intracranial volume as brain reserve indicator	Cognitive change scores (Follow up score – baseline score) for: Speed (SDMT); Immediate recall, delayed recall (CVLT)	Longitudinal prospective cohort study Follow up every 4 years – data presented for baseline and wave 1 follow-up Linear regression models	Inverse association between education and decline in immediate and delayed recall over 4 years. No significant effect of education on decline in mental speed. No association between brain atrophy or WMH severity and cognitive change scores. No significant interaction effect for education with WMH or atrophy (i.e. did not support moderation model of CR between age-related pathology and cognitive decline).
Conroy et al. (2010)	N: 802 M 74.2 yrs. (range 65-102) 53% female Community-dwelling, aged 65+	Randomly selected from electoral register	***CR composite*** Latent variable representing cognitive reserve using CLV analysis (social activity, marital status, loneliness, boredom proneness)	Global cognition (AMT) – categorised to possible cognitive impairment (>8) or low normal performance (8 or 9), normal (10)	Cross-sectional Clustering around latent variable (CLV) analysis	Low scores in CR cluster significantly associated with higher prevalence of low normal performance and possible cognitive impairment i.e. low CR associated with greater likelihood of low normal cognitive performance; and possible cognitive impairment.(Analyses controlled for depression and physical disability).
Correa-Ribeiro et al. (2013)	N: 624 67% female 35% aged 65-74; 48% aged 75-84; 17% aged ≥85	Stratified random sample (by age and gender), of clients from health care and social foundation in Rio de Janeiro aged 65+	***Occupation*** Categorised as low, intermediate or high complexity of primary lifetime occupation on 3 dimensions (data, people, things) – classified using	Global cognition (MMSE)	Cross-sectional, survey design Linear regression models	In linear regression models controlling for gender, age, family income, years of schooling, duration of occupation, greater occupational complexity with data and things associated with better cognitive performance.

	65+, client of health company for min 12 months		Dictionary of Occupational Titles			No significant association between complexity of work with people and cognitive performance.
Crane et al. (2010)	N: 2502 M: 76.6 yrs. (SD3.8) 100% male Dementia free at enrolment; complete cognitive score, CR exposure and covariate data available for at least one wave	Subsample from Honolulu-Asia Aging Study cohort (all participants who were cognitively normal in 1991 and had necessary data available) Second-generation Japanese men from Oahu island, Hawaii born between 1900-1919	***Bilingualism*** Use of spoken and written Japanese as second language (all spoke English) categorised into 3 groups: did not speak/write; spoke but did not write; spoke and wrote	Cognitive Abilities Screening Instrument	Longitudinal prospective cohort study Up to 4 assessments over 8 years Linear mixed effects models	Mixed effects models controlling for age, income, education, smoking, ApoE e4 allele and number of study visits. No significant relationship between use of spoken or written Japanese and rate of cognitive decline.
Czernochowski et al. (2008)	N: 30 (15 young; 15 older adult) *Young* M 21 yrs. range 18-26 *Older* M 73 yrs. range 65-82 100% Female Right handed; native English speakers; good physical/mental health; no CNS meds; Older adults dementia free, depression free, not limited ADL	Convenience sample (volunteers) Young adult and older adult group	***SES (Education, Occupation)*** Dichotomised into low vs high SES using SES score based on education and occupation	Recency and recognition memory (Fabiani & Friedman paradigm) – accuracy and RT	Cross-sectional, experimental Mixed design, repeated measures ANOVAs	No significant effect of SES on recognition memory – older low SES and older high SES groups performed at similar levels to young controls. Significant SES effect on recency memory – low SES older adults' recency memory accuracy significantly lower than high SES older adults ($p < .05$) and young controls ($p < .0001$). No significant differences in recency memory accuracy between high SES older adults and young controls. Therefore SES appears to moderate the relationship between age and recency memory performance.
Foubert-Samier et al. (2012)	N: 331 M 76.1 yrs. SD 3.9 57.4% female	Subset of Three Cities Bordeaux cohort with available data	***Education; Occupation; Leisure activities*** Dichotomised as high vs low education level (5	Verbal semantic fluency (IST)	Cross-sectional Multivariate linear regression analysis	In model adjusted for age, gender and ApoE status, there were significant positive associations for education, occupation, midlife activity and current activity with IST performance.

	Not institutionalised, aged 65+	(MRI, CR, cognitive) Overall sample randomly selected from electoral roles in three French cities	point categorical variable transformed); Dichotomised as high vs low occupational status (4 point categorical variable based on ISCO classification) Number of midlife and number of current activities participated in			Higher education associated with higher MRI brain volume (ICV). No significant relationship with brain volume for occupation or leisure activities.
Fritsch et al. (2007)	N: 269 M 75.6 yrs. (SD1.0) 53.9% female	Subset of CLASS cohort (all with adolescent IQ data from specific test; living independently) Overall cohort a population sample of all students who graduated from same high school in 1940s	***IQ*** Dichotomised as low (bottom 25% of distribution) vs high (top 75%) adolescent IQ (AIQ) measured using Otis Self-Administering Test of Mental Ability (from high school records)	Memory performance; benefit from cognitive support in memory task (word list learning task with increasing cognitive support)	Cross-sectional analysis of wave 2 data from longitudinal cohort study ANOVA, ANCOVA	Low AIQ associated with lower memory performance in men but not women. Significant gender x AIQ x cognitive support interaction – men with higher AIQ performed better at each level of cognitive support (effects non-significant for women). Therefore higher AIQ associated with increased benefit of cognitive support for men but not women.
Giogkaraki et al. (2013)	N: 483 M 73.33 yrs. (SD6.36) 41.61% female Native Greek speaker; MMSE>23; GDS ≤9; functional ADL; no history of stroke, head trauma, neurological or neurodegenerative disorder, hospitalisation for severe psychiatric/ emotional disorder.	Subsample from Neurocognitive Study on Aging – Cyprus meeting inclusion/ exclusion criteria for analysis Convenience sample of volunteers	***CR Composite*** Latent construct – years of education, receptive vocabulary (PPVT) and reading performance (pseudoword reading task) as indicators in MIMIC model	Latent factors representing: 1. Executive function (TMT A and B, SDMT, verbal fluency); Episodic memory (HVLT Trial 1, total immediate and delayed recall, Logical Memory immediate and delayed recall)	Cross-sectional Analysis of baseline data from longitudinal prospective cohort study Structural equation models (MIMIC)	Significant negative relationship between age and cognitive function. CR moderated the relationship between age and cognitive function. Higher CR associated with significantly lower negative effect of age on episodic memory and executive function.

Gonzalez et al (2013)	N: 8,833 M 73.9 yrs. SD0.1 59.3% female	Subsample of HRS aged 65+, non-institutionalised, excluded proxy interviews and lowest 5% cognitive test scores Nationally representative sample	***CR composite*** Latent construct (adult intellectual achievement) with years of education, adult household income, adults household wealth as indicators	Global cognitive function (abbreviated TICS score); rate of longitudinal change in TICS score	Longitudinal Up to 7 assessments over 14 yrs. Latent growth curve analyses	In analyses controlling for health status, age, sex and race, significant positive association between childhood SES and baseline cognitive function. Significant associations between adult achievement (years of education, wealth, income) and baseline cognitive status. No significant association between any CR indicator and rate of cognitive decline.
Gooding et al (2014)	N: 237 M 77.4 yrs. +/- 6.4 67.1% female Cognitively intact, aged 60+, no prevalent neurological, psychiatric or disabling medical disorder.	Convenience sample of participants already taking part in longitudinal study of cognition	***Musical training (cognitively stimulating activity)*** Classified as low, medium or high musical knowledge based on musical training survey	Longitudinal performance on category fluency (animal naming) and immediate recall (Logical Memory story A immediate recall)	Longitudinal, retrospective analysis Annual cognitive assessment with average length of follow-up since baseline 7.8 +/- 5.6 yrs. Linear mixed models	Linear mixed models controlling for age, time since baseline, years of education, sex, showed that participants with high musical knowledge scored significantly higher on episodic memory and category fluency measures than participants in the low musical knowledge group at each assessment point. Participants in the medium knowledge group did not differ significantly from either the low or high group on cognitive measures. Higher CR (musical training) associated with higher level of cognitive function in late-life.
Gordon et al. (2012)	N: 24 older adults, 24 young controls (in each of 3 experiments) *Expt. 1* Older Adult M 68.2 yrs. SD4.6, 58.3% female; Young M23.5 yrs. SD 2.5, 58.3% female *Expt. 2* Older Adult M 67.9 yrs. SD 6.5, 83.3% female; Young M	Convenience sample of volunteers recruited through advertisement and volunteer databases Normal/corrected-to-normal vision, free from neurological and psychiatric disease, older	***CR Composite*** Average of z-scores for NART-IQ, WAIS Vocabulary and years of education	Priming – accuracy and RT on repetition priming task (shown to decline with age)	Cross-sectional, experimental Multiple regression	Significant correlations between CR and performance on the priming task (RT but not accuracy) in older adult groups, but not in young controls. Findings suggest that high CR may protect against age-associated reductions in priming performance.

	19.6 yrs. SD1.2 45.83% female *Expt. 3* Older Adult M68.6 yrs. SD 7.5, 79.16% female; Young M18.8 yrs. SD 0.8, 62.5% female	adults dementia free				
Kaplan et al (2009)	N: 95 M 82.2 yrs. SD4.0 59.8% female MMSE>24; No history of sensory deficit, mobility-limiting conditions, mediation impairing motor function, unstable cardiovascular disease, pulmonary disease requiring oxygen, excessive alcohol intake, weight>250lb	Convenience sample of volunteers	***Education*** Years of education	RBANS; TMT; Stroop Task; California Computerised Assessment Package Factor analysis of battery to produce 3 domain scores representing: verbal memory, visual-spatial ability and processing speed/executive function	Cross-sectional Hierarchical multiple regression (Controlled for age and gender)	Education influenced cognitive functioning differentially within different cognitive domains Higher education associated with better cognitive performance in all 3 domains, although percentage variance explained by education was relatively small. Differential effect across domains suggests that CR does not affect all areas of cognitive functioning equally.
Kave et al (2008)	N: 814 ≥75 yrs. at baseline M 83 yrs. (SD5.4) 42% female	Cross Sectional and Longitudinal Aging Study Stratified random sample of older Israeli Jewish population	***Multilingualism*** Categorised as bilingual, trilingual or multilingual Number of languages spoken (self-report)	Katzman Cognitive Screening Test; MMSE	Longitudinal, observational Up to 3 assessments (incl. baseline) over period of 12 years ANCOVA; Hierarchical regression analysis	Significant difference between bilingual, trilingual and multilingual groups in performance on Katzman test at each assessment wave. These differences were also present for MMSE administered at wave 2. Higher number of languages spoken associated with higher level of cognitive performance at each assessment point. In regression analyses controlling for age, gender, education and other demographic variables number of languages was a significant predictor of performance on two cognitive-screening tests across all 3 interview waves.

Manly et al (2005)	N: 1002; Age at baseline: *High literacy group* M 75.5 yrs. SD6.2 *Low literacy group* M 75.9 yrs. SD5.9 68.5% Female Community-dwelling; No diagnosis of cognitive impairment, stroke, PD	Subsample of WHICAP cohort; Stratified random sample of Medicare recipients aged 65+ in selected census tracts	***Literacy/Reading Level*** Dichotomised as low vs high literacy based WRAT-3 Reading Test score (median split)	Factor scores representing 3 cognitive domains: 1. Memory (SRT subtests); 2. Language (BNT total and un-cued); 3. executive function (BVRT, matching; WAIS similarities; RDT; verbal fluency, comprehension; Identities oddities)	Longitudinal cohort study Mean 3.4 years (SD1.75) follow up assessments at 18 month intervals Generalised estimated equations	Significant main effect of literacy group – high literacy associated with higher cognitive performance (baseline) in memory (β 15.9 P .000), executive function (β 11.6 P .000) and language (β 1.2 P .000) Significant literacy x time interaction – low literacy (CR) group had steeper decline in memory (β 3.2; P 0.002), executive function (β 1.0; P 0.002) and language (β 0.2; P 0.000) scores
Marioni et al (2012)	N: 12,492 ≥65 at baseline Baseline M 75 yrs. 59.7% Female	Subsample (data from 5 of 6 centres) MRC-CFAS cohort Selected sample from Family Health Service Authority lists within specified geographical areas	***CR Composite*** Categorised as high, medium or low based on gender specific tertiles for cognitive lifestyle score calculated using years of education, occupational status at midlife, social engagement (based on self-report)	MMSE-based cognitive state: no cognitive impairment (27-30); slight cognitive impairment (23-26); moderate cognitive impairment (18-22); severe cognitive impairment (<18)	Longitudinal cohort study Up to 10 assessments over 16 year period Multi-state modelling	Significant relationship between cognitive lifestyle score and change in cognitive function over 16 years. Hazard ratios showed significant differences between high (upper tertile) and low (lower tertile) cognitive lifestyle groups: High cognitive lifestyle associated with decreased risk of moving from non-impaired to slightly impaired state (0.58, 95%CI 0.45, 0.74); and with greater chance of cognitive recovery from slightly impaired to non-impaired state (2.93 (1.35, 6.38). High cognitive lifestyle score associated with increased risk of mortality from severely impaired state (1.28 (1.12, 1.45).
McGinnis (2012)	N: 100 (34 young adult; 34 young-old; 32 old-old) Young adult M 21.0 yrs. (SD2.45) 58.82% female Young-old M 72.09 yrs.(SD3.10) 73.53% female Old-old	Convenience sample University students and older adults through advertising for volunteers	***Education, vocabulary*** Years of education (assigned based on highest qualification obtained); WAIS-R Vocabulary score	Reading Distraction Task (Connelly et al, 1991) – susceptibility to distraction calculated based on number of foil (distractor within text) responses vs target responses to questions following short stories	Cross-sectional, experimental PCA factor analysis; regression analysis	Susceptibility to distraction by semantically related text significantly increased with age. PCA analysis showed that a factor score including education and vocabulary (i.e. CR) accounted for a significant proportion of variance in distraction susceptibility scores. This effect remained significant in regression analyses that controlled for the effects of age. Higher CR was associated with lower age-related increase in distraction susceptibility.

	M 83.0 yrs. (SD2.97) 78.13% female WAIS-R>10					
Murphy et al (2010)	N: 99 M 60.89 yrs. (SD5.32) 65.7% female Community-dwelling; MMSE >23; no antidepressant or anxiolytic medications	Convenience sample Recruited through advertisements for volunteers	***Education, Leisure activity*** Years of education; High (≥3 hours daily) or low (<3 hours daily) participation in activities involving physical or cognitive effort	Immediate recall, delayed recall and savings scores from CERAD battery	Cross-sectional, survey Multiple regression	Education was the only significant unique predictor of delayed recall and savings scores Significant positive association between education level (CR) and memory performance; no significant associations between leisure activity (CR) and memory performance
Murray et al (2011)	N: 249 67-69 yrs. Community-dwelling, living independently; no dementia or known neurological disease; usual contraindications to MRI	Subsample of Aberdeen 1936 Birth Cohort who underwent MRI from 2003-5	***Education, Occupation*** Educational attainment 9 level categorical score (qualification and maximal occupational grade); Occupational status 9 level categorical score	General cognitive ability Estimated using PCA with raw scores from 4 cognitive tests (Ravens Progressive Matrices; AVLT; Uses of Common Objects test; DSST)	Cross-sectional analysis from longitudinal cohort study (Biannual cognitive testing) Structural equation modelling	Education had a significant positive effect on late-life cognitive function, in model allowing for the influence of childhood IQ and 2 most common subclinical brain pathological burdens associated with ageing (WMH and hippocampal atrophy). No significant effect for occupation on late-life cognitive function. WMH and hippocampal atrophy had a significant negative influence on late-life cognitive function. Positive contribution of education was greater than combined effect of WMH and hippocampal atrophy to late-life cognitive performance.
Nebes et al. (2006)	N: 141 M 73.2 yrs. (SD3.7) Community-dwelling; no stroke, AD, major head injury, PD, Huntington's disease, substance abuse or major depression in past 5 years. No	Convenience sample of community-dwelling volunteers	***Education*** Dichotomised as high (greater than college degree) vs low (less than college degree) education level	Processing speed (DSST, Number comparison task); Working memory (N-back task, listening span task); Inhibitory efficiency (Stroop)	Cross-sectional Multivariate multiple regressions with education as binary variable (to examine interaction between education and WMH)	Education (CR) moderated the relationship between WMH (i.e. age-related neuropathology) and processing speed: significant WMH X education interaction on processing speed, less educated group showed greater decrement in processing speed for increasing WMH severity than high educated group.

	psychoactive medications. No cognitive impairment – short screening test.					No significant relationship between WMH severity and working memory or inhibitory efficiency. No significant relationship between age and WMH severity (narrow age range).
Puccioni and Vallesi (2012b)	N: 45 (23 older adults; 22 young controls) Older M 71 yrs. (range 65-79) 52.17% female Young M 24 yrs. (Range 18-34) 45.45% female Right handed, native Italian speakers, normal/corrected vision; normal colour perception; MMSE ≥28; MoCA ≥26	Convenience sample of volunteers	***CR Composite*** CRIq (Nucci et al, 2011) – questionnaire with formula to calculate score combining education, occupation and leisure/social activity (CR measured in older adults only)	Colour-word Stroop task: Conflict resolution (RT difference congruent vs incongruent); conflict adaptation (effect of preceding trial congruency)	Cross-sectional, experimental Correlational analyses	Significant negative effect of age on Stroop performance and conflict resolution. Among older adults, mean RT, RT Stroop effect were negatively correlated with CR. Higher CR associated with less age-related deficit in conflict resolution.
Puccioni and Vallesi (2012a)	N: 17 older adults, 18 young controls (education and gender matched) Older M 73 yrs. (range 69-79) 47.06% female Young M 34 yrs. (range 18-34) 50% female Non-demented, right handed, native Italian speakers, normal	Convenience sample of volunteers	***CR Composite*** CRIq (Nucci et al, 2011) – questionnaire with formula to calculate score combining education, occupation and leisure/social activity (CR measured in older adults only)	Performance on spatial Stroop task – conflict resolution (RT difference congruent vs incongruent)	Cross-sectional, experimental ANCOVA, correlational analysis	Significant age effect on task performance – older adults performed worse than young controls Higher CR associated with reduced influence of incongruent trials. ANCOVA showed significant reduction of RT differences for incongruent sequences for high CR (i.e. better spatial conflict resolution). Higher CR associated with lower age-related deficit in spatial conflict resolution.

	colour perception, normal/corrected-to-normal vision					
Ritchie et al (2012)	*Sample 1* N: 550 M 79.06 yrs. (SD0.58) *Sample 2* N: 1078 M 69.49 yrs. (SD 0.83)	Lothian Birth Cohorts 1921 and 1936 Population sample – all individuals in geographic area who took part in Scottish Mental Survey 1932 (sample 1) and 1947 (sample 2)	***Education*** Years of education	Late-life IQ (Moray House Test administered in late life); Processing speed (simple and 4 choice reaction time and inspection time)	Longitudinal Retrospective analysis of childhood IQ scores in relation to late-life cognitive measures (2 assessment waves) Hierarchical multiple regression models	In regression models controlling for childhood IQ, age, sex and parental SES; years of education had a significant positive effect on late-life IQ; but no significant relationship was found between education and late-life processing speed Non-linear effect – years of education more strongly associated with late-life IQ for participants with lower childhood IQ
Singh-Manoux et al (2009)	N: 7454 M: 56 yrs. SD 6 at baseline 29.78% female	Whitehall II cohort Population study – all London based office staff in 20 civil service departments at study inception period (1985-88)	***Occupation; Education; height*** Categorised into high, intermediate or low occupation based on civil service grade; Categorised as high (university or more), intermediate (higher secondary school), low (lower secondary or below) education Height high, medium, low based on mean for sample	Reasoning (Alice Heim 4-I test); Short-term verbal memory (20 word immediate recall); Verbal fluency (phonemic and semantic fluency); Vocabulary (Mill Hill Vocabulary test); Global cognitive score – average of z-scores on all 5 cognitive measures	Longitudinal Up to 3 cognitive assessments over 10 yrs. ANOVA; Linear mixed models	Significant positive relationship between each CR indicator and baseline cognitive performance. Significant effect of time on cognitive function – evidence for decline in all functions except vocabulary over 10 years. No significant relationship between education or height and rate of cognitive decline. Higher occupation associated with greater rate of cognitive decline over 10 years.
Staff et al (2004)	N: 92 Age: 79 42.39% female MRI data available	Subsample of Aberdeen 1921 birth cohort study Random sample of participants invited for MRI	***Education, occupation*** Years of education; Highest ever occupational level attained classified into 9 level categorical variable	Reasoning (Raven's Progressive Matrices); memory (AVLT immediate and delayed recall)	Cross-sectional, observational ANCOVA	Using ANCOVAs that controlled for childhood cognitive ability (Moray House Test Scores aged 11), age-related brain burden (WMH) and sex, occupation accounted for significant proportion of variance in non-verbal reasoning, but not for verbal memory. Education accounted for significant proportion

						of variance in verbal memory, but not for non-verbal reasoning. CR indicators significantly contributed to variance in cognitive test scores in old age. CR modified relationship between WMH and cognitive performance – at fixed level of WMH and childhood ability, higher CR (education, occupation) associated with better cognitive performance
Tucker-Drob et al (2009)	N: 690 Range 65-89 yrs. 74% female Living independently; Good cognitive and functional status	No-contact control group in ACTIVE cognitive training RCT Randomly assigned to no-contact control from convenience sample of 2,832 participants	***Education, Vocabulary*** Years of education Ekstrom vocabulary measure (synonym selection) – standardised score	Standardised composite scores representing: 1. Reasoning (word series; letter series; letter sets) 2. Processing speed (three tasks from Field of View measure)	Longitudinal, observational Baseline, 12 week and 5 annual assessments Hierarchical regression (cross-sectional); latent curve growth modelling (longitudinal)	Education and vocabulary were related to level of cognitive performance, but was not associated with rates of cognitive decline over time (both before and after baseline education/vocabulary were controlled for)
Van Gerven et al (2012)	N: 571 M 62.3 yrs. (SD8.8) at baseline No chronic neurological pathology, mental retardation, major psychiatric disorder, chronic use of psychotropic drugs. Did not develop dementia over 12 year follow up (this subsample)	Subsample of Maastricht Aging study cohort (all aged 49+ at baseline with necessary data types available and who did not develop dementia over follow up) Stratified random sample	***Education*** Dichotomised as high (intermediate vocational or higher) vs low (primary /lower vocational) education level	Global cognitive function (MMSE); Interference control (Stroop Colour-Word Test); Set shifting ability (Concept Shifting Test); Speed (Letter-Digit Substitution Test); Immediate and delayed recall (Verbal Learning Test)	Longitudinal prospective cohort study Up to 5 assessments over 12 years (follow up at 3, 6, 9, 12 yrs.) Linear mixed models	In analyses controlling for ApoE status, age at baseline, sex, and self-perceived physical and mental health, there was no significant association between education and cognitive decline over 12 years.
Van Gerven et al (2007)	N: 84 (40 older, 44 young adult)	Convenience sample – community-	***Education***	Switching of focal attention during working memory task	Cross-sectional, experimental	Significant negative association between age and switching of focal attention – older group

	Older M 56.14 yrs. SD 3.43 Young M 25.01 yrs. SD 3.21 No cerebrovascular pathology, psychiatric disturbance, neurological disorder, renal dialysis, dyslexia, excessive alcohol use, psychoactive medications, clinically overt auditory/visual deficit	dwelling volunteers	High versus low education (classified based on 8 point categorical variable)	(N-back) – accuracy and RT	Repeated measures ANOVA	performed significantly worse than young controls. No significant interaction for education – CR (education) had no significant effect on age-related decline in switching focal attention.
Vuoksimaa et al (2013)	N: 494 M 55.67 yrs. SD2.62 at baseline 100% male	Subsample of Vietnam Era Twin Study of Aging with MRI and CR data available Representative sample of men who served in US military	***IQ*** General cognitive ability – scores on Armed Forces Qualification Test at average 20 yrs. Used as continuous measure and also low vs high groups	Verbal learning (CVLT-2 total immediate recall) Free recall (Short delay and long delay recall CVLT-2)	Longitudinal Linear mixed effect models	In models controlling for TICV, age, and ApoE e4 status, significant positive association between CR and verbal learning performance. No significant main effect of hippocampal volume on verbal learning. Significant CR x hippocampal volume interaction – positive relationship between hippocampal volume and verbal learning for low cognitive reserve only. Significant main effect of CR on episodic memory (free recall). No significant main effect of hippocampal volume on free recall. No significant interaction for CR x hippocampal volume on short-delay or long-delay free recall.
Wilson et al (2005)	N: 576 M 80.2 yrs. (SD7.6) 73.3% female Dementia free	Subsample of longitudinal cohort - Rush Memory & Aging Project Selected sample recruited from	***Cognitively stimulating activity*** Frequency of participation - Wilson et al 39-item cognitive activity scale (lifetime participation)	Composite scores representing 5 cognitive domains: 1.Episodic memory (immediate and delayed recall, word list recall, recognition)	Cross-sectional, observational Baseline data from longitudinal cohort study Linear regression models	Higher frequency of cognitive activity at any age associated with higher level of cognitive function in old age – associations with cognitive activity were stronger for current activity than for past activity

		residential facilities (retirement homes, communities, subsidised senior housing)		2. Semantic memory (BNT, verbal fluency, reading) 3. Working memory (Digit span forward and back, Digit ordering) 4. Perceptual speed (SDMT, Number Comparison, two indices from modified version of Stroop test) 5. Visuospatial ability (Benton Line Orientation, Raven Standard Progressive Matrices)		
Wilson et al (2013)	N: 294 ≥55 yrs. at baseline M 89.3 yrs. (SD5.9) (at baseline) 67.7% female Dementia free at baseline	Subsample from Rush Memory and Aging Project All participants with longitudinal cognitive data (at least 1 follow up) and neuropathologic data available	***Cognitively stimulating activity*** Frequency of participation in cognitive activities across lifespan - 37 item questionnaire	Global cognitive function (composite score – average of z-scores using baseline mean and SD for 19 cognitive tests)	Longitudinal cohort study (clinical-pathologic) Annual clinical evaluations and brain autopsy at death Mean follow up 5.8 yrs. (SD2.7) Mixed-effects models	Mixed effects models showed significant cognitive activity x time interactions – frequency of both early- and late-life cognitive activity accounted for significant proportion of residual variance in cognitive decline after controlling for neuropathologic burden, age at death, sex, years of education. More frequent cognitive activity (early and late life) associated with slower rate of cognitive decline not attributable to pathologic burden (i.e. non-pathological decline)
Zahodne et al (2013)	N: 1067 (637 monolingual; 430 bilingual) Monolingual M 75.66 yrs. SD5.79 72% female Bilingual M 74.78 yrs. SD5.66 64% female	Subsample of WHICAP – Hispanic, Spanish speaking participants Overall cohort random sample of community-dwelling	***Bilingualism*** 4 level categorical variable re English proficiency (second language) (‘not at all’, ‘not very well’, ‘well’ or ‘very well’)	Composite scores: average z-scores for tests in each domain, at each testing occasion: Episodic Memory (SRT); Language (modified BNT; Boston Diagnostic Aphasia	Longitudinal prospective cohort study Follow-up assessments at 18-24 mth. Intervals up to 23 yrs. Multilevel model for change	Performance in each cognitive domain shown to decline significantly over time. Greater level of bilingualism associated with better initial performance on all four cognitive composites. No significant relationship between degree of bilingualism and rate of cognitive decline.

	Did not meet criteria for dementia at initial study visit, Spanish speaking	Medicare recipients aged 65+ from selected census tracts		Examination repetition and comprehension) Executive functions (WAIS-R similarities subtest; Identities and oddities; letter fluency) Task switching (CTT) Speed (CTT)		
Zahodne et al (2011)	N: 1014 M 68.8 yrs. (SD6.8) 63.31% female Community-dwelling; without serious health condition	Two subsamples from Victoria Longitudinal Study Convenience sample of community-dwelling volunteers	***Education*** Dichotomised as low vs. high based on years of schooling (≤13 yrs. vs. ≥14 yrs.)	Composite scores: 1. Verbal processing speed (lexical decision, sentence verification) 2. Working memory (sentence construction, 2 span tests) 3. Verbal fluency (3 written fluency tests: controlled associates, opposites, figures of speech) 4. Verbal episodic memory (immediate recall from 2 word list learning and 2 story memory tasks)	Longitudinal sequential design Up to 5 follow up assessments over 12 years Unconditional and conditional growth models	After controlling for age at baseline and gender, higher education related to better performance in all cognitive domains. No significant association between education and change in any of the cognitive composites over 12 years Education (CR) did not moderate age-related cognitive decline.

ACTIVE = ; Advanced Cognitive Training for Independent and Vital Elderly; AD = Alzheimer's disease; ADL = activities of daily living; AIQ = adolescent IQ; AMT = Abbreviated Mental Test; AVLT = Auditory Verbal Learning Test; BNT = Boston Naming Test; BR = brain reserve; BVRT = Benton Visual Retention Test; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CLASS = Cleveland Longitudinal Aging Studies of Students; CLV = clustering around latent variables; CNS = central nervous system; CR = cognitive reserve; CRIq = Cognitive Reserve Index questionnaire; CTT = Colour Trails Test; CVLT = California Verbal Learning Test; DSST = Digit Symbol Substitution Test; GDS = Geriatric Depression Scale; HRS = Health and Retirement Study; HVLT = Hopkins Verbal Learning Test; ICV = intracranial volume; ISCO = International Standard Classification of Occupations; IST = Isaacs Set Test; MIMIC = multiple indicators multiple causes factor; MMSE = Mini Mental State Examination; MRC-CFAS = ; MRI = magnetic resonance imaging; NART-IQ= National Adult Reading Test estimated IQ; PCA = principal components analysis; PD = Parkinson's disease; PPVT = Peabody Picture Vocabulary Test; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; RDT = Rosen Drawing Test; RT = reaction time; SDMT = Symbol Digit Modalities Test; SES = socio-economic status; SHARE = Survey of Health, Aging and Retirement in Europe; SRT = Selective Reminding Test; TICS = Telephone Interview of Cognitive Status; TICV = total intracranial volume; TMT = Trail Making Test; WAIS = Wechsler Adult Intelligence Scale; WHICAP: Washington Heights/Hamilton Heights Inwood Columbia Aging Project; WMH = white matter hyper-intensities; WRAT-3 = Wide Range Achievement Test 3

2.4 Discussion

This systematic narrative review aimed to establish how CR has been measured using proxy indicators in studies of ageing and cognition among generally healthy older adults, and to investigate the relationship of CR, as measured by proxy indicators, with cognitive function during normal, non-pathological ageing. Considerable heterogeneity was observed in the methods used to measure CR across studies, which included use of a single proxy indicator variable, analysis of several proxy indicator variables separately, or a combination of multiple proxy indicators using various methods. Education was the most commonly used proxy indicator of CR, and was included in 22 of the 35 studies reviewed, either as the sole measure of CR or in combination with other indicators. Other commonly used proxy indicators included occupation (9 studies), leisure/cognitively stimulating activities (9 studies), and reading ability/literacy (6 studies). CR indicators that were less widely used included IQ (4 studies), multilingualism/bilingualism (3 studies), and socioeconomic status (2 studies). A final study used a data-driven approach to identify a cluster of variables including loneliness, boredom-proneness, marital status, and social engagement that loaded onto a latent construct that the authors termed CR, but it is unclear how this method of defining CR relates to wider literature on the topic. Each of the indicator variables have also been assessed or operationalised using different methods across studies, resulting in further heterogeneity in study designs, even among those using the same variable to index CR.

The evidence reviewed in this chapter largely supports a positive relationship between CR indicators and level of cognitive function in late life. The majority of studies investigating cross-sectional relationships between CR and cognitive function found a significant positive effect of CR indicators on cognition, using outcome measures of global cognitive function, memory, executive function, processing speed, reasoning, visual-spatial ability, and language. Seven quasi-experimental studies compared older adult and young control groups, and CR was found to moderate the negative relationship between age and performance on several cognitive tasks, although the effect of CR varied by indicator in one study, and no significant effect was found for CR in another study. The evidence from studies investigating whether CR might

mitigate age-related cognitive decline is less consistent, with a number of studies finding a significant inverse relationship between CR and rate of decline, but other studies failing to find any significant effects. Studies that included neuropathological markers of ageing, such as WMH, generally supported a moderating role for CR indicators, such that those with higher CR could tolerate a greater level of age-related brain changes for a given level of cognitive function; although findings differed across cognitive domains and one study failed to support this hypothesis. Contradictory evidence for the relationship of CR to rate of cognitive decline during normal ageing may be explained, at least in part, by heterogeneity in measures used to index CR, along with variance in study designs, statistical methodologies, and confounding variables controlled for in analyses. Further research using a more consistent approach to measurement of CR may help to clarify the nature of the relationship, if any, between CR and age-related cognitive decline.

The theoretical rationale for use of each of the proxy indicators as a measure of CR, on the basis that they might constitute a facet of reserve, is clearly documented. Education may directly influence neural processing by promoting synaptic growth and connections, positively impacts cognitive function and flexibility, and may be linked with the development of cognitive strategies and skills thought to underlie the protective effects of CR (Jones et al., 2011). Higher educational attainment may also lead to a chain of events (e.g. more complex occupation, higher SES that provides greater access to resources for leisure activity) that provide greater physical and mental stimulation across the lifespan (Meng & D'Arcy, 2012). Given that a simple count of years of formal education may not account for differences in the quality, nature, and content of education across cohorts, nationalities, and social groups (Opdebeeck et al., 2015), it has been suggested that reading tests designed to assess literacy or vocabulary may better reflect educational quality and may serve as a useful proxy for CR (Manly et al., 2005). Occupational activity represents an important source of mental stimulation across our adult lives, and may provide opportunities for regular social interaction, which is also thought to contribute to CR (Adam et al., 2013; Correa-Ribeiro et al., 2013). Cognitive leisure activities provide continuing intellectual engagement and may be particularly important in late life and after retirement, when the mental stimulation derived from occupational activity is no longer available. Engagement in cognitively stimulating activities may contribute to structural and functional neuroplasticity, which

has been shown to occur across the lifespan and may allow individuals to compensate for age-related brain changes and tolerate a greater degree of neuropathology without cognitive impairment (Wilson et al., 2005; Wilson et al., 2013). IQ, although not extensively used as a CR indicator in studies included in this review, represents innate ability thought to result from a combination of genetic and early-life environmental factors, explains a significant proportion of variance in late-life cognitive function, and has been suggested by some authors to be a closer reflection of the neural processes implied by the CR concept than other indicator variables (Murray et al., 2011; Watson & Joyce, 2015). Multilingualism or bilingualism may reflect either innate linguistic skills that might relate to the efficiency or capacity of neural processing, lifelong cognitive stimulation gained from the cognitive demands of using and switching between two or more languages, or a combination of both (Kavé et al., 2008). It is important to note that findings for a relationship between bilingualism/ multilingualism and late-life cognitive function are mixed, with several studies failing to demonstrate any significant effects. These contradictory findings may relate to methodological issues, such as inconsistency in how bilingualism/multilingualism is defined across studies. Potentially confounding factors related to, for example, the age of language acquisition, or the sociocultural circumstances surrounding bilingual development (i.e. circumstantial versus elective bilingualism), may also have contributed to the inconsistent pattern of findings in the current literature (for a review see Calvo, Garcia, Manoiliff and Ibanez, 2016).

However, there is less theoretical justification for use of any of these variables as a single proxy indicator of CR, since CR is hypothesised to be a fluid, dynamic construct that derives from a range of experiences and exposures across the lifespan (Pettigrew et al., 2013; Stern, 2009, 2012). Therefore, any one proxy measure may not provide the full picture or constitute an adequate measure of CR (Opdebeeck et al., 2015). Studies demonstrating an independent contribution of several CR indicators to cognitive function substantiate the need for measures of CR that combine a range of intellectually enriching experiences. For example, Kavé et al. (2008) found that number of languages spoken was a significant predictor of MMSE score after controlling for the effects of education (which also had a significant effect on the outcome), but found no significant effect for an interaction between education and number of languages spoken, suggesting that these two variables explain a unique proportion of variance in late-life cognitive

function. Multiple-indicator measures of CR that combine a number of proxy indicators are therefore considered preferable, and have become increasingly popular in more recent literature. Methods that quantify CR as a latent variable representing the shared variance between several common proxy indicators may be a useful approach, particularly for evaluating the construct validity of CR (Jones et al., 2011; Siedlecki et al., 2009), and latent variable measures of CR were employed in five of the studies included in this review. However, latent constructs used to date have not combined the full range of indicators that are used in the literature as single proxies for CR, or in parallel with other proxy indicators.

It is important to note a number of methodological limitations of this review. All articles were published in English, as it was not feasible from a practical perspective to include foreign-language papers, and this may have introduced a language bias. Given the heterogeneity in study designs, outcome measures, and indicators of CR used in the included literature, a meta-analysis was not attempted, and a narrative review approach was adopted. This approach was considered sufficient to meet the primary aim of this chapter in providing an overview of CR indicators used in recent literature related to cognitive function during normal, non-pathological ageing. However, we acknowledge that narrative reviews are subject to bias (Lyman & Kuderer, 2005), which may have been avoided had a meta-analysis been possible.

The findings of this review support the need for consensus on how best to define and measure CR (Harrison et al., 2015). Table 2.4 (page 63) summarises the key proxy measures of CR employed by studies included in this review, and highlights some key measurement issues associated with each approach. While the advantages of a multiple-indicator approach to CR measurement are increasingly acknowledged, further research is required to adequately define the variables that should be included in these multiple-indicator models, and the nature of their weighted contribution (Harrison et al., 2015). Studies that evaluate the validity of a CR construct measured by an appropriate combination of indicators are an important avenue for further empirical investigation. Efforts to harmonise the measurement of CR across future studies will increase confidence in the validity of the construct, aid comparability of findings, and may help to clarify the current contradictory findings in relation to CR and age-related cognitive decline.

Table 2.4: Summary of key CR proxy measurement approaches

CR Measure	No. of studies	Measurement Issues: Key Considerations
Single Indicator Approaches[1]		
Education	14	• Most consistently used CR indicator • Operationalised relatively consistently across studies • Important to consider cohort effects; differences in educational quality across cohorts, nationalities etc. • Single indicator measure may not fully capture CR
Occupation	6	• Important to consider cohort effects • Single indicator measure may not fully capture CR
Leisure/cognitively stimulating activities	6	• Considerable heterogeneity in methods used to operationalise this proxy measure • Single indicator measure may not fully capture CR
IQ	4	• Can typically only be measured using reading based estimates of premorbid function • Single indicator measure may not fully capture CR
Literacy/reading ability	3	• Operationalised relatively consistently across studies • May provide a better indication of educational quality than a simple count of years of education • Single indicator measure may not fully capture CR
Bilingualism/ multilingualism	3	• Mixed findings for relationships between bilingualism/multilingualism and cognitive function • Single indicator measure may not fully capture CR
SES	1	• Not widely used • Single indicator measure may not fully capture CR
Multiple Indicator Approaches		
Composite scores	2	• Provide a relatively straightforward way to calculate CR score incorporating multiple indicators • Do not account for measurement error; typically assume an equally weighted contribution for each indicator
Published scales	2	• May contribute to standardisation of measurement of CR • Provide a relatively straightforward way to calculate CR score incorporating multiple indicators • Not yet widely used or validated • Mainly used in studies with non-English speaking populations to date
Latent variable models	5	• May provide a more theoretically valid measure of CR • Can account for measurement error and weighted contribution of different proxies • To date have not combined full range of indicators used as single proxies for CR

[1] Includes studies that use this proxy as the sole indicator of CR and those that conduct separate analyses for several indicators in parallel

Chapter 3: Construct validity of cognitive reserve in a highly educated, normally ageing cohort

3.1 Introduction

While cognitive reserve is now a widely cited and studied concept, the related literature is characterised by inconsistencies in terminology, definitions, and measurement approaches. A range of terms and related variables are used, often interchangeably, to refer to different conceptualisations of reserve that overlap considerably with each other (Satz et al., 2011). The most consistently used conceptual model is that proposed by Yaakov Stern, with reserve divided into the separate but related constructs of brain reserve (BR) and cognitive reserve (CR), and the latter further divided into two mechanistic components of neural reserve and neural compensation (Stern, 2002, 2003, 2009, 2012). Christensen et al (2007, 2008) describe a 'brain reserve hypothesis' that appears to incorporate both BR and CR as described by Stern. Valenzuela and colleagues discuss a concept they term 'brain reserve' that is defined at a behavioural level using measures of education, occupation, and late-life mental activity (Valenzuela, 2008; Valenzuela & Sachdev, 2006a). Jones et al. (2010) discuss 'neurocognitive reserve' (Chibnall & Eastwood, 1998; Raiha, Kaprio, Koskenvuo, Rajala, & Sourander, 1998), which they employ as a more general term to reflect overlap between BR and CR, but it is unclear how the indicators used to measure this more general construct differ from those currently used to represent CR.

The existence and nature of inter-relationships between indicators used to measure BR (e.g. brain size, neuronal count) and CR (e.g. education, cognitively stimulating activity) remains poorly understood, and this likely contributes to difficulty in differentiating between concepts (Harrison et al., 2015; Stern, 2012). More theoretical work is required to clearly define reserve concepts, their causes, indicators, and manifestations, and the relations between them (Jones et al., 2010; Satz et al., 2011).

While BR is a concept of considerable theoretical importance, and is likely to overlap considerably with CR (Barulli & Stern, 2013; Stern, 2012), this thesis is primarily concerned with CR. This chapter evaluates the validity of a CR construct based on Stern's theoretical model, and aims to contribute to literature examining whether CR

can be considered an independent construct and a distinct dimension of individual differences in models of ageing. However, it must be acknowledged that variables commonly used to measure CR, such as educational attainment or complex mental activity, are likely to contribute to both brain and cognitive reserve (Murray et al., 2011).

3.1.1 Measuring cognitive reserve

The absence of one clear conceptual definition of CR has likely contributed to a general lack of clarity around the operationalisation and measurement of the construct. Given that inconsistent measurement and definition may limit the conclusions that can be drawn from empirical findings claiming to support the CR hypothesis, the topic has received relatively little attention in the literature. A wide range of variables have been used as proxy indicators of the hypothetical CR construct. The diversity of indicators used in studies investigating the effects of CR on age-related cognitive outcomes, and the problems associated with use of any single indicator measure, were reviewed in Chapter 2. Similar diversity exists in literature examining the effects of CR in clinical populations. A recent systematic review of existing meta-analyses relating to CR and Alzheimer's disease (AD) detailed findings related to a range of proxy indicator measures including education, occupational attainment, work complexity, social network, premorbid intelligence, socioeconomic status, leisure activities, and mentally stimulating activities (Harrison et al., 2015). In addition to highlighting the diverse range of indicators used to measure CR, the authors noted considerable variability in how each indicator was defined; for example, some studies used very broad characterisations of leisure activities, whereas other studies narrowed their focus to complex mentally stimulating activities only (Harrison et al., 2015). Heterogeneity in study design and indicators used to measure CR is problematic for comparability across studies and raises concerns about the validity of the construct (Harrison et al., 2015; Siedlecki et al., 2009). An important review article by Satz et al. (2011) concluded that the inconsistent use of various indicators left CR "wanting as an explanatory concept" (p. 121), and highlighted the need for theoretical work to develop empirically testable conceptual models of CR, and to establish their construct validity. This opinion was echoed by Jones et al. (2011) in their seminal article detailing conceptual and measurement challenges related to CR.

One important step towards improved measurement of CR is a shift from the use of single proxies towards measures that represent a combination of multiple indicators (Jones et al., 2011). As discussed in Chapter 1, there is a clear theoretical rationale for use of multiple-indicator models to represent CR (see page 23). While multiple-indicator models have become increasingly popular in more recent literature, a considerable proportion of studies using several CR indicators continue to separately examine the relationship of each proxy with the outcomes of interest, rather than using methods to study the combined effects of these indicators (e.g. Singh-Manoux et al., 2011; Staff et al., 2004). Other studies have created composite variables that combine several indicators, typically by averaging z-scores for the various indicator variables (e.g. Bastin et al., 2012; Gordon et al., 2012; Pettigrew et al., 2013; Puente, Lindbergh, & Miller, 2015; Soldan et al., 2013). While this approach has the advantage of being relatively straightforward to apply, these composite scores do not provide information about the validity of the construct they are used to represent; they assume that each indicator makes an equally weighted contribution; and they do not provide any means of accounting for measurement error related to each of the single indicators (Borsboom, 2005). A number of authors have developed instruments that attempt to summarise the various proxy indicators and provide an index of overall CR (e.g. Nucci et al., 2012; Rami et al., 2011; Valenzuela & Sachdev, 2007). These published questionnaires may contribute to standardisation of measurement across future studies, but – with the exception of the Lifetime of Experiences Questionnaire (LEQ) (Valenzuela & Sachdev, 2007) – English-language versions of these instruments are either not available, or have not yet been widely used or validated. An alternative approach to multiple-indicator measurement involves using structural equation modelling (SEM) to create latent variable models of CR. It has been suggested that this analytic strategy may provide a more theoretically valid measure of the construct (Jones et al., 2011).

3.1.2 Structural equation modelling

Structural equation models represent a series of theoretically derived hypotheses about how constructs of interest to the analysis are generated, and how they are related to each other (Hu & Bentler, 1999; Mueller & Hancock, 2008). These analytic tools extend general linear modelling procedures such as multiple regression and ANOVA to allow investigation of more complex research questions, since multiple equations can be simultaneously estimated to describe the pattern of inter-relationships among variables

(Lei & Wu, 2007; Nachtigall, Kroehne, Funke, & Steyer, 2003; Weston & Gore, 2006). The relationships between variables are specified a priori based on relevant theory, and the goal of SEM is to establish whether this hypothesised theoretical pattern of relations is consistent with the data collected (Lei & Wu, 2007).

A key advantage of SEM is the ability to test relationships between both observed and latent variables, with the latter not directly measured but typically represented as the shared variance between a set of observed indicators of the hypothetical latent construct (Bowen & Guo, 2012; MacCallum & Austin, 2000). The process of combining multiple indicators results in a latent variable from which measurement error specific to any one indicator has been removed, and allows for error to be represented in the model as the variance not explained by the latent variable (Buhi, Goodson, & Neilands, 2007; Hoyle, 2011; Weston & Gore, 2006). The use of simplified statistical models that combine multiple indicators into a smaller number of latent variables also reduces problems associated with multicollinearity and statistical power restrictions (Mitchell, Shaughnessy, Shirk, Yang, & Atri, 2012). The capacity to model relationships between latent variables renders SEM a powerful and useful technique, as it shifts the focus of the analysis from variables to constructs (Hoyle, 2011). As such, it has been suggested that this analytic method may be better suited to the study of complex and multidimensional psychological concepts than traditional univariate and bivariate methods (Buhi et al., 2007; Weston & Gore, 2006). Latent variables representing cognitive domains such as memory, processing speed, or executive function have been widely used in studies of cognitive ageing, on the basis that these variables may provide purer measures of the underlying construct that individual cognitive tests are designed to measure (Mitchell et al., 2012; Salthouse, Atkinson, & Berish, 2003; Salthouse, Berish, & Siedlecki, 2004).

SEM typically comprises a measurement model, which specifies relations between observed indicators and latent variables, and assesses how well the latent construct is defined by the combination of measured indicators, and a structural model, which specifies and evaluates the hypothesised relationships among latent variables (Weston & Gore, 2006). The researcher must evaluate the overall fit of the model to the data using a variety of fit indices, before moving on to interpret the strength of individual parameter estimates as appropriate (Kline, 2010).

3.1.3 Latent variable models of cognitive reserve

A number of studies using latent variables to represent CR have emerged in the scientific literature. In a study of PET activation in AD patients, Scarmeas et al. (2004) used principal components analysis to create a CR variable combining years of education and two vocabulary measures. Siedlecki et al. (2009) evaluated a model in which CR was a latent variable representing the shared covariance between two vocabulary tests and a measure of educational attainment. Brickman et al (2011) used a latent variable combining years of education and scores on the Wide Range Achievement Test (WRAT), to evaluate the role of CR in the relationship between white matter hyper-intensities (WMH) and cognition in neurologically healthy older adults. Giogkaraki et al. (2013) found that CR moderated the negative relationship between age and both verbal episodic memory and executive function, using a latent CR construct that incorporated education, vocabulary, and reading performance as measured indicators. Lojo-Seoane et al. (2014) used a structural model to evaluate the influence of CR on episodic memory, working memory, and general cognitive performance in a sample of older adults with subjective memory complaints. This study defined CR using a complex latent variable structure, specifying a second-order "CR macro-construct" reflected by two first-order latent constructs: one which comprised years of education, occupational complexity, reading habits, and two vocabulary tests, and a second representing frequency of social and cultural activities (Lojo-Seoane et al., 2014). These latent variable approaches are a promising attempt to "move the field beyond simple demographic proxies for reserve" (Jones et al., 2011 p.596). However, these latent constructs have largely been based on a priori groupings of indicators and implicit assumptions related to construct validity (Satz et al., 2011). Salthouse and Davis (2006) highlight the importance of establishing construct validity when grouping indicators into a latent variable, and note that there is rarely sufficient objective evidence available to justify these groupings a priori.

Important preliminary evidence for construct validity of CR was provided by Siedlecki et al. (2009), who compared factor loadings of three CR indicators (education and performance on two vocabulary tests) along with neuropsychological test scores on the constructs of CR, memory, processing speed, and executive function, using data from three samples of participants. Satz et al. (2011) proposed a four-factor model of CR for

validation including latent constructs of executive function, processing speed, complex mental activity, and intelligence. However it is unclear whether they intended for each latent variable in their model to represent a dimension of CR, or whether the model was designed to test the validity of complex mental activity as a measure of CR with the remaining three cognitive constructs included to test discriminant validity (Mitchell et al., 2012). Mitchell et al. (2012) validated a model comprising CR and three cognitive domains using confirmatory factor analysis and tests of measurement invariance in a sample of normally ageing adults and a second sample with memory deficits consistent with amnestic mild cognitive impairment (aMCI) and AD. The hypothesised CR construct in this model was represented by two indicators: education and scores on the American National Adult Reading Test (AMNART) (Mitchell et al., 2012). The results provided support for the validity of CR as a unique construct, with only moderate correlations between CR and the other cognitive constructs (Mitchell et al., 2012). The models showed relative stability across groups with acceptable absolute model fit across each of the invariance assumptions apart from the most stringent, strict invariance level (Mitchell et al., 2012). Using a sample of participants with moderate to severe traumatic brain injury, Levi, Rassovsky, Agranov, Sela-Kaufman, and Vakil (2013) tested the validity of a number of models of CR and found that a three-factor structure with latent constructs representing SES, premorbid intelligence, and premorbid leisure activity (cognitive, social, and physical) provided the best fit for their data. Lojo-Seoane et al. (2014) interpreted the strong factor loadings of CR indicators on their respective constructs as evidence of convergent validity, but did not conduct any further tests of construct validity beyond this. Further research is needed to evaluate the construct validity of latent CR variables that incorporate a wider range of proxy indicators, and across a range of conditions where reserve is thought to have a protective effect, in both normally ageing and clinical populations. This study will add to this literature by testing the construct validity of a latent variable model of CR that incorporates a greater range of proxy indicators than have been included in previous models. The latent CR variable evaluated in this chapter therefore better reflects the range of variables that are thought to contribute to CR across the lifespan, and that have been used as single indicator measures in the existing literature.

3.1.4 Testing construct validity

One method of establishing construct validity is to employ an individual differences approach and investigate whether the variables hypothesised to represent a construct have both convergent and discriminant validity (Salthouse et al., 2003; Satz et al., 2011). Evidence of convergent validity is present when the target variables are systematically related to each other, as demonstrated by moderate to high loadings on the target latent construct (Salthouse & Davis, 2006). Discriminant validity is then established by demonstrating that these target variables are also not related, or much less strongly related, to other non-target constructs (Salthouse et al., 2003; Salthouse & Davis, 2006).

Salthouse et al. (2003) described a series of four structural equation models that are designed to each provide a progressively more demanding test of construct validity (Salthouse et al., 2003; Salthouse et al., 2004). The first model (Model A) assesses only convergent validity by evaluating whether the target variables hypothesised to represent the target latent construct have significant variance in common. Model B extends Model A to provide an initial test of discriminant validity, by examining relations between the hypothesised latent construct and constructs representing other abilities. Discriminant validity is established in Model B if the correlations of the target construct with the non-target constructs are substantially less than 1.0. The third model (Model C) extends Model B to allow the non-target constructs to be related to each of the measured target variables, one at a time, and retaining any relationship between a non-target construct and a target variable that results in a significantly improved fit of the overall model. As in the preceding models, convergent validity is established in Model C if the target variables continue to have a significant relationship with the hypothesised target construct; and discriminant validity is tested by investigating whether correlations with the non-target constructs are less than 1.0. The final model (Model D) provides the most stringent test of construct validity, by investigating the influence of non-target constructs at the level of individual variables rather than at the level of the hypothesised construct. Correlations between the hypothesised construct and non-target constructs are no longer estimated, and instead, each of the non-target constructs is allowed to be related to each of the measured target variables simultaneously. Convergent validity is established in Model D if a significant amount

of residual variance is shared among the target variables, and discriminant validity is established if there are weak relations of the individual variables to non-target constructs.

This set of models was first used by Salthouse et al. (2003) to assess convergent and discriminant validity of an executive function construct, and the same group of authors subsequently applied the methodology to test the construct validity of prospective memory (Salthouse et al., 2004) and source memory (Siedlecki, Salthouse, & Berish, 2005). Of particular relevance to this chapter, these models were also used in the earlier-mentioned investigation of CR construct validity by Siedlecki et al. (2009), using education together with performance on two vocabulary tests as CR indicators. Consistent loadings of the CR indicator variables on the CR latent factor across the four models provided support for convergent validity of the hypothesised CR construct (Siedlecki et al., 2009). Discriminant validity of the CR construct was only partially supported by the study findings, because in the most demanding test of construct validity (Model D) the CR variables were highly related to the executive function construct (Siedlecki et al., 2009). The authors acknowledge that CR is "fairly narrowly defined" in their model (Siedlecki et al., 2009 p. 567), and the CR indicators in their study do not include some commonly used proxies such as occupational attainment and participation in mentally stimulating activities.

3.1.5 Current study

The current study employed the models proposed by Salthouse et al. (2003) to evaluate the convergent and discriminant validity of a CR construct with five indicators: years of education, premorbid IQ, reading ability, occupational complexity, and frequency of participation in leisure activities.

For the purposes of this study, CR was defined as a reflective latent construct. As depicted in Figure 3.1, latent variable measurement models can be specified as reflective or formative, which differ in terms of the direction of hypothesised relationships between the latent construct and observed variables (Kline, 2010). In a reflective measurement model, the observed indicators are thought to be caused by the unobserved, latent variable. In a formative measurement model, the latent variable is hypothesised as the consequent cause of the observed formative indicators.

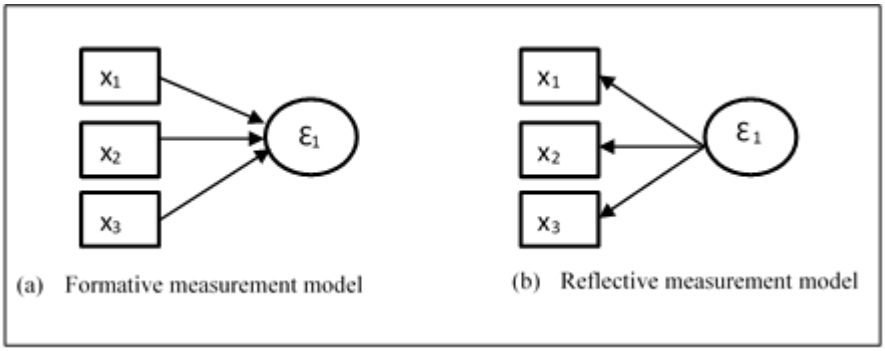

Figure 3.1: Formative and reflective latent variable measurement models

Note: In each model above, the latent variable is represented by a circle labelled $\mathcal{E}_1$, and the manifest or observed variables are represented by rectangles (labelled x_1-x_3). Model (a) is a formative measurement model, in which the observed indicators are hypothesised to have a causal influence on the latent construct. Model (b) is a reflective measurement model, in which the observed indicators are hypothesised to be caused by the latent construct.

Jones et al. (2011) note that commonly used CR indicators are partially consistent with a formative model, since they reflect an accumulation of lifetime experiences thought to build CR. They therefore argue that a purely reflective measurement model of CR may be somewhat incompatible with the underlying theory (Jones et al., 2011). However, formative measurement models have identification problems (Kline, 2010) and provide no information about the validity of the latent construct because they are statistically equivalent to multiple regression models (Jones et al., 2011). Since the aim of this study was to investigate construct validity, all observed CR indicators were therefore specified as reflective. The decision to define CR as a reflective latent construct was also influenced by the fact that reflective measurement models were employed in the construct validity studies that this chapter builds upon (Mitchell et al., 2012; Siedlecki et al., 2009). However, it is important to acknowledge that there are some conceptual issues related to this specification of the construct, given that the observed indicators are typically considered as contributors to, rather than effects of, CR (Jones et al., 2011).

3.1.5.1 Cognitive reserve construct

The variables selected as observed indicators of the latent CR construct have each been the subject of investigation as single proxy indicators of CR in the literature. Each of these variables reflect intellectually enriching experiences thought to contribute to the development of adaptive cognitive skills, strategies, and processes with the potential to

buffer against cognitive impairment in the face of brain damage or pathology (Stern, 2009, 2012).

Education is the most widely used proxy indicator of CR, perhaps because it is relatively easy to measure and quantify, and in many studies it is used as the sole indicator of CR (Farias et al., 2012; Valenzuela & Sachdev, 2006a, 2006b). The popularity of education as a CR indicator is evident in a recently published meta-analysis of findings related to CR and normal ageing, in which education was used as a proxy indicator in 109 of the 135 included studies (Opdebeeck et al., 2015). Studies vary in terms of the exact metrics of education used to indicate CR; authors have used years of completed education as a continuous variable, assigned scores based on the highest level of education completed (Siedlecki et al., 2009), compared groups of participants categorised according to their level of education (e.g. Singh-Manoux et al., 2011), and used dichotomous high- versus low-education variables (e.g. Foubert-Samier et al., 2012). The aforementioned meta-analysis of cross-sectional findings found a moderate positive association between education and overall cognitive function in healthy older adults (Opdebeeck et al., 2015). An inverse relationship between educational attainment and risk for dementia or Alzheimer's disease is widely reported in the CR literature (Basu, 2012; Meng & D'Arcy, 2012; Stern et al., 1994). Studies demonstrating a moderating role for education in the relationship between indicators of AD neuropathology (regional cerebral blood flow and FDG-PET imaging in vivo, or post-mortem indices) and cognitive function are interpreted as providing strong support for the CR hypothesis (Bennett et al., 2003; Perneczky et al., 2006; Stern et al., 1992).

It has been suggested that due to differences in the nature, content, and quality of education encountered across age cohorts, regions, and social groups, a simple measure of duration of completed schooling may not provide an equivalent indication of attainment in diverse samples (Manly et al., 2002; Opdebeeck et al., 2015). Some authors have therefore suggested that measures of literacy or reading ability, to reflect educational quality, may be a more powerful proxy for CR. In a longitudinal study of 136 ethnically diverse, English-speaking, non-demented older adults, Manly et al. (2003) found that lower levels of literacy were associated with a steeper decline in immediate and delayed recall after controlling for age at baseline and education. The authors found similar results with a larger sample of over 1,000 ethnically diverse older

adults, demonstrating that decline in memory, executive function, and language skills was more strongly predicted by literacy than by years of education (Manly et al., 2005).

Individual differences in intellectual ability that persist across the lifespan play a significant role in differential risk for late-life cognitive decline, and premorbid intellectual ability may therefore be an important indicator of CR (Watson & Joyce, 2015). A case-control study by Whalley et al. (2000) found that individuals diagnosed with late-onset dementia at age 72 had significantly lower scores on mental ability tests at age 11. An inverse relationship between childhood cognitive ability and rate of decline in memory, speed, and concentration in midlife has also been documented (Richards et al., 2004). Estimates of crystallised abilities such as vocabulary and reading are often used to indicate premorbid intellectual capacity (Barker-Collo et al., 2008; Crawford, Deary, Starr, & Whalley, 2001). These measures are considered a valid method for estimating premorbid intelligence because they remain stable over time and appear relatively resistant to the biological effects of ageing or mild dementia (Barker-Collo et al., 2008). When used as proxy indicators of CR, estimates of verbal intelligence were found to be associated with risk for incident dementia (Schmand, Smit, Geerlings, & Lindeboom, 1997), with degree of AD pathology at a given level of dementia severity (Alexander et al., 1997), and to predict neuropsychological test performance after controlling for age, education, overall cognitive status, and demographic factors (Krasean, 2014). Verbal IQ as estimated by the National Adult Reading Test (NART) was associated with better strategy selection among cognitively normal older adults, which the authors suggest may be one cognitive mechanism underlying the protective effects of CR (Barulli et al., 2013). The number of studies using these variables as indicators of CR is limited, and further research is needed to investigate their potential to contribute to CR and protect against cognitive impairment.

Occupational attainment has been less widely studied than other indicator variables, but the available evidence suggests that it may be an important contributor to CR. Current cross-sectional evidence suggests a general positive effect of occupational status on cognitive function in normal ageing, although effect sizes vary across individual cognitive domains (Opdebeeck et al., 2015). Several authors have suggested that complex occupations are an important source of sustained intellectual engagement and motivation that may contribute to CR, and high occupational complexity has been

associated with reduced risk of dementia and AD, and better maintenance of cognitive function among non-demented older adults (Andel et al., 2005; Dekhtyar et al., 2015; Karp et al., 2009; Kröger et al., 2008; Schooler, Mulatu, & Oates, 1999). Higher occupational complexity was also associated with a faster cognitive decline after diagnosis of AD, consistent with the CR hypothesis that individuals with higher CR (occupational complexity) are at a more advanced stage of pathological disease when they reach the cognitive threshold for diagnosis (Andel, Vigen, Mack, Clark, & Gatz, 2006). Valenzuela and Sachdev (2006b) reported significant protective effects of occupational attainment in nine of the twelve studies included in their meta-analysis, with combined odds ratios indicating that individuals with high occupational status had a 44% reduced risk of incident dementia compared to those in the low group. A recent study found that protective effects of education against incident dementia were no longer significant when occupational complexity (with data) was introduced into the fully adjusted model, underlining the importance of occupational stimulation for CR (Dekhtyar et al., 2015).

Leisure activities, particularly those that are cognitively challenging, are an important source of mental stimulation across the lifespan, and therefore have the potential to modulate CR even in late life (Wilson et al., 2013). A systematic review of epidemiological evidence by Fratiglioni and Wang (2007) concluded that there was strong evidence for a reduced risk of dementia and AD associated with physical, mental, and social leisure activities. Scarmeas et al. (2001) found that participants who engaged in a high number of leisure activities (6 or more in a 13-item self-report scale) were at a 38% reduced risk of dementia than those who engaged in fewer activities. Frequency of engagement in mentally stimulating leisure activity has also been shown to be positively associated with cognitive function in late life (Opdebeeck et al., 2015), and to have an inverse relationship with rate of age-related, non-pathological cognitive decline (Wilson et al., 2013).

3.1.5.2 Non-target cognitive constructs

In order to evaluate discriminant validity of the proposed CR construct, two non-target latent constructs, representing cognitive domains of episodic memory and executive function, were included in Models B, C, and D. These non-target variables measure cognitive abilities that are thought to be sensitive to the effects of ageing (Giogkaraki et

al., 2013), and were also selected for comparability with previous literature, since similar non-target variables were used in studies evaluating the construct validity of a latent CR variable (Mitchell et al., 2012; Siedlecki et al., 2009).

3.2 Method

3.2.1 Exclusion/inclusion criteria and screening

Exclusion and inclusion criteria were given careful consideration. Christensen, Moye, Armson and Kern (1992) note that failure to consider health status and other variables related to cognition during sample recruitment may result in confounding of these variables with age. However, the application of stringent exclusion criteria representing all age-extrinsic factors associated with cognitive performance may be impractical and prohibitive for an older population, because the high prevalence of some of these factors may result in exclusion of the majority of potential participants. Furthermore, there is debate as to whether exclusion criteria for studies of older adults should be designed for the selection of a perfectly healthy sample, or one that is more representative of the general population (Tisserand & Jolles, 2003). Applying criteria for a perfectly healthy, successfully ageing sample may arguably produce a "super-elderly" group that are not representative of the normally ageing population of Ireland aged 50 and over, many of whom will have health conditions (e.g. hypertension) or engage in behaviours (e.g. smoking) that could influence cognition.

For the purposes of this study, a generally healthy, "normally ageing" sample, rather than a successfully ageing sample, was considered preferable. In consultation with clinical and academic ageing experts, the following exclusion/inclusion criteria were selected: participants should be native English speakers aged 50 and over, with no history of stroke, epilepsy, major neurological conditions, major psychiatric disorder, alcohol or drug abuse within the past 5 years, or significant difficulties with eyesight or hearing even when using reading glasses or hearing aids. Participants were also excluded if they were currently taking anti-convulsant or anti-psychotic medications. These criteria were selected to achieve a balance between importance and practicality, excluding participants who had medical conditions or were taking medications that would be expected to have a significant impact on cognitive performance, without excluding an inordinate amount of participants.

Self-report measures are a practical and valid method of screening participants for medical conditions affecting cognition (K. J. Christensen et al., 1992). Christensen et al (1992) have developed a standard self-report instrument for this purpose, that has been

used extensively in cognitive research (e.g. Bucur et al., 2008; Madden et al., 1999; Prull, Crandell Dawes, McLeish Martin, Rosenberg, & Light, 2006; Van der Linden et al., 1999). An adapted version of this instrument was used as a health screening questionnaire for participants in this study (Appendix B). Adaptations included changing the wording of several items to be more appropriate for the population of interest, and the inclusion of additional items about family history of AD. The screening questionnaire, which was administered by phone, contained 38 items relating to a wide range of health conditions, a subset of which were used to determine whether participants met exclusion criteria for this study. Participants were also asked to provide a full list of medications that they were currently taking on a regular basis. This medication inventory was collected over the phone by asking participants to read verbatim the name, dosage, and frequency of each medication from its label. A list of excluded anti-psychotic and anti-convulsant medications was created in consultation with a clinical expert (Appendix C). The use of a comprehensive health screening questionnaire allowed for participants with additional health conditions (that were not excluded from the overall study) to be excluded from particular analyses, if more stringent exclusion criteria were deemed appropriate for the research question.

3.2.2 Participants

Participants for this study were a group of older adults taking part in an ongoing longitudinal study of cognitive function at the NEIL Memory Research Unit in Trinity College Dublin (Hannigan, Coen, Lawlor, Robertson, & Brennan, 2015). Participants were recruited through a variety of channels, including advertisements on websites and in newsletters of ageing organisations (e.g. Age Action, Active Retirement Ireland, Third Age); at conferences and other ageing-related events; announcements on national radio and in other media; at outreach talks conducted by members of the research team; through word of mouth, and so on. Participants were sent a study information pack, and provided written consent by return post before being contacted for an initial telephone screening. Of the 877 people who returned signed consent forms, 68 failed to satisfy the inclusion/exclusion criteria during this initial screening. A further 114 were not available, not contactable, or decided not to take part in the study.

Three participants failed to complete the test battery due to voluntary withdrawal during the testing session. In addition, data from five participants were excluded for quality

control purposes due to incorrect test administration; and data from a further 12 participants who completed testing but were taking an excluded class of medication were also removed from analysis. For the analyses presented in this chapter, we excluded participants with diabetes (n = 8), Parkinson's disease (n = 4), and those with scores for the Montreal Cognitive Assessment (MoCA) that were at or below the 5th percentile (n = 25) using nationally representative age- and education-adjusted norms (R. A. Kenny et al., 2013). Data for 638 participants (65.7% female; mean age = 64.14; SD = 6.83) were analysed for this study. Descriptive statistics for the sample are provided in Table 3.1.

Table 3.1: Demographic characteristics of the sample

Variable	**N**	
Age (mean, SD)	638	64.14 (6.83)
Sex (%)		
Female	419	65.7
Male	219	34.3
Years of education (mean, SD)	637	15.09 (3.44)
Highest level of education (%)		
Primary	23	3.6
Secondary	137	21.6
Tertiary	475	74.8
Self-rated health (%)		
Excellent	164	26
Very good	338	53.7
Good	109	17.3
Fair	16	2.5
Poor	3	0.5
Self-rated memory (%)		
Excellent	46	7.3
Very good	230	36.3
Good	273	43.1
Fair	74	11.7
Poor	10	1.6

The sample used for this study was highly educated, with a significant majority of participants having completed third level education. In a nationally representative sample of Irish adults aged 50 and over, only 21.41% of participants had completed third level education (Kearney et al., 2011). Therefore, levels of educational attainment in this study were considerably higher than those observed among the general population of Ireland with a similar age profile. Table 3.2 details the age distribution of

the population of Ireland aged 50 and over, based on data from the 2011 Census (Central Statistics Office, 2012) and the age distribution of the sample used for this study. At the time of the 2011 Census, 27.75% of the Irish population were aged over 50 years. The age distribution of the sample for this study indicated that participants aged between 60 and 69 were over-represented, and those aged between 50 and 59 and aged 80 and over were under-represented. The proportion of participants aged between 70 and 79 was relatively in line with what would be expected based on the Census data.

Table 3.2: Proportion by age group, Irish population and study sample

	2011 Census		**Study sample**			
Age group	**N**	**% of population aged 50+**	**N**	**% of sample**	χ^2	p^1
50-59	518,908	40.76	167	26.18	55.57	<.001
60-69	392,424	30.82	348	54.55	167.13	<.001
70-79	233,226	18.32	107	16.77	0.92	0.34
80+	128,529	10.10	16	2.50	39.63	<.001
Total population aged 50+	1,273,087					
Total population	4,588,252					

Note: Data for these calculations were taken from the "Profile 2: Older and Younger" report of the 2011 Census of Ireland (Central Statistics Office, 2012)
[1] Results of two-sample test for equality of proportions

All study procedures were approved by the School of Psychology Research Ethics Committee at Trinity College Dublin (Appendix D). Written, informed consent was obtained from all participants (Appendix E) and participants were free to withdraw from the study at any time. Participants were also entitled to request that their data be withdrawn from the study after they had completed testing, and to have that request honoured in accordance with relevant Data Protection legislation and the Trinity College Policy on Good Research Practice (Trinity College Dublin, 2009).

3.2.3 Materials

The measures used in this study were administered to participants as part of a longer testing protocol which included an extended battery of cognitive tests, neuropsychological measures, self-report questionnaires, basic physical measures, and an electroencephalogram. A full list of measures included in the overall testing protocol is provided in Appendix F.

The materials included in the testing protocol were informed by the literature and chosen in consultation with a group of clinical and academic ageing experts. Based on a review of the literature, a range of CR proxy measures were selected, in order to allow for the combination of these indicators in latent variable models. Experimental and neuropsychological measures were chosen based on their ability to measure a range of cognitive functions with varying susceptibility to age-related change. Measures that screen for clinical levels of cognitive impairment, reading difficulties, psychological conditions (e.g. anxiety, depression), and other potentially confounding variables were also included in the protocol.

3.2.3.1 Cognitive reserve indicators

Five variables were hypothesised to represent the latent CR construct: education, occupational complexity, leisure activity participation, and performance on the WRAT-3 reading test and the NART. Each of these variables reflect life experiences with the potential to protect against cognitive decline associated with normal ageing or neuropathology, and have been used as proxy indicators of CR in the literature.

Education

Self-report measures of years of full time education and highest level of education were included in the background questionnaire completed by participants (Appendix G). A variable representing years of full time education was included as an indicator of CR in the current analyses.

Literacy/reading ability

The reading subtest of the WRAT-3 (Wilkenson, 1993) was included as a measure of reading ability/educational quality. This subtest assesses an individual's ability to recognise and pronounce 42 words out of context. This test has been used as a CR proxy indicator reflecting educational quality in several previous studies (Manly et al., 2005; Manly et al., 2003). The measure has been shown to have high internal consistency ($\alpha > .90$ across age groups) (Strauss, Sherman, & Spreen, 2006) and acceptable test-retest reliability in older adults with and without cognitive impairment (Ashendorf, Jefferson, Green, & Stern, 2009).

Premorbid IQ

The NART (Nelson, 1982) was used to estimate premorbid intellectual ability. Participants are required to read aloud 50 phonetically irregular words, with one point awarded for each correctly pronounced word. The NART is a test of over-learned skills, and is based on the assumption that pronunciation of the words included in the test (which do not follow common English grammatical rules and cannot be "sounded out") implies prior knowledge of them and therefore, higher premorbid intelligence (Barker-Collo et al., 2008; Lowe & Rogers, 2011). The NART was chosen because it provides a good estimate of verbal intelligence, is the most commonly used test of its kind for estimating premorbid IQ (Barker-Collo et al., 2008), and has been used as a proxy indicator of CR in several previous studies (e.g. Barulli et al., 2013; Habeck et al., 2003; Rentz et al., 2007; Siedlecki et al., 2009). It is considered a valid measure of premorbid intellectual ability because it remains highly stable over time (Barker-Collo et al., 2008; Schmand, Geerlings, Jonker, & Lindeboom, 1998), and it has been found to explain a significant proportion of variance in IQ measured both in late life and in childhood (Barker-Collo et al., 2008; Crawford et al., 2001). NART IQ estimates at age 77 correlated highly with IQ scores obtained at age 11, indicating only minimal effects of age and life experience on NART estimates (Crawford et al., 2001). The test has demonstrated good internal consistency ($\alpha = 0.90$), inter-rater reliability (0.96 - 0.98), and test-retest reliability (0.98) (Crawford, Parker, Stewart, Besson, & Lacey, 1989).

An additional advantage of this measure is the availability of the Short NART method (Beardsall & Brayne, 1990), which allows for discontinuation of the test after the first 25 items for participants who fail more than 5 of these initial items, with a formula available to estimate full NART score based on the first 25 words. This discontinuation method avoids undue distress for participants failing a significant amount of items early in the test, given that the words become progressively more difficult. The accuracy of this Short NART method in predicting premorbid IQ was found to be virtually equivalent to the full NART in a cross-validation study (Crawford, Parker, Allan, Jack, & Morrison, 1991). Raw NART scores representing the total number of words correctly pronounced were used as a CR indicator for the models presented in this chapter.

Occupation

An adapted version of the occupation item included in the Nucci et al. (2012) Cognitive Reserve Index questionnaire (CRIq) was included in the background questionnaire completed by participants (Appendix G). This item collects data relating to all jobs held throughout a person's life, and creates a score that reflects occupational complexity by multiplying the number of years spent in each occupation by a value reflecting the cognitive load involved (Nucci et al., 2012). This item was selected to provide a rich measure of intellectual stimulation due to occupation across the entire lifespan, rather than just considering an individual's current or most recent occupation.

The item included in the CRIq asks participants to list the number of years spent working in each of five occupational categories during their life: low skilled manual work; skilled manual work; skilled non-manual work; professional occupation; and highly responsible or intellectual occupation. During pilot assessments for the current study, some participants expressed concerns regarding the examples used for each category of occupation, and found the classification of certain occupations as "low skilled" versus "skilled" to be inconsistent and unacceptable. On the basis of this feedback, the item was adapted for this study to be open-ended rather than categorical, asking the participant to name each occupation held during their lives and to indicate how many years they spent working in that occupation.

The Standard Occupational Classification 2010 was used to classify each occupation listed by participants into one of four skill levels, which are defined to reflect the duration of training and/or work experience normally required for one to become fully competent in the performance of tasks associated with a job (Office for National Statistics, 2010). A description of each skill level, and examples of occupations included in this category, is provided in Table 3.3 below. An online coding tool provided by the UK Office of National Statistics (Office for National Statistics) was used to code occupations into one of four skill levels. For each occupation listed, this skill level score (ranging from 1-4, with higher scores reflecting greater skill level) was then multiplied by the number of years spent working in that occupation, to create a complexity score. These complexity scores were then summed to create a total lifetime occupational complexity score for each participant. Homemaking was coded to a skill level of 0, and as such did not contribute to the occupational complexity scores, which

were designed to reflect complexity of paid occupations across the lifespan. A previous study using occupational complexity as an indicator of CR found that excluding homemakers from the analysis did not affect the results as compared to including homemakers with occupational complexity classified according to paid "other housekeeping or related work" (Karp et al., 2009).

Table 3.3: Descriptions of skill levels from Standard Occupational Classification 2010

Skill level	**Description** ***Examples***
1	Occupations at this level typically require competence associated with a general education, usually acquired through completion of compulsory education and demonstrated by satisfactory school-leaving examination grades. Knowledge of appropriate health and safety regulations are also required for competent performance of jobs at this level. Short periods of employment-based training may also be required. *Examples: postal workers, hotel porters, cleaners, catering assistants*
2	Occupations at this level also require competence associated with a general education, but a longer period of work-related training and/or experience are required compared to jobs at skill level 1. *Examples: machine operation, retailing, clerical and secretarial occupations, caring occupations.*
3	Occupations at this level normally require a body of knowledge associated with post-compulsory education, but not normally to degree level. For some occupations within this category (e.g. small business proprietors), qualifications at a sub-degree level or lengthy training periods may not necessarily be required, but a significant period of work experience is typical. *Examples: skilled trades (e.g. electrical, construction, building, agricultural), protective service occupations, business and public service associate professionals*
4	'Professional' occupations and high level managerial positions in corporate enterprise or local/national government. A qualification of degree level or above and/or an equivalent period of relevant work experience are typically required. *Examples: health professionals, science, research engineering and technology professionals, teaching and educational professionals*

Note: Adapted from Volume 1 of the Standard Occupational Classification 2010 (Office for National Statistics, 2010)

Leisure activities

A leisure activities scale (House, Robbins, & Metzner, 1982) that is included within The Irish Longitudinal Study on Ageing (TILDA) Wave 1 Self-Completion Questionnaire (TILDA, 2009) was included in the background questionnaire completed by participants (Appendix G). This 14-item scale includes questions about frequency of

participation in both structured (e.g. undertaking voluntary activities, attending classes) and unstructured (e.g. reading a book, listening to music) activities (R. A. Kenny et al., 2010). This scale captures participation in a wide range of social and recreational activities, and has considerable overlap with items included in a leisure activity scale used as a proxy for CR in several previous studies (e.g. Helzner et al., 2007; Scarmeas et al., 2001; Scarmeas et al., 2003).

3.2.3.2 Cognitive variables

The non-target cognitive variables included in this study were collected as part of a larger battery of standardised neuropsychological tests and experimental tasks designed to measure cognitive function across a range of domains including overall function/forgetfulness, episodic memory, working memory, sustained attention, processing speed, and executive function (see Appendix F). Ordering of measures was carefully considered to avoid interference between tests and to incorporate appropriate timings between test conditions as detailed in administration manuals. The cognitive measures included in this analysis were chosen to reflect episodic memory and executive function, two domains of cognitive function that are thought to be sensitive to the neural changes associated with biological ageing (Giogkaraki et al., 2013).

Overall function

The MoCA (Nasreddine et al., 2005) was used as a screening instrument for possible cognitive impairment in this study. The MoCA is a short screening test that provides an indication of overall cognitive status, and assesses domains including attention and concentration, memory, language, visuo-constructional skills, calculation, and orientation. It was developed in an effort to provide a more sensitive instrument that could detect mild cognitive impairment (MCI) among patients with mild subjective cognitive complaints, who usually perform within the normal range on other common screening tests such as the Mini Mental State Examination (MMSE) (Nasreddine et al., 2005). Validation studies have shown that the test distinguishes between normal ageing, MCI, and early AD with high sensitivity and specificity (Luis, Keegan, & Mullan, 2009; Nasreddine et al., 2005). The instrument has demonstrated high internal consistency (Cronbach's $\alpha = 0.83$), and moderate to high test-retest reliability (72 - 90%) over one month (Lonie, Tierney, & Ebmeier, 2009; Nasreddine et al., 2005). For the current study, nationally representative, age- and education-adjusted normative data

for the MoCA (R. A. Kenny et al., 2013) were used to identify participants with percentile scores indicative of possible cognitive impairment.

Episodic memory

The Logical Memory I and II subtests of the Wechsler Memory Scale IV (WMS IV) (Wechsler, 2009) assess episodic memory under immediate and delayed free recall conditions respectively. Two short stories are orally presented, and the participant is asked to retell each story immediately after hearing it (Logical Memory I); and following a delay of at least 20 minutes (Logical Memory II). The participant is then asked a series of yes/no questions about each story to provide a delayed recognition score.

The WMS-IV includes a significant procedural change from previous versions, in that there is an Adult and Older Adult battery available, and stories administered to the participant for the Logical Memory subtest vary depending on which battery they receive (Wechsler, 2009). Within the Older Adult battery (ages 65-90) participants are administered Stories A and B, whereas the Adult battery (ages 16-69) uses Stories B and C. For participants aged between 65 and 69, either battery can be administered, depending on which is judged to be most appropriate for the participant's level of functioning (Wechsler, 2009). Following advice from an expert in clinical neuropsychology, for the purposes of this study it was considered most practical to administer the Adult battery to all participants aged up to 69 years, and the Older Adult battery to those aged 70 and over. Scaled scores for immediate and delayed recall were used in this study, as these values are comparable across Adult and Older Adult versions of the test. Delayed recognition performance was indicated by participants' raw recognition scores for Story B, which was administered in both the Adult and Older Adult test versions. The WMS-IV is a well-validated battery of tests designed to assess memory and learning, and has been shown to have acceptable construct, content, and concurrent validity (Wechsler, 2009). Reliability coefficients reported in the WMS-IV technical manual indicate that the Logical Memory I and II subtests have high internal consistency ($\alpha = 0.82$; 0.85 respectively for the Adult version; and $\alpha = 0.86$; 0.87 respectively for the Older Adult version), acceptable test-retest correlations ($r = 0.74$, 0.71 respectively), and very high inter-rater reliability (correlations ranging from 0.98 - 0.99) (Wechsler, 2009).

Executive Function

Visual Reasoning was assessed using the relevant task from the CAMDEX-R (Cambridge Examination for Mental Disorders of the Elderly - Revised) battery (Roth, Huppert, Mountjoy, & Tym, 1998). This task comprises six trials, during which the participant is presented with a card containing a grid of four boxes, three of which contain a shape and one of which is empty. The participant must select one of six shapes presented below the grid (marked A-F) that should go into the empty section of the grid. The number of correct trials provides a visual reasoning score (range 0-6).

Verbal fluency was assessed by asking participants to name as many animals as possible in one minute, with one point for each correctly named animal. Phonetic and semantic fluency tasks of this nature are widely used in cognitive ageing research, and performance on category fluency tasks has been shown to decline steadily with advancing age (Brickman et al., 2005; Strauss et al., 2006; Tombaugh, Kozak, & Rees, 1999). High test-retest correlations (typically above 0.7) have been found in healthy adults over both short and long intervals (Bird, Papadopoulou, Ricciardelli, Rossor, & Cipolotti, 2004; Mitrushina, Boone, Razani, & D'Elia, 2005).

The Letter Number Sequencing test (LNS) is a subtest of both the Wechsler Adult Intelligence Scale III (WAIS-III) (Wechsler, 1997a) and the Wechsler Memory Scale III (WMS-III) (Wechsler, 1997b). This test is based on a working memory task developed by Gold and colleagues (J. M. Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997). A series of alternating numbers and letters are presented to the participant at a rate of one item per second (e.g. D, 5, B, 2), and the participant must then recall the numbers first in ascending order, followed by the letters in alphabetical order (e.g. 2, 5, B, D). Working memory tasks with a manipulation component, that require rearrangement of items prior to recall, are thought to be more sensitive to the effects of ageing than simple serial recall tasks (such as digit span), perhaps because the additional manipulation component requires greater prefrontal involvement (Wager & Smith, 2003). Reliability coefficients provided in the technical manual for this test indicate that the subtest has high internal consistency ($\alpha = 0.82$) and good test-retest reliability (0.74) (The Psychological Corporation, 2002).

The Colour Trails Test (CTT) (D'Elia, Satz, Lyons Uchiyama, & White, 1994) is an adapted version of the widely used trail making test. The test was developed to allow broader application of the trail making test by using colours as a substitute for English alphabet letters to minimise cultural and linguistic bias. This test consists of a set of circles with either a vivid yellow or pink background (colours that are perceptible to colour blind individuals) with a number between 1 and 25 printed inside each circle. For CTT 1, the numbers 1 to 25 are each presented once, and participants are required to draw a line connecting the circles in ascending numeric order as quickly as possible. For CTT2, each number is presented twice – once with a yellow background and once with a pink background – and participants are required to again connect the circles in sequence as quickly as possible, while also alternating between yellow and pink circles. The time taken (in seconds) to complete the task is recorded as the score for each task. The test has been validated for use with adults aged between 18 and 89 years, and performance has been shown to decline with advancing age (D'Elia et al., 1994; Strauss et al., 2006). Test-retest reliability was found to be adequate over two weeks (D'Elia, Satz, Uchiyama, & White, 1996), although test-retest reliability data for longer time intervals are not currently available. CTT1 is primarily a test of simple perceptual tracking and sustained attention. CTT2 also assesses these abilities, but provides a more direct measure of frontal systems functioning, since the added complexity involved in switching between colours and numbers requires participants to divide their attention (D'Elia et al., 1994). Scores for CTT2 were therefore included as an indicator of executive function in the model. A difference score representing the time taken to complete CTT2 minus the time taken to complete CTT1 is used as an indicator of cognitive flexibility (Siedlecki et al., 2009) and was also included in the present analysis.

3.2.4 Piloting

Piloting was conducted to inform the design of the research protocol, to assess whether it was realistic and practical, to elicit feedback from participants on the acceptability of the protocol and its impact in terms of fatigue etc., and to identify any logistical problems or confounds. Ordering of task administration and appropriate timing of tests as outlined in administration manuals (e.g. required time between immediate and delayed recall conditions etc.) was carefully considered in the protocol design to ensure the validity of the data collected and to minimise participant fatigue (e.g. completing

the cognitive battery at the beginning of the session). Pilot assessment sessions were conducted with 20 participants in May 2012.

On the basis of pilot assessments, it was determined that the protocol could be administered in one testing session with an approximate duration of three hours including breaks, without causing undue participant fatigue. Piloting did not reveal the need for any major changes to the study protocol, and information obtained on minor logistical issues such as the timing of breaks or test instructions requiring clarification was incorporated into the design of the study. A testing manual, containing standard operating procedures and scripts for test administration, was developed to ensure consistency of administration across participants.

3.2.5 Study Procedures

Volunteers who registered their interest in the study were sent an information pack containing a study information sheet and consent form (Appendix E). Once signed consent forms were returned, participants were contacted by telephone to conduct the health screening interview using an adapted version of the Christensen Health Screening Questionnaire (K. J. Christensen et al., 1992) and to record a medication inventory. The purpose of this telephone interview was twofold: to determine whether the participant met any of the study exclusion criteria, and to collect data relating to history of a range of health conditions, family history of AD/dementia, and a full list of medications taken on a regular basis by the participant.

Participants who did not meet exclusion criteria and remained eligible to take part were sent a questionnaire to complete (Appendix G), and a copy of the Short Form IQCODE (Informant Questionnaire on Cognitive Decline in the Elderly) (Jorm, 1994) for a close relative or friend to complete. The background questionnaire and IQCODE were completed offsite prior to testing. Participants then attended one testing session in Trinity College Dublin. Testing for this study was conducted between June 2012 and September 2014. All testing sessions took place at either 10am or 2pm. During the testing session, participants completed remaining self-report measures along with a battery of neuropsychological tests and experimental tasks. Participants also completed some basic physical measures and an EEG to measure resting-state brain activity, which were not analysed as part of this study. All measures were administered in the same

order to each participant, using standard operating procedures and a script to ensure consistency of the testing process.

3.2.6 Analytic strategy

Descriptive statistics, histograms, Mahalanobis D^2 scores, and tests of multivariate normality were used to clean the data, screen for univariate and multivariate outliers, test distributional assumptions and determine the level of missing data. To simplify subsequent analysis procedures, multiple imputation was used to deal with missing data. Multiple imputation is a general technique that creates a number of different plausible complete datasets by replacing missing values with imputed values that are consistent with the data's multivariate structure (Sterne et al., 2009; Von Hippel, 2009). Statistical analyses are then repeated using each of the imputed datasets, and the results of these analyses are combined to produce a single set of final estimates that reflect missing-data uncertainty (Schafer & Olsen, 1998).

Four structural equation models (Salthouse et al., 2003) were used to evaluate the construct validity of the proposed CR construct (see Figure 3.2):

- The first model (Model A) included only the target construct and the five target indicators hypothesised to represent CR.
- The next model (Model B) allowed the hypothesised CR construct to be related to the non-target constructs.
- The third model (Model C) allowed the target CR variables to be related to the non-target constructs, if the inclusion of their relation significantly improved the fit of the model (as determined by a chi-square difference test).
- The final model (Model D) investigated the variance common to the CR construct when all relations of target CR variables to the non-target constructs were included.

In each of the four models, moderate to strong loadings of the target CR variables on the hypothesised CR construct (represented by the red lines in Figure 3.2) would provide evidence of convergent validity (Salthouse et al., 2003). Discriminant validity is established by weak relationships (represented by the blue lines in Figure 3.2) between the hypothesised CR construct and the non-target constructs (in Models B and C) and between the target CR variables and the non-target constructs (in Models C and D) (Salthouse et al., 2003).

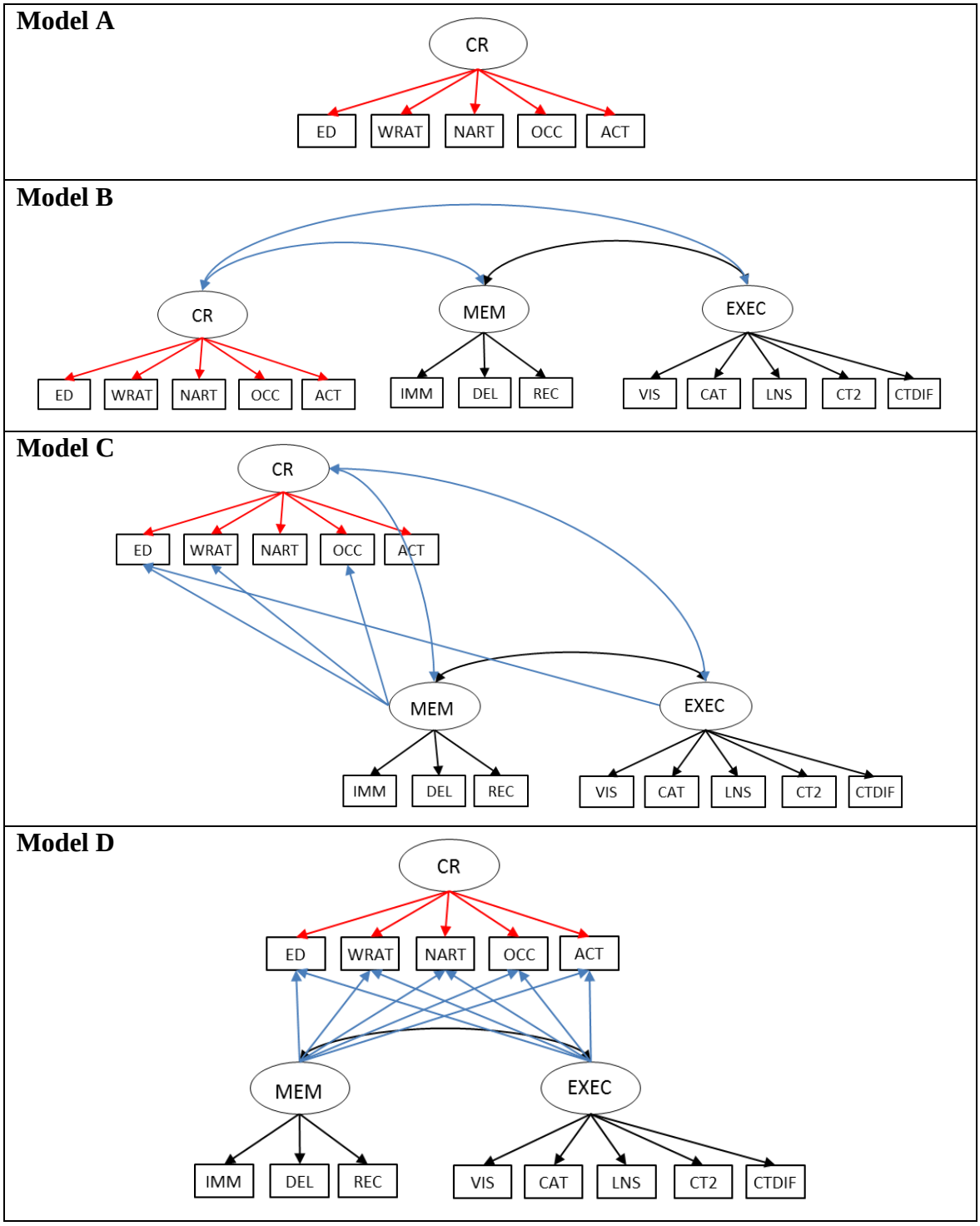

Figure 3.2: Four models for the investigation of construct validity

Note: adapted from Salthouse et al. (2003) Convergent validity is supported when the relations represented by red lines are large; and discriminant validity is supported when the relations represented by blue lines are small. CR= cognitive reserve; MEM = memory; EXEC = executive function; ED = education; WRAT = WRAT-3 reading; NART = National Adult Reading Test; OCC = occupational complexity; ACT = activity participation; IMM = immediate recall (Logical Memory I); DEL = delayed recall (Logical Memory II); REC = recognition (Logical Memory II story B); VIS = visual reasoning; CAT = category fluency; LNS = Letter Number Sequencing Test; CT2: Colour Trails 2 time; CTDIF = Colour Trails difference.

Several fit statistics were used in order to evaluate and compare the fit of each model. These fit statistics included the chi-square (χ^2), the root mean square of error approximation (RMSEA) (Steiger & Lind, 1980), the comparative fit index (CFI) (Bentler, 1990), and the standardised root mean square residual (SRMR). The χ^2 goodness-of-fit test is the most basic and commonly used fit statistic, and evaluates the degree of discrepancy between the observed and model-implied covariance matrices (Bowen & Guo, 2012). Good model fit is indicated by χ^2 values that result in non-significant *p* values (i.e. $p > .05$) (Kline, 2010). However, the χ^2 test is extremely sensitive to sample size, and is therefore likely to be significant even when only trivial differences exist between the implied and observed covariance matrices (Hoyle, 2011). As a result, it is now generally recommended that the chi-square statistic be reported mainly for its historical significance, rather than for the purposes of evaluating model fit (Mueller & Hancock, 2008). Bentler's CFI (Bentler, 1990) is an incremental fit index that reflects the improvement in fit from the specified model compared to a null model (Hoyle, 2011). Values range from 0 to 1.0, with values closer to 1 indicative of better fit. While much of the literature uses a widely accepted cut-off of CFI > 0.9 for acceptable model fit, a more rigorous criterion of ≥ 0.95 is now recommended (Hu & Bentler, 1999), at least for the measurement portion of the model (Hoyle, 2011). The RMSEA and SRMR are both absolute fit indices that assess how well the specified model reproduces the sample data, with lower values indicative of better fit (Hu & Bentler, 1999). The RMSEA is a parsimony-adjusted index and therefore includes a built-in correction for model complexity (Kline, 2010). Another advantage of the RMSEA is that it is typically computed with 90% confidence intervals that allow the researcher to consider the effects of sampling error on model fit (Hoyle, 2011; Kline, 2010). RMSEA values < .06 are considered indicative of good/acceptable fit for the data, values between .06 and .08 indicate reasonable fit, values ≥ 0.1 indicate poor/unacceptable fit (Hu & Bentler, 1999). Upper limits of the 90% confidence interval for RMSEA should also be inspected to ensure they are within the range of acceptable fit indices (Mueller & Hancock, 2008). The SRMR measures the overall difference between the observed and predicted correlations, with a general rule of values ≤ .08 for acceptable fit (Kline, 2010; Schreiber, Amaury, Stage, Barlow, & King, 2010).

Initial descriptive statistics and correlations were conducted using SPSS (Version 22) and all subsequent analyses were conducted using R (Version 3.1.3) (R Core Team, 2015).

3.3 Results

3.3.1 Data cleaning and pre-processing

Descriptive statistics were used to screen for invalid or extreme scores that were indicative of data entry errors. Invalid scores were checked against paper records and corrected, or recoded to missing if the correct score could not be obtained from paper records.

For the Colour Trails Test (CTT), nine cases had negative difference scores (time to complete CTT2 minus time to complete CTT1). Since CTT2 is designed to be a more complex task that should take longer than CTT1 to complete (D'Elia et al., 1994), these negative values were considered to indicate invalid data due to administration errors, or extraneous factors such as participant distraction. Therefore all CTT data for these nine cases were considered invalid and recoded to missing. Normative data published in the professional manual for this test (D'Elia et al., 1994) does not provide scores for CTT times less than 10 seconds or greater than 240 seconds, and as such, these values could be considered to represent the lower and upper limit of valid scores respectively. There were no values less than 10 seconds in the dataset. A number of cases contained values greater than 240 seconds, and these were recoded to 240 (see Appendix H).

Mahalanobis D^2 scores were calculated for each case in order to screen for multivariate outliers. Cases with a probability associated with Mahalanobis D^2 of .001 or less were considered multivariate outliers. Twenty-four cases meeting this criterion were removed from further analysis (see Appendix H). The distribution of each variable was examined for univariate outliers, which were defined as cases that had absolute value z-scores greater than 3.3, and also appeared disconnected from the distribution based on visual inspection of histograms. Thirty-two univariate outliers were deemed to be extreme but valid cases (i.e. from the population intended for sampling), and were truncated to a value 3.3SD from the mean. A further five univariate outliers were deemed to be invalid due to measurement error or not part of the population intended for sampling, and these cases were therefore removed from further analysis. Following removal of outlying cases, data for 609 participants were retained for analysis.

Histograms and descriptive statistics were inspected to assess the univariate normality of each variable relevant to the analysis. Following Kline's (2010) recommendations, absolute values for skewness and kurtosis > 3 and > 10 respectively were considered extreme violations of univariate normality assumptions that were problematic for SEM analyses. None of the variables met these criteria for extreme non-normality, and no transformations were therefore conducted prior to imputation and SEM analysis.

Table 3.4 details the percentage of missing data for each variable included in this analysis. Across the 15 relevant variables and 609 participants, 2.1% of data were missing, and the percentage of missing data was below 3% for all variables except leisure activities, for which 14.3% of data were missing. Missing data for total leisure activity score were typically due to one, or a small number, of missing data points from the overall 14-item scale, and the larger percentage of missing data for this variable may have been attributable to the format of the paper questionnaire. The layout of check boxes to indicate frequency of participation in each item on the scale may have increased the likelihood of participants skipping an item unintentionally.

Table 3.4: Number of missing observations

	Valid	**Missing**	
Variable	**N**	**N**	**%**
Age	609	0	0
Sex	609	0	0
Education (years)	608	1	0.2
NART	606	3	0.5
WRAT-3 reading	609	0	0
Occupational complexity	594	15	2.5
Leisure activities	522	87	14.3
Category fluency	607	2	0.3
Visual reasoning	591	18	3
Letter number sequencing	606	3	0.5
CTT2 time	595	14	2.3
CTT difference	594	15	2.5
LMI recall	593	16	2.6
LMII recall	598	11	1.8
LMII recognition	598	11	1.8
Total	**9535**	**209**	**2.1**

Note: CTT = Colour Trails Test; LMI = WMS-IV Logical Memory I subtest; LMII – WMS-IV Logical Memory II subtest; NART = National Adult Reading Test; WRAT-3 Wide Range Achievement Test 3.

In order to address missing data, multiple imputation was implemented using the "Amelia II" package (version 1.7.3) (Honaker, King, & Blackwell, 2011) for R. Data

were considered to be missing at random and therefore suitable for multiple imputation. Variables included in the imputation model comprised all variables to be included in the subsequent substantive analysis, along with additional covariates that may be predictive of missing values. Ten imputed datasets were created. All subsequent analyses were run using these 10 imputed datasets, and unless stated otherwise, all results presented are pooled estimates using Rubin's (1987) rules.

In order to assess multivariate normality, Mardia's, Royston's and Henze-Zirkler's tests were performed on each of the 10 imputed datasets using the MVN package (Korkmaz, Goksuluk, & Zararsiz, 2014) for R. Mardia's test is based on multivariate extensions of skewness and kurtosis measures (Mecklin & Mundfrom, 2004). Royston's test extends the Shapiro-Wilk test for univariate normality to the multivariate case, and computes a statistic *H* that has an approximate chi-square distribution (Mecklin & Mundfrom, 2004). The Henze-Zirkler test is based on the distance between the hypothesised distribution (multivariate normal) and the observed distribution (Mecklin & Mundfrom, 2004). For each of these tests, non-significant values at an alpha level of 0.05 indicate multivariate normality (Korkmaz et al., 2014; Mecklin & Mundfrom, 2004). Results of these tests indicated that data did not meet the assumptions of multivariate normality (see Appendix H).

3.3.2 Construct validity analyses

Structural equation models were conducted using the lavaan (version 0.5-18) (Rosseel, 2012) and semTools (version 0.4-6) (Pornprasertmanit, Miller, Schoemann, & Rosseel, 2014) packages for R. Since data did not meet the assumptions of multivariate normality, the MLM (maximum likelihood mean-adjusted) estimator was used for all structural equation models. This estimator uses the Satorra-Bentler scaling correction (Satorra & Bentler, 1994) to produce robust standard errors and fit statistics that are corrected for non-normality (Hoyle, 2011). Satorra-Bentler rescaled statistics are therefore reported throughout this section.

SEM is a large sample technique, and while sample size requirements remain a topic of considerable debate (Mueller & Hancock, 2008), there is general consensus that a ratio of at least 10 participants per parameter to be freely estimated in the model constitutes acceptable sample size (Nachtigall et al., 2003; Schreiber et al., 2010). The number of

free parameters to be estimated in the models presented ranged from 10 (Model A) to 37 (Model D). Therefore the number of participants per parameter was above the acceptable limit for all models (range: 16.46 - 60.9 participants per parameter).

Means and standard deviations for each variable are presented in Table 3.5, along with correlations (Pearson's *r*) of each variable with age. Age was significantly correlated with four of the five executive function variables; the direction of these relationships indicated poorer performance was associated with advanced age (the positive correlation of CTT2 with age is in the expected direction, since smaller values for CTT2 indicate faster performance). The memory variables were negatively correlated with age, but none of these values were statistically significant. The pattern of relationships between CR variables and age was mixed. There was a significant negative correlation between age and years of education. However, occupational complexity was positively related to increased age. For the remaining CR variables there was no significant relationship with age.

Table 3.5: Descriptive statistics and correlations with age

Variable	**Mean (SD)**	**Age *r***
Age	64.05 (6.82)	
Cognitive Reserve		
Education (years)	15.06 (3.31)	-.10*
NART	35.83 (6.07)	.05
WRAT 3 reading	53.27 (3.53)	.02
Occupational complexity	112.13 (51.22)	.13**
Leisure activities	63.14 (8.11)	.01
Memory		
LMI immediate recall	10.06 (2.71)	-.05
LMII delayed recall	9.80 (2.83)	-.06
LMII recognition	12.17 (2.04)	-.01
Executive function		
Visual reasoning	3.89 (1.15)	-.24**
Letter number sequencing	11.01 (2.78)	-.25**
Category fluency	22.22 (5.81)	-.23**
CTT 2 time	100.67 (34.42)	.36**
CTT difference	52.16 (28.01)	.02

Note: Mean and r values pooled across 10 imputed datasets using Rubin's rules (implemented in SPSS). SD values pooled following a procedure recommended by Van Burren (2013). CTT = Colour Trails Test; NART = National Adult Reading Test; WRAT-3 = Wide Range Achievement Test
**p < .05; **p < .01.*

The correlation coefficients between all variables included in the construct validity models are presented in Table 3.8 (page 102). Before assessing the construct validity of the CR construct, a confirmatory factor analysis was performed for the two non-target cognitive constructs. This model comprised a memory latent variable with three reflective indicators and an executive function latent variable with five reflective indicators. The two latent variables were allowed to correlate. This two-factor model fit the data well (χ^2 (19) = 43.88, p = .001; CFI = .98; RMSEA = .05 [CI_{90}=.03, .06]; SRMR = .05), and all indicators loaded significantly on their respective latent factors and were above the recommended cut-off of 0.3, with the exception of the Colour Trails difference score, for which the loading did not reach significance (see Table 3.6). The two latent constructs of memory and executive function were not significantly correlated in the confirmatory factor analysis model (r = -.03; p = .556).

Table 3.6: Standardised coefficients from the confirmatory factor analysis of the two-factor model of non-target constructs

	Factor	
	Memory	Executive
Variable		
LMI immediate recall	.90***	
LMII delayed recall	.92***	
LMII recognition	.58***	
Visual reasoning		.38***
Letter number sequencing		.48***
Category fluency		.47***
CTT difference		.06
CTT 2 time		-.60***
Factor correlation		
Memory	-	
Executive	-.03	-

Note: CTT = Colour Trails Test; LMI = WMS-IV Logical Memory I subtest; LMII = WMS-IV Logical Memory II subtest.
****p < .001*

For the first test of construct validity, a confirmatory factor analysis was run on a simple one-factor model comprising the five hypothesised indicators of CR and the latent CR construct (Model A, see Figure 3.2). The results of this model are summarised in column A of Table 3.7 (page 101). Values for the CFI (.96) and SRMR (.03) indicated that the model had an acceptable fit for the data. The RMSEA value for this model (.07) was slightly above the cut-off (≤ .06) for acceptable fit proposed by Hu and Bentler (1999), but other authors have suggested that RMSEA values in the range of .06 to .08 can be considered to indicate reasonable fit for the data (Schreiber et al.,

2010). However, the upper limit of the 90% confidence interval was at the cut-off of 0.1 for poor fit, suggesting the need for some caution when interpreting the results of this model. Each of the five variables hypothesised to represent CR had significant loadings on the latent construct. Inspection of the standardised coefficients suggested that the latent CR construct accounted for only a small proportion of the variance in the occupational complexity and leisure activity variables. Findings relating to this model provided preliminary evidence of convergent validity of the proposed CR construct.

In Model B (see Figure 3.2), the CR construct was examined in relation to the two non-target cognitive constructs (memory and executive function) in order to assess discriminant validity. Results of this analysis are presented in column B of Table 3.7 (page 101). For this model, the CFI (.94) was slightly below the suggested cut-off of ≥0.95 for acceptable fit, but the values of the SRMR (.05), RMSEA (.05), and upper limit of the 90% confidence interval for RMSEA (CI_{90} [.04, .06]) all suggested that the model was a good fit for the data. The loadings of each of the five indicators on the CR construct remained significantly different from zero, providing further evidence for convergent validity. There was no significant correlation between the CR construct and the non-target memory construct, but there was a relatively strong correlation between CR and the non-target executive function construct ($r = 0.61$, $p < .001$). The magnitude of this correlation was larger than the magnitude of factor loadings for some of the CR variables. However, the confidence interval for this correlation, 95% CI [0.5, 0.73], did not include 1.0, indicating that the correlation was significantly less than 1.0. This model therefore provided some evidence of discriminant validity.

Model C provided a more stringent test of convergent and discriminant validity by allowing each observed CR indicator to be related to the non-target cognitive constructs, one at a time, and then retaining any paths that significantly improved the fit of the model for the final Model C. Satorra-Bentler scaled χ^2 difference tests indicated that four paths significantly improved the model fit: education-memory ($\chi^2_{diff} = 6.28$; $p = .012$) ; education-executive ($\chi^2_{diff} = 4.04$; $p = .044$); occupational complexity-memory ($\chi^2_{diff} = 4.43$, $p = .035$); and WRAT-3 reading-memory ($\chi^2_{diff} = 4.32$; $p = .038$). These paths were retained in the final Model C (see column C of Table 3.7 for results). All fit statistics indicated that the model had acceptable fit for the data. The loadings of each

CR variable on the hypothesised construct remained significantly different from zero, providing further evidence of convergent validity. As in Model B, there was no significant correlation between CR and memory constructs, and the significant correlation between CR and executive function ($r = .61$, $p < .001$) remained significantly below 1.0, 95% CI [0.49, 0.72]. As in Model B, the correlation between executive function and the latent CR construct, although significantly less than 1.0, was larger in magnitude than the factor loadings of three of the target indicators on the CR construct. Model C provided additional evidence of discriminant validity.

Model D provided the most demanding test of construct validity, by allowing each of the observed target variables to be related to the non-target cognitive constructs simultaneously. Results are presented in Table 3.7 overleaf. Correlations between the CR construct and non-target cognitive constructs are no longer estimated. Values for all fit statistics were in the recommended range and indicated good model fit. Although the loadings of each CR variable on the target construct remained significant, three of these variables (education, NART, and WRAT-3 reading) also had significant loadings on the executive function construct, and two variables (education and WRAT-3 reading) also had significant relationships with the memory construct. Inspection of the standardised coefficients indicated that the loadings of the CR variables on the target construct were all of greater magnitude than their respective loadings on the non-target cognitive constructs.

Table 3.7: Statistics for construct validity models for variables hypothesised to reflect CR

Variable	Model A	Model B	Model C	Model D
		Fit statistics		
χ^2 scaled	17.90*	148.44***	130.02***	132.47***
df	5	62	58	54
CFI scaled	0.96	0.94	0.95	0.95
RMSEA scaled	0.07	0.05	0.05	0.05
RMSEA scaled CI_{90}	[0.03, 0.1]	[0.04, 0.06]	[0.04, 0.06]	[0.04, 0.06]
SRMR scaled	0.03	0.05	0.04	0.04
	Loadings on CR construct (standardised coefficients)			
CR → Education	.41***	.42***	.30***	.35***
CR → NART	.87***	.86***	.86***	.76***
CR → WRAT-3 reading	.74***	.74***	.61***	.60***
CR → Occupational complexity	.30***	.30***	.30***	.29***
CR → Leisure activities	.17*	.17*	.17*	.17*
	Correlations with other constructs			
CR ↔ Memory	-	.01	.00	-
CR ↔ Executive function	-	.61***	.61***	-
	Memory		**Executive**	
	Loadings on other constructs (standardised coefficients)			
Model C				
Education			.09	
Education	-.08*			
Occupational complexity	-.09*			
WRAT-3 reading	.05			
Model D				
Education	-.11*		.18**	
NART	-.01		.46***	
WRAT-3 reading	.15*		.23**	
Occupational complexity	-.09		.04	
Leisure activities	-.05		.03	

Notes: In the top part of the table, each column corresponds to a model (A-D). Values of fit statistics for each model are reported in the first set of rows, followed by the loadings of each target variable on the target CR construct in the second section. Values presented in the third set of rows correspond to inter-factor correlations between the CR construct and the two non-target cognitive constructs. In the bottom section of the table, each column corresponds to a non-target construct. For Model C, the loadings are presented for paths that significantly improved the fit of the model. For Model D, the loadings for all paths between CR target variables and non-target constructs are presented. NART = National Adult Reading Test; WRAT-3 = Wide Range Achievement Test 3.
**p < .05; **p < .01 ***p < .001*

Table 3.8: Pearson's r correlation matrix for observed model variables

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Education (years)	-												
2. NART	.35***	-											
3. WRAT 3 reading	.27***	.64***	-										
4. Occupational complexity	.25***	.24***	.22***	-									
5. Leisure activities	.10*	.15***	.12**	.05	-								
6. LMI immediate recall	-.07	.04	.07	-.05	-.02	-							
7. LMII delayed recall	-.11**	-.02	.04	-.11**	-.07	.83***	-						
8. LMII recognition	-.03	.03	.05	-.01	-.03	.53***	.54***	-					
9. Visual reasoning	.14**	.19***	.18***	.13**	-.04	-.04	-.03	-.03	-				
10. Letter number sequencing	.23***	.35***	.28***	.11**	.06	-.03	-.04	.01	.23***	-			
11. Category fluency	.14**	.26***	.21***	.10*	.13**	.03	.03	.01	.17***	.20***	-		
12. CTT 2 time	-.08	-.16***	-.17***	-.02	-.04	-.14	.00	.04	-.20***	-.28***	-.30***	-	
13. CTT difference	.06	.04	-0.4	.14**	.06	.02	-.18***	-.19***	-.02	.10*	-.02	-.03	-

Note: CTT = Colour Trails Test; LMI = WMS-IV Logical Memory I subtest; LMII = WMS-IV Logical Memory II subtest; NART = National Adult Reading Test; WRAT-3 = Wide Range Achievement Test 3
**p < .05; **p <. 01; ***p < .001*

3.4 Discussion

This study aimed to evaluate the construct validity of a multiple-indicator, latent variable model of CR, employing a series of four structural equation models designed to provide progressively more demanding tests of convergent and discriminant validity (Salthouse et al., 2003; Salthouse et al., 2004; Siedlecki et al., 2005). The analyses aimed to build on previous studies evaluating the construct validity of latent variable models of CR, by specifying a model with a greater number of observed CR indicators, to more closely reflect the full range of variables that are thought to contribute to CR across the lifespan, and that have been investigated as single indicators in the extant literature.

Results of all four structural equation models provided evidence to support convergent validity of the variables hypothesised to reflect CR, because factors loadings of each indicator on the latent CR construct were significantly different from zero. However, the loadings of occupational complexity and leisure activity variables on the CR construct were relatively small, suggesting that CR may account for only a small proportion of the variance in these indicators. In order to establish construct validity, it was also necessary to demonstrate discriminant validity, by testing whether the inter-factor correlations between the hypothesised CR construct and other non-target cognitive constructs were significantly less than 1.0. Ideally, the magnitude of factor loadings of the observed target indicators on the CR construct should also be similar to or larger than the correlations between the target and non-target constructs (Siedlecki et al., 2009). In Models B and C, the magnitude of the CR loadings were considerably larger than the correlation between the latent CR and episodic memory constructs, and the inter-factor correlation between CR and episodic memory was significantly less than 1.0, providing strong support for discriminant validity. The magnitude of the correlation between CR and executive function was larger than some of the CR factor loadings, but remained significantly less than 1.0. Model D provides the most stringent test of construct validity, by allowing the observed CR variables to load on both the latent CR construct and the non-target latent constructs simultaneously. In this model, all CR indicators continued to load significantly on the CR construct (i.e. convergent validity continued to be supported), but a number of indicators also had significant

loadings on the non-target constructs. However, the loadings of each of these variables on the CR construct were larger in magnitude than their respective loadings on the non-target construct. Overall, the pattern of findings across each of the models provides consistent support for convergent validity and at least partial support for discriminant validity of the hypothesised latent CR construct.

The results of this study replicate and extend the findings of Siedlecki et al. (2009) suggesting that CR is a distinct dimension of individual differences in models of cognitive ageing, but may have some overlap with executive function. As noted by Siedlecki et al. (2009), it is perhaps unsurprising that the constructs of CR and executive function are found to overlap, since executive function is typically measured by tasks involving abilities such as problem solving, mental flexibility, and strategy selection, all of which could be considered important elements of the skills and processes accumulated through intellectually enriching experiences that are conceptualised to reflect CR. While the CR construct evaluated by Siedlecki et al. (2009) was noted to be "fairly narrowly defined", and only included education and two vocabulary tests as observed indicators, the current study demonstrated the construct validity of a latent CR construct incorporating indicators that reflect a broader range of lifetime intellectual experiences thought to contribute to CR. Defining CR as a latent variable that incorporates this broad range of measured indicators may provide a more theoretically valid measure of the construct (Jones et al., 2011), since CR is considered to be a dynamic process that evolves throughout one's life, rather than a stable characteristic (Sanchez, Torrellas, Martin, & Barrera, 2011).

It is important to note a number of limitations of the current study when interpreting the findings. Firstly, the characteristics of the sample studied may limit the generalisability of the results. Participants in this study were highly educated; the proportion with third-level education was much higher in this sample than in the general population of Ireland aged 50 and over. This is a common limitation in cognitive ageing research that perhaps relates to the methods used to recruit participants; samples in many of the studies conducted to date have consisted of well-educated, high-functioning, motivated volunteers (Nebes et al., 2006). In the current study, participants in the youngest age band (50-59 years) and oldest age band (80-89 years) of the sample were under-

represented compared to the population, which may limit the generalisability of the findings to these age groups.

Secondly, for practical reasons, it was not possible to repeat the analyses with a replication sample in the current project. In the previous study using this methodology to evaluate construct validity of CR, analyses were repeated with two replication samples, in order to demonstrate the generalisability of the findings (Siedlecki et al., 2009). Replication of findings using the same model in new samples from the same population is considered an important step in establishing construct validity, and greatly enhances the value of any proposed model (Raykov & Marcoulides, 2000). Further research with replication samples is therefore required, in order to investigate generalisability to other samples and populations.

A final limitation, likely to have resulted from the high-performing, highly educated nature of the sample, was the relatively narrow range of variation observed in the CR indicator variables, which may in turn have limited the models' fit (Mitchell et al., 2012). However, the majority of the fit statistics remained within an acceptable range across each of the models studied.

It should be noted that the specification of all CR measured variables as reflective indicators of the latent CR construct may be somewhat incompatible with the underlying theory, because some of the indicators are conceptualised as contributors to CR rather than effects of the underlying construct (Jones et al., 2011). Reflective indicators are required for investigating the validity of constructs in measurement models, and have been used in previous studies that this chapter builds upon. However, it is important to consider these conceptual issues when interpreting the study findings. Future advancements in statistical modelling methodologies may provide new methods that will allow evaluation of the validity of measurement models that include formative indicators.

The current study provided preliminary evidence for construct validity of a latent variable model of CR incorporating a wider range of indicators than was used in previous construct validation studies. The findings suggest that it is meaningful for researchers to refer to and investigate CR as a distinct construct, although it is important

to be cognisant that the construct may overlap to a certain extent with executive function. These findings also support the use of a multiple-indicator model of CR, to study the combined influence of a range of proxy indicators that are thought to contribute to CR throughout our lives. Further replication of these analyses with additional samples is required in order to investigate the generalisability of the findings, particularly given the high-performing, highly educated nature of the sample studied.

Chapter 4: Relationships between age, cognitive reserve, and cognitive function in a highly educated, normally ageing cohort

4.1 Introduction

Early evidence for cognitive reserve (CR) was primarily derived from studies of Alzheimer's disease (AD) and other dementias, but CR has now been shown to have beneficial effects for cognitive outcomes across a range of clinical conditions including Parkinson's disease (M. J. Armstrong et al., 2012), multiple sclerosis (Sumowski, Chiaravalloti, Wylie, & Deluca, 2009; Sumowski, Wylie, Gonnella, Chiaravalloti, & Deluca, 2010); stroke (Glymour, Weuve, Fay, Glass, & Berkman, 2008; Ojala-Oksala et al., 2012); traumatic brain injury (Green et al., 2008; Kesler et al., 2003; Ropacki & Elias, 2003); HIV (Foley et al., 2012; Morgan et al., 2012) and neuropsychiatric disorders (Kontis, Huddy, Reeder, Landau, & Wykes, 2013). In addition to this diverse range of clinical and neuropathological conditions, CR has also been found to apply to cognitive changes associated with normal, non-pathological ageing (Tucker & Stern, 2011).

As detailed in Chapter 1, it is generally accepted that normal ageing is associated with some subtle declines in cognition, although considerable heterogeneity is observed in individual trajectories of cognitive change (Anderson, 2008; Salthouse, 2012). Age-related changes in cognition are thought to result from a series of deleterious neurobiological processes, including volumetric shrinkage, grey and white matter atrophy, synaptic degeneration, decreased neural connectivity, increased white matter abnormalities, and changes in neurochemical transmission (Anderson, 2008; Nyberg et al., 2012). These neural changes appear to selectively affect certain brain regions with advancing age; frontal and striatal regions are thought to be particularly susceptible to age-related degradation (Buckner, 2004; Raz & Rodrigue, 2006). The differential impact of neurobiological ageing processes in underlying brain regions may explain why the effects of normal ageing are found to vary across cognitive domains (Keller, 2006). Age-related declines are typically observed in domains including executive function, episodic memory, processing speed, and working memory, whereas other abilities such as vocabulary show relative stability or even improvement as we get older (Deary et al., 2009; Hedden & Gabrieli, 2004; Rog & Fink, 2013). For cognitive

domains shown to decline with advancing age, the magnitude of these declines is found to vary widely between individuals (H. Christensen, 2001; Yaffe et al., 2009).

The concept of CR provides one framework to explain the considerable inter-individual variability observed in age-related cognitive outcomes. Rather than protecting against the occurrence of age-related neural changes, CR is thought to allow some individuals to cope with these changes more effectively, and to better maintain cognitive function through more flexible use of cognitive processes and/or compensatory strategies (Stern, 2009, 2012). Cross-sectional studies using samples of generally healthy older adults have demonstrated that CR (as measured by proxy indicators such as education) is positively associated with cognitive performance across a range of domains including executive function, memory, visuospatial ability, and language; the strength of these relationships have been found to vary by cognitive domain and CR proxy indicator (Opdebeeck et al., 2015). There is some evidence that CR may protect against decline in cognition during normal ageing; several longitudinal studies have demonstrated an inverse relationship between CR and rate of decline in cognitive measures over the follow-up interval (e.g. Manly et al., 2003; Marioni et al., 2012; Singh-Manoux et al., 2011). However, evidence for a protective effect against age-related decline is mixed, since other longitudinal studies have found that CR was positively related to cognitive performance at baseline, but had no significant effect on subsequent rates of change in cognitive measures (e.g. Gonzalez et al., 2013; Tucker-Drob et al., 2009; Zahodne et al., 2011; Zahodne et al., 2014). Several studies have found that CR moderated the relationship between markers of age-related neuropathology, such as white matter hyper-intensities (WMH), and cognitive function, and attenuated the negative impact of WMH on cognition (for a review, see Pinter, Enzinger, and Fazekas (2015)). The hypothesised moderating role of CR was also supported in a cross-sectional study by Giogkaraki et al. (2013), who found that CR reduced the negative effect of age on both episodic memory and executive function in healthy older adults.

The current study aimed to investigate whether CR played a moderating role in relationships between age and cognitive function in a large cohort of generally healthy older adults. CR was measured as a latent factor representing the shared variance between five proxy indicators (education, occupational complexity, leisure activities, and two reading tests). The validity of this construct was demonstrated in Chapter 3.

The cognitive outcomes studied included measures of episodic memory and executive function, two cognitive domains that have been shown to be sensitive to the neurobiological processes of ageing, and to decline with advancing age (Anderson, 2008; H. Christensen, 2001; Giogkaraki et al., 2013). It was hypothesised that increasing age would be inversely related to cognitive performance at baseline, and would be associated with greater decline in cognitive function over two years; CR was hypothesised to moderate the relationships between age and both baseline cognitive function and decline in cognitive function. Structural equation modelling (SEM) was used to test the hypothesis that the latent CR construct moderated the cross-sectional relationship between age and both episodic memory and executive function at baseline. Moderation analyses were used to investigate whether CR moderated the relationship between age and decline in the cognitive outcome variables over two years.

4.2 Methods

4.2.1 Participants

Participants for this study were a group of older adults taking part in an ongoing longitudinal study of cognitive function at the NEIL Memory Research Unit in Trinity College Dublin (Hannigan et al., 2015). A full description of the study, including participant recruitment, inclusion/exclusion criteria, testing protocols, and procedures, is provided in Chapter 3 (see pages 77 - 90). All study procedures were approved by the School of Psychology Research Ethics Committee at Trinity College (Appendix D) and written, informed consent was obtained from all participants (Appendix E).

Two datasets (referred to as Dataset 1 and Dataset 2 for the purposes of this study) were used for the analyses presented in this chapter. Descriptive statistics for participants in each dataset are presented in Table 4.1 below. Dataset 1, used for all cross-sectional analyses, was the same dataset used for the construct validity analyses presented in Chapter 3. The sample for Dataset 1 were 638 adults aged 50 and over (65.7% female; mean age = 64.14; SD = 6.83), who completed baseline assessments at the NEIL Memory Research Unit between June 2012 and September 2014. A detailed description of this sample is provided in Section 3.2.2 (page 78). As noted in Chapter 3, participants had a significantly higher level of education than the general population of Ireland aged 50 and over (Kearney et al., 2011). Based on the age profile of the 2011 Census data for the population of Ireland aged 50 and over (Central Statistics Office, 2012), participants aged between 60 and 69 years were over represented in the current sample, whereas participants aged between 50 and 59 years and aged over 80 years were under-represented (see page 80).

Dataset 2, used for all longitudinal analyses presented in this chapter, contained two-wave panel data for a subset of participants from Dataset 1 who completed a 2-year follow-up assessment between June 2014 and April 2015. Of the 638 participants from Dataset 1, 172 were due to complete a follow-up assessment between June 2014 and April 2015, and were therefore eligible for inclusion in Dataset 2. Of the 172 eligible participants, 17 declined to take part in a follow-up assessment and a further six participants were not contactable at follow-up. This represents an attrition rate of

13.37%. Dataset 2 therefore contained 149 cases (58.4% female, mean age at baseline = 63.69, SD = 7.82).

Table 4.1: Demographic characteristics of the samples

Variable	Dataset 1	Dataset 2
N	638	149
Age at baseline (mean, SD)	64.14(6.83)	63.69(7.82)
Sex (%)		
Female	65.7	58.4
Male	34.3	41.6
Years of education (mean, SD)	15.09(3.44)	14.51(3.55)
Highest level of education (%)		
Primary	3.6	6.0
Secondary	21.6	24.2
Tertiary	74.8	69.8
Self-rated health (%)		
Excellent	26	29
Very good	53.7	48
Good	17.3	16.5
Fair	2.5	4.8
Poor	0.5	0.7
Self-rated memory (%)		
Excellent	7.3	5.4
Very good	36.3	36.5
Good	43.1	46.6
Fair	11.7	10.8
Poor	1.6	0.7

4.2.2 Measures

4.2.2.1 Cognitive reserve

Five proxy indicator variables were used to measure CR in the current analyses: years of education, occupational complexity score, leisure activity score (House et al., 1982), WRAT-3 reading score (Wilkenson, 1993) and NART score (Nelson, 1982). Detailed descriptions of these measures and the rationale for their use as CR proxy indicators are provided in Chapter 3 (see pages 81 - 85). For the cross-sectional structural equation models presented in this chapter, CR was measured as a latent variable representing the shared variance between these five proxy indicators. The construct validity of this latent CR variable was demonstrated in Chapter 3. Moderation regression models were used

for longitudinal analyses of Dataset 2. In order to create a CR variable suitable for use in these analyses, CR factor scores for each participant were extracted from the cross-sectional structural equation models.

4.2.2.2 Cognitive outcome variables

The structural equation models presented in this chapter are an extension of the construct validity models evaluated in Chapter 3. Therefore, the latent cognitive constructs included in the construct validity models presented in Chapter 3 were used as cognitive outcome variables for the cross-sectional analyses presented in the current chapter. Memory was represented as a latent variable with three measured indicators: WMS-IV Logical Memory I immediate recall score, and WMS-IV Logical Memory II delayed recall and story B recognition scores (Wechsler, 2009). Five measures were used as indicators of the latent executive function variable: time to complete the Colour Trails Test (CTT) 2 (D'Elia et al., 1994), Colour Trails difference score (CTT2 minus CTT1) (D'Elia et al., 1994), WMS-III Letter Number Sequencing subtest score (Wechsler, 1997a), category fluency score, and CAMDEX Visual Reasoning subtest score (Roth et al., 1998). Detailed descriptions of these memory and executive function indicator measures are provided in Chapter 3 (see pages 85 - 88).

The analytic methods used for the longitudinal analyses presented in this chapter cannot accommodate latent variables with multiple observed indicators. Therefore, rather than using the latent memory and executive function constructs from the cross-sectional models, observed indicator variables for each of these constructs were included as separate cognitive outcomes in moderation analyses conducted with the longitudinal dataset.

4.2.3 Analytic strategy

SEM analyses were used to investigate cross-sectional relationships between age, CR, and cognitive performance. These analyses extended the models presented in Chapter 3, introducing age as an observed variable. The first model tested first-order effects of age and CR on both memory and executive function. In the second model, an interaction term was introduced in order to test whether CR moderated the relationships between age and the respective cognitive outcome variables. Latent variable interaction effects were tested using an unconstrained product indicator approach. While several

approaches have been proposed for estimating interactions between latent variables, the unconstrained product indicator method was considered most appropriate for this study because it is relatively straightforward to apply, and has been shown to have comparable performance to more traditional constrained approaches (e.g. Algina & Moulder, 2001; Joreskog & Yang, 1996; D. A. Kenny & Judd, 1984), which require the researcher to impose a series of complex, non-linear constraints within the model specification (Marsh, Wen, & Hau, 2004). Furthermore, constrained approaches have been shown to produce biased estimates when assumptions of multivariate normality are violated, whereas the unconstrained approach has been shown to be more robust under these conditions (Marsh et al., 2004). The unconstrained product indicator approach was implemented by mean-centring each of the observed indicators (i.e. age and each of the CR indicators), and using the products of the centred indicators to define the latent interaction factor.

Several fit statistics were used in order to evaluate and compare the fit of the models, including the chi-square (χ^2), the root mean square of error approximation (RMSEA) (Steiger & Lind, 1980), the comparative fit index (CFI) (Bentler, 1990) and the standardised root mean square residual (SRMR). These fit statistics are fully described in Section 3.2.6 (page 90). Chi-square values were reported mainly for historical significance rather than for the evaluation of model fit. Cut-off values considered to indicate acceptable fit for the remaining indices were as follows: Bentler's CFI $\geq$ 0.95 for good fit and $\geq$ 0.90 for marginal fit (Hu & Bentler, 1999); RMSEA and RMSEA CI_{90} < .08 for reasonable fit and < .06 for good fit (Hu & Bentler, 1999; Mueller & Hancock, 2008); and SRMR $\leq$ .08 (Kline, 2010).

SEM is a large-sample technique and is typically not recommended for use with sample sizes less than 200 (Hoyle, 2011) or with less than 10 participants per free parameter (Nachtigall et al., 2003; Schreiber et al., 2010). The sample size of the longitudinal dataset did not meet these requirements (n = 149). Therefore, it was not possible to use SEM to investigate whether CR moderated the relationship between age and change in cognitive function over two years, and regression based techniques were instead employed for these research questions. Moderation analyses were implemented using the PROCESS macro for SPSS, which uses an ordinary least squares or logistic

regression-based path analytic framework to estimate coefficients in mediation, moderation, and conditional process models (Hayes, 2012). This analytic approach cannot accommodate latent variables with multiple observed indicators. Therefore, CR factor scores for each participant were extracted from the cross-sectional structural equation model, and used as a continuous moderator variable in the moderation analyses. Dependent variables for these moderation analyses were scores for each of the cognitive measures that served as observed indicators of latent memory and executive function constructs in the cross-sectional models. In order to investigate change in each of the cognitive variables over two time points, a conditional change approach was employed, whereby the predictors and covariates of interest were regressed on the Time 2 score while controlling for the mean-centred Time 1 score. A detailed discussion of approaches to analysis of change in two-wave panel data, and justification for use of a conditional change approach, is provided in Chapter 5 (see pages 151 - 152).

4.3 Results

4.3.1 Data cleaning and pre-processing

4.3.1.1 Dataset 1

Dataset 1, analysed for cross-sectional research questions in this chapter, was also used for the construct validity analyses presented in Chapter 3. The steps taken to clean and prepare this dataset are described in detail in Section 3.3.1 (page 94), and will therefore only be summarised briefly here. Data for the Colour Trails Test (CTT) were considered invalid for nine cases and recoded to missing. Following removal of cases considered to be multivariate outliers (n = 24) and univariate outliers that were not part of the population (n = 5), the final dataset for analysis contained 609 cases. A further 32 univariate outliers were considered extreme but valid cases and truncated to a value 3.3SD from the mean. Since missing data are problematic for SEM, multiple imputation was implemented using the "Amelia II" package (version 1.7.3) (Honaker et al., 2011) for R, to create 10 imputed datasets that were used for all subsequent analyses. Data were considered missing at random and use of multiple imputation was therefore considered appropriate. Results of analyses from the 10 imputed datasets were pooled using Rubin's (1987) rules. Tests of multivariate normality, implemented using the MVN package (Korkmaz et al., 2014) for R, indicated that the data did not meet the assumptions of multivariate normality.

4.3.1.2 Dataset 2

CR factor scores were not available for six cases in Dataset 2, as these cases had been removed as multivariate outliers before conducting the cross-sectional SEM analyses. These six cases were therefore also removed from further analysis of Dataset 2, and the final dataset for analysis contained 143 cases.

Descriptive statistics were conducted in order to screen for invalid or extreme scores that were indicative of data entry errors. Invalid scores were checked against paper records and corrected, or recoded to missing if the correct score could not be obtained from paper records. Using an approach consistent with data cleaning steps applied to Dataset 1, and in Chapters 3 and 6, cases with a negative CTT difference score (time to complete CTT2 minus time to complete CTT1) were considered to indicate invalid

data, since CTT2 is designed to be a more complex task that should take longer to complete than CTT1 (D'Elia et al., 1994). In Dataset 2, two cases had negative Time 1 CTT difference scores, and all Time 1 CTT data for these cases were recoded to missing. There were no cases with negative CTT difference scores at Time 2. One case in Dataset 2 had a Time 2 CTT2 score that was outside the valid range (> 240), and this score was therefore recoded to 240, again using an approach consistent with cleaning procedures applied throughout this thesis (see Appendix H).

Table 4.2 details the percentage missing data for each variable relevant to analyses of Dataset 2 presented in this chapter. For the moderation analyses conducted using Dataset 2, missing data were handled with case-wise deletion.

Table 4.2: Number of missing observations in Dataset 2

	Valid	**Missing**	
Variable	**N**	**N**	**%**
Age	143	0	0
Sex	143	0	0
CR factor score	143	0	0
T1 CESD	140	3	2.1
T2 CESD	140	3	2.1
T1 HADS-A	139	4	2.8
T2 HADS-A	140	3	2.1
T1 LMI immediate recall	138	5	3.5
T1 LMII delayed recall	139	4	2.8
T1 LMII recognition	139	4	2.8
T2 LMI immediate recall	142	1	0.7
T2 LMII delayed recall	142	1	0.7
T2 LMII recognition	141	2	1.4
T1 Visual reasoning	143	0	0
T1 Letter number sequencing	142	1	0.7
T1 CTT2 time	140	3	2.1
T1 CTT difference	140	3	2.1
T1 Category fluency	143	0	0
T2 Visual reasoning	143	0	0
T2 Letter number sequencing	143	0	0
T2 CTT2 time	141	2	1.4
T2 CTT difference	141	2	1.4
T2 Category fluency	142	1	0.7

Notes: CESD = Centre for Epidemiologic Studies Depression Scale; CR = cognitive reserve; CTT = Colour Trails Test; HADS-A = Hospital Anxiety and Depression Scale – Anxiety subscale; LM1 = WMS-IV Logical Memory I subtest; LMII = WMS-IV Logical Memory II subtest; T1 = Time 1; T2 = Time 2

4.3.2 Cross-sectional results: relationships between age, cognitive reserve, and baseline cognitive performance

Structural equation models were analysed using the lavaan (version 0.5-18) (Rosseel, 2012) and semTools (version 0.4-6) (Pornprasertmanit et al., 2014) packages for R. Since data did not meet the assumptions of multivariate normality, the MLM estimator was used for all models. This estimator uses the Satorra-Bentler scaling correction (Satorra & Bentler, 1994) to produce robust standard errors and fit statistics that are corrected for non-normality (Hoyle, 2011). Satorra-Bentler rescaled statistics are therefore reported throughout this section. Across all models, the ratio of participants to free parameters (range = 12.96 to 21 participants per parameter) was above the acceptable sample size limit of 10 participants per parameter to be freely estimated (Nachtigall et al., 2003; Schreiber et al., 2010). A correlation table with means and standard deviations for all model variables is provided in Table 4.6 (see page 122).

4.3.2.1 Model 1: First-order effects of age and CR on cognitive performance

In order to first evaluate the measurement portion of the model, a confirmatory factor analysis was conducted. This model comprised a memory latent variable with three reflective indicators; an executive function latent variable with five reflective indicators; and a CR latent variable with five reflective indicators. The latent variables were allowed to correlate with each other. Fit statistics indicated that the model had acceptable fit for the data (χ^2 (62) = 148.44, $p < .001$; CFI = .94; RMSEA = .05 [CI_{90}=.04, .06]; SRMR = .05); the CFI was very slightly below the stringent cut-off of ≥0.95 (Hu & Bentler, 1999), but above the widely used cut-off of ≥ 0.9 (Hoyle, 2011). All indicators loaded significantly on their respective latent factors, with the exception of the CTT difference score, for which the loading did not reach significance (see Table 4.3). There was a significant correlation between the executive function and CR latent variables (r = .61; $p < .001$), and the remaining inter-factor correlations were non-significant. Squared multiple correlation (SMC) values (see Table 4.3) indicate the proportion of variance in each indicator variable accounted for by the underlying construct, and ranged from .01 (executive function - CTT difference score) to .85 (memory - LMII scaled score).

Table 4.3: Confirmatory factor analysis of the measurement model

	Factor					
	Memory		Executive		CR	
	β	R^2	β	R^2	β	R^2
Variable						
LMI immediate recall	.91[a]	.82				
LMII delayed recall	.92***	.85				
LMII recognition	.58***	.34				
Visual reasoning			.39[a]	.15		
Letter number sequencing			.59***	.35		
Category fluency			.45***	.21		
CTT difference			.07	.01		
CTT 2 time			-.47***	.22		
Years of education					.42[a]	.17
NART					.86***	.74
WRAT-3 reading					.74***	.55
Occupational complexity					.30***	.09
Leisure activity					.17*	.03
Factor correlation						
Memory	-					
Executive	-.04		-			
CR	.01		.61***		-	

Note: CR = cognitive reserve; CTT = Colour Trails Test; LM1 = WMS-IV Logical Memory I subtest; LMII = WMS-IV Logical Memory II subtest; NART = National Adult Reading Test; WRAT-3 = Wide Range Achievement Test 3.

[a] Unstandardised loadings fixed to 1.0, standard errors not estimated

**p < .05; ***p < .001*

Following evaluation of the measurement model, the full structural model was estimated, in order to investigate the first-order effects of age and CR on the two latent cognitive outcome variables (memory and executive function). The model is described graphically in Figure 4.1. Fit statistics indicated that the model had adequate fit for the data (χ^2 (72) = 179.62, p = <.001; CFI = .94; RMSEA = .05 (CI_{90}=.04, .06); SRMR = .05); again, the CFI was slightly below the stringent cut-off of ≥ 0.95 (Hu & Bentler, 1999), but above the cut-off of ≥ 0.9 for marginal fit (Hoyle, 2011). Parameter estimates for the structural paths representing first-order effects are presented in Table 4.4, and a full list of parameter estimates for Model 1 is provided in Appendix I. Age had a significant negative effect on executive function, but the negative relationship between age and memory did not reach the level of significance. CR had a significant positive effect on executive function, and did not have a significant effect on memory.

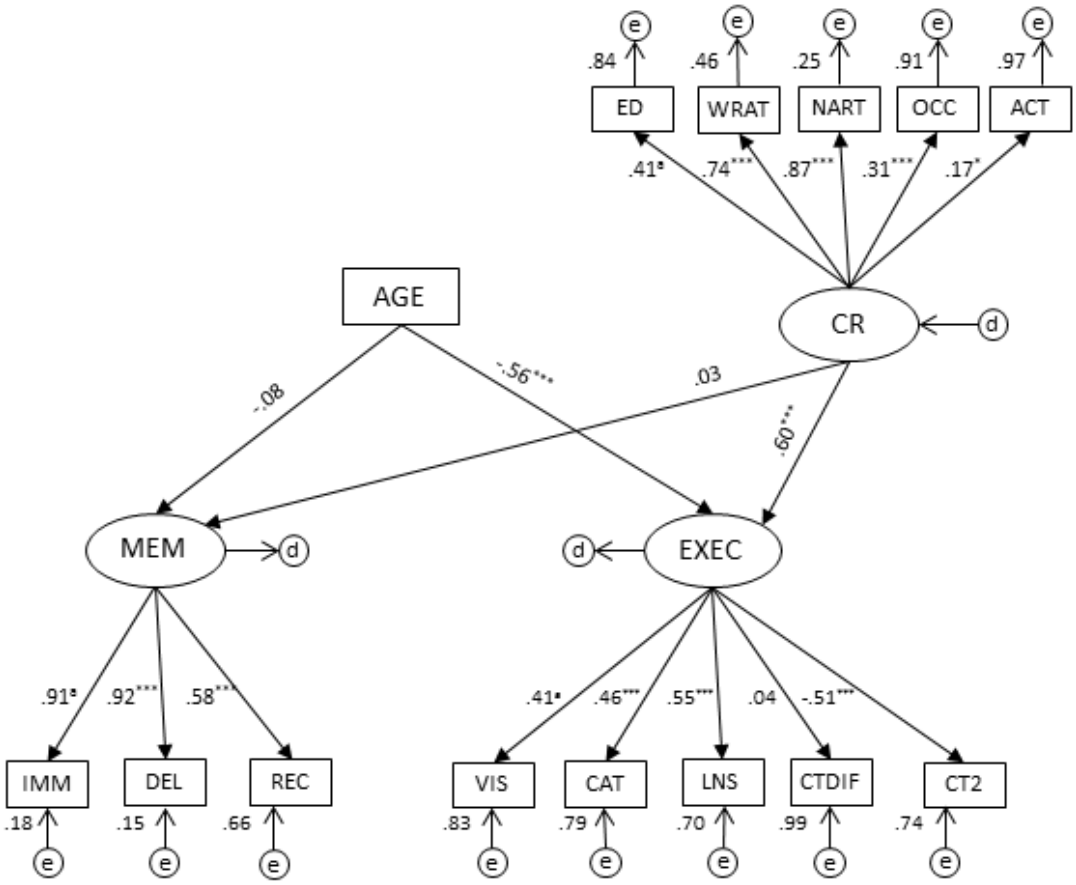

Figure 4.1: Model 1

Note: Standardised coefficients are presented. Co-variances between the latent variables and disturbance coefficients are omitted to improve readability of the figure, and are presented in Appendix I. ACT = leisure activity score; CAT = category fluency; CR = cognitive reserve; CTDIF = Colour Trails difference score; CT2 = Colour Trails Test 2; EXEC = executive function; DEL = WMS-IV Logical Memory II delayed recall; IMM = WMS-IV Logical Memory I immediate recall; LNS = WMS-III Letter Number Sequencing subtest; MEM = memory; NART = National Adult Reading Test; OCC = occupational complexity score; REC = WMS-IV Logical Memory II delayed recognition (story B); VIS = visual reasoning; WRAT = Wide Range Achievement Test 3 reading subtest
[a] Unstandardised loadings fixed to 1.0, standard errors not estimated.
**p < .05; ***p < .001*

Table 4.4: Parameter estimates for structural paths in Model 1

Parameter	***B***	***SE***	***p***	**β**
Structural Model				
Paths				
Age → EXEC	-8.04	1.20	<.001	-.56
Age → MEM	-0.22	0.12	.058	-.08
CR → EXEC	1.70	0.29	<.001	.60
CR → MEM	0.02	0.03	.511	.03

Note: CR = cognitive reserve; EXEC = executive function; MEM = memory

4.3.2.2 Model 2: Moderation effect of CR in relationships between age and cognitive performance

In Model 2, first-order effects from Model 1 were estimated along with the effects of an interaction between age and CR, in order to investigate whether CR moderated the relationship between age and both memory and executive function. The mean-centred products of age and each of the observed CR variables were used as indicators of a latent variable representing the interaction between age and CR. The model is graphically represented in Figure 4.2. The CFI for this model (CFI = 0.90) was at the recommended cut off of ≥ 0.9 for marginal fit, suggesting the need for some caution when interpreting the findings. However, values for the remaining indices were all suggestive of good fit (χ^2 (143) = 244.71, p = <.001; RMSEA = .03 (CI_{90}=.03, .04); SRMR = .05). Parameter estimates for the structural paths representing first-order and interaction effects are presented in Table 4.5, and a full list of parameter estimates for Model 2 is provided in Appendix J. As in Model 1, age had a significant negative effect on executive function, and no significant effect on memory; CR had a significant positive effect on executive function and no significant effect on memory. The effect of the interaction between age and CR was not significant for either executive function or memory, and the results of this model therefore failed to support a moderation effect.

Table 4.5: Parameter estimates for structural paths in Model 2

Parameter	***B***	***SE***	***p***	**β**
	Structural Model			
Paths				
Age → EXEC	-7.99	1.19	<.001	-.56
Age → MEM	-0.22	0.12	.058	-.08
CR → EXEC	1.70	0.29	<.001	.60
CR → MEM	0.02	0.03	.509	.03
INT → EXEC	2.58	2.24	.248	.12
INT → MEM	-0.21	0.19	.269	-.05

Note: CR = cognitive reserve; EXEC = executive function; INT = Age x CR Interaction; MEM = memory

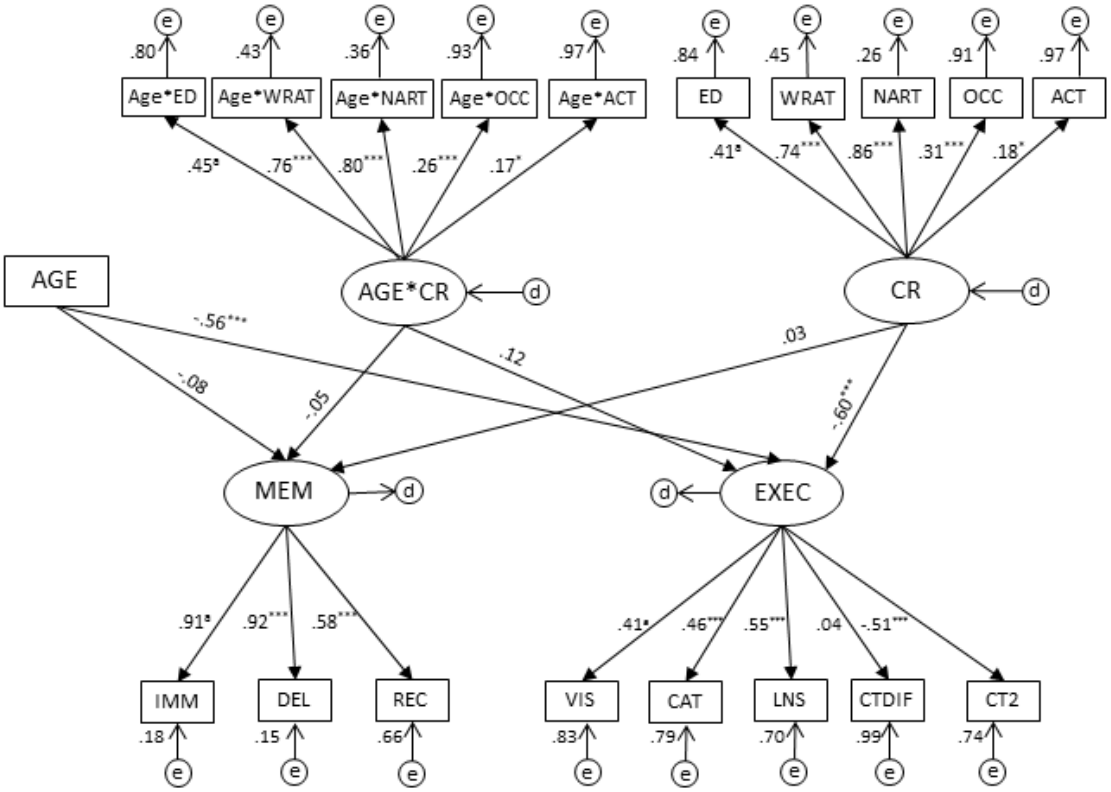

Figure 4.2: Model 2

Note: Standardised coefficients are presented. Co-variances between the latent variables and disturbance coefficients are omitted to improve readability of the figure, and are presented in Appendix J. ACT = leisure activity score; CAT = category fluency; CR = cognitive reserve; CTDIF = Colour Trails difference score; CT2 = Colour Trails Test 2; EXEC = executive function; DEL = WMS-IV Logical Memory II delayed recall; IMM = WMS-IV Logical Memory I immediate recall; LNS = WMS-III Letter Number Sequencing subtest; MEM = memory; NART = National Adult Reading Test; OCC = occupational complexity score; REC = WMS-IV Logical Memory II delayed recognition (story B); VIS = visual reasoning; WRAT = Wide Range Achievement Test 3 reading subtest

[a] Unstandardised loadings fixed to 1.0, standard errors not estimated.

**p < .05; ***p < .001*

Table 4.6: Correlations, means and standard deviations for observed model variables

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Age	-													
2. Education (years)	-.10*	-												
3. NART	.05	.35***	-											
4. WRAT 3 reading	.02	.27***	.64***	-										
5. Occupational complexity	.13**	.25***	.24***	.22***	-									
6. Leisure activities	.01	.10*	.15***	.12**	.05	-								
7. LMI immediate recall	-.05	-.07	.04	.07	-.05	-.02	-							
8. LMII delayed recall	-.06	-.11**	-.02	.04	-.11**	-.07	.83***	-						
9. LMII recognition	-.01	-.03	.03	.05	-.01	-.03	.53***	.54***	-					
10. Visual reasoning	-.24***	.14**	.19***	.18***	.13**	-.04	-.04	-.03	-.03	-				
11. Letter number sequencing	-.25***	.23***	.35***	.28***	.11**	.06	-.03	-.04	.01	.23***	-			
12. Category fluency	-.23***	.14**	.26***	.21***	.10*	.13**	.03	.03	.01	.17***	.20***	-		
13. CTT 2 time	-.36***	-.08	-.16***	-.17***	-.02	-.04	-.14**	.00	.04	-.20***	-.28***	-.30***	-	
14. CTT difference	.02	.06	.04	-.04	.14**	.06	.02	-.18***	-.19***	-.02	.10*	-.02	-.03	-
Mean	64.05	15.06	35.83	53.27	112.13	63.14	10.06	9.80	12.17	3.89	11.01	22.22	100.67	52.16
SD	6.82	3.31	6.07	3.53	51.22	8.11	2.71	2.83	2.04	1.15	2.78	5.81	34.42	28.01

Note: Mean and r values pooled across 10 imputed datasets using Rubin's rules (implemented in SPSS). SD values pooled following a procedure recommended by Van Burren (Van Burren, 2013). CTT = Colour Trails Test; LMI = WMS-IV Logical Memory I subtest; LMII = WMS-IV Logical Memory II subtest; NART = National Adult Reading Test; WRAT-3 = Wide Range Achievement Test 3.
**p < .05; **p < .01; ***p < .001*

4.3.3 Longitudinal results: relationships between age, cognitive reserve, and change in cognitive function over two years

Change scores (Time 2 score minus Time 1 score) for each of the cognitive outcome variables were calculated for descriptive purposes. Paired-samples *t*-tests were used to investigate whether there was significant change over two years for any of the cognitive outcomes studied. Descriptive statistics and *t*-test results are presented in Table 4.7. Paired-samples *t*-tests indicated that there was a significant change in WMS-IV Logical Memory II delayed recall and recognition scores, and WMS-III Letter Number Sequencing subtest score. However, this change was in an unexpected direction for both WMS-IV Logical Memory II measures, suggesting that performance improved at Time 2, compared to Time 1 (see Table 4.7). Therefore significant change in a direction consistent with decline was observed for only one of the cognitive outcomes studied (WMS-III Letter Number Sequencing). There was no significant difference between Time 1 and Time 2 scores for the remaining cognitive outcomes (see Table 4.7).

Table 4.7: Descriptive statistics for cognitive change scores and paired-sample t-tests comparing Time 1 and Time 2 cognitive scores

Variable	N	Min	Max	*M*	*SD*	*t*	*p*
LMI immediate recall change	137	-9	9	0.36	2.86	1.46	.147
LMII delayed recall change	138	-7	9	0.51	2.54	2.35	.021
LMII recognition change	137	-3	6	0.34	1.76	2.28	.024
Visual reasoning change	143	-3	3	-0.11	1.18	-1.13	.259
LNS change	142	-8	10	-0.58	2.55	-2.70	.008
Category fluency change	142	-13	14	-0.53	5.27	-1.20	.234
CTT2 change	139	-61	93	2.03	23.73	1.01	.315
CTT difference change	139	-55	86	3.63	24.86	1.72	.087

Note: CTT = Colour Trails Test; LMI = WMS-IV Logical Memory I subtest; LMII = WMS-IV Logical Memory II subtest; LNS = WMS-III Letter Number Sequencing subtest.

To test the hypothesis that CR moderates the relationship between age and change in cognitive function over two years, moderation analyses were conducted using the PROCESS macro for SPSS (Hayes, 2012). Change in each of the cognitive outcome measures was investigated by analysing effects of the predictors on the Time 2 score while controlling for the Time 1 score. A separate model was run for each cognitive outcome measure. In each of the models, the effects of age, CR, and the interaction term between age and CR on the Time 2 cognitive score were tested while controlling

for covariates of sex, depression (at Time 1 and Time 2), anxiety (at Time 1 and Time 2), and the Time 1 score for the cognitive outcome measure (mean-centred to reduce problems associated with collinearity).

For each of the memory measures studied, the main effects of age and CR were not significant. The interaction term between age and CR also had no significant effect on change in each of the memory measures (see Tables 4.8, 4.9, and 4.10).

There was a significant main effect of age on CTT2 score and CTT difference score (see Tables 4.11 and 4.12). Age had a positive effect on both of these measures; increasing age was associated with slower performance on CTT2 and a larger difference between CTT1 and CTT2 times (i.e. greater decrement in performance due to added complexity of CTT2, suggesting poorer cognitive flexibility). There was no significant effect of age on the remaining executive function measures (WMS-III Letter-Number Sequencing subtest; visual reasoning task; category fluency task). There was no significant main effect of CR on any of the executive function measures studied; the interaction term between age and CR also had no significant effect across all models (see Tables 4.11 - 4.15)

Table 4.8: Moderation analysis for the interaction of age and CR on Logical Memory I immediate recall score at Time 2

Variable	***B***	***SE***	***p***	**95% CI**
(Constant)	10.0	2.03	<.001	[5.98, 14.03]
CR	-0.46	1.49	.761	[-3.41, 2.50]
Age	0.03	0.03	.374	[-0.03, 0.09]
INT Age*CR	0.01	0.02	.686	[-0.04, 0.06]
Sex	-0.13	0.12	.271	[-0.36, 0.10]
T1 CESD	0.04	0.05	.405	[-0.06, 0.14]
T1 HADS-A	0.02	0.10	.848	[-0.18, 0.22]
T2 CES-D	-0.04	0.06	.483	[-0.16, 0.08]
T2 HADS-A	-0.16	0.10	.123	[-0.37, 0.05]
T1 LMI immediate recall	-0.44	0.09	<.001	[0.27, 0.61]
$F(9,118)$	4.40			
R^2	.251***			

Notes: CESD = Centre for Epidemiologic Studies Depression Scale; CR = cognitive reserve; HADS-A = Hospital Anxiety and Depression Scale – anxiety subscale; INT = interaction term; LMI = WMS-IV Logical Memory I subtest; T1 = Time 1; T2 = Time 2.
*** *p < .001*

Table 4.9: Moderation analysis for the interaction of age and CR on Logical Memory II delayed recall score at Time 2

Variable		*B*	*SE*	*p*	95% CI
(Constant)		12.19	1.68	.271	[-1.47, 5.19]
CR		1.49	1.24	.232	[-0.97, 3.95]
Age		-0.00	0.03	.867	[-0.05, 0.05]
INT Age*CR		-0.02	0.02	.292	[-0.06, 0.02]
Sex		-0.27	0.10	.006	[-0.46, -0.08]
T1 CESD		-0.04	0.04	.341	[-0.12, 0.04]
T1 HADS-A		-0.04	0.08	.668	[-0.20, 0.13]
T2 CES-D		-0.00	0.05	.997	[-0.10, 0.10]
T2 HADS-A		-0.01	0.09	.943	[-0.18, 0.16]
T1 LMII delayed recall		-0.45	0.07	<.001	[0.32, 0.58]
$F(9,119)$	7.54				
R^2	.363***				

Notes: CESD = Centre for Epidemiologic Studies Depression Scale; CR = cognitive reserve; HADS-A = Hospital Anxiety and Depression Scale – anxiety subscale; INT = interaction term; LMII = WMS-IV Logical Memory II subtest; T1 = Time 1; T2 = Time 2.
$^{***}p < .001$

Table 4.10: Moderation analysis for the interaction of age and CR on Logical Memory II story B recognition score at Time 2

Variable		*B*	*SE*	*p*	95% CI
(Constant)		14.92	1.13	<.001	[12.68, 17.15]
CR		0.99	0.82	.234	[-0.65, 2.62]
Age		-0.03	0.02	.077	[-0.06, 0.00]
INT Age*CR		-0.01	0.01	.317	[-0.04, 0.01]
Sex		-0.01	0.06	.931	[-0.13, 0.12]
T1 CESD		-0.02	0.03	.377	[-0.08, 0.03]
T1 HADS-A		0.03	0.06	.623	[-0.08, 0.14]
T2 CES-D		0.00	0.03	.903	[-0.06, 0.07]
T2 HADS-A		-0.05	0.06	.416	[-0.16, 0.07]
T1 LMII recognition		0.39	0.07	<.001	[0.24, 0.54]
$F(9,118)$	5.62				
R^2	.300***				

Notes: CESD = Centre for Epidemiologic Studies Depression Scale; CR = cognitive reserve; HADS-A = Hospital Anxiety and Depression Scale – anxiety subscale; INT = interaction term; LMII = WMS-IV Logical Memory II subtest; T1 = Time 1; T2 = Time 2.
$^{***}p < .001$

Table 4.11: Moderation analysis for the interaction of age and CR on Colour Trails Test 2 score at Time 2

Variable	***B***	***SE***	***p***	**95% CI**
(Constant)	23.7	19.74	.230	[-15.30, 62.85]
CR	-9.77	13.28	.463	[-36.07, 16.53]
Age	1.16	0.29	<.001	[0.58, 1.74]
INT Age*CR	0.12	0.21	.563	[-0.29, 0.53]
Sex	0.10	1.01	.923	[-1.90, 2.10]
T1 CESD	0.14	0.42	.751	[-0.71, 0.98]
T1 HADS-A	0.35	0.86	.682	[-1.34, 2.05]
T2 CES-D	-0.09	0.53	.873	[-1.13, 0.96]
T2 HADS-A	0.21	0.89	.811	[-1.54, 1.97]
T1 CTT2 score	0.58	0.08	<.001	[0.43, 0.73]
$F(9,120)$	18.56			
R^2	.582***			

Notes: CESD = Centre for Epidemiologic Studies Depression Scale; CR = cognitive reserve; CTT = Colour Trails Test; HADS-A = Hospital Anxiety and Depression Scale – anxiety subscale; INT = interaction term; T1 = Time 1; T2 = Time 2.
*** *p < .001*

Table 4.12: Moderation analysis for the interaction of age and CR on Colour Trails difference score at Time 2

Variable	***B***	***SE***	***p***	**95% CI**
(Constant)	-7.80	18.53	.675	[-44.50, 28.89]
CR	-19.69	13.19	.138	[-45.80, 6.42]
Age	0.89	0.28	.002	[-0.34, 1.44]
INT Age*CR	0.28	0.21	.176	[-0.13, 0.69]
Sex	0.77	1.01	.445	[-1.23, 2.77]
T1 CESD	-0.104	0.43	.736	[-0.99, 0.70]
T1 HADS-A	0.64	0.86	.457	[-1.06, 2.34]
T2 CES-D	-0.22	0.53	.673	[-1.27, 0.83]
T2 HADS-A	0.41	0.89	.643	[-1.35, 2.17]
T1 CTT difference score	0.36	0.10	<.001	[-0.17, 0.56]
$F(9,120)$	5.10			
R^2	.277***			

Notes: CESD = Centre for Epidemiologic Studies Depression Scale; CR = cognitive reserve; CTT = Colour Trails Test; HADS-A = Hospital Anxiety and Depression Scale – anxiety subscale; INT = interaction term; T1 = Time 1; T2 = Time 2.
*** *p < .001*

Table 4.13: Moderation analysis for the interaction of age and CR on category fluency score at Time 2

Variable		*B*	*SE*	*p*	95% CI
(Constant)		23.61	3.68	<.001	[16.33, 30.89]
CR		-3.42	2.61	.193	[-8.60, 1.75]
Age		-0.03	0.05	.565	[-0.14, 0.08]
INT Age*CR		0.06	0.04	.140	[-0.02, 0.14]
Sex		0.26	0.21	.206	[-0.15, 0.67]
T1 CESD		-0.01	0.09	.901	[-0.18, 0.16]
T1 HADS-A		-0.19	0.17	.286	[-0.53, 0.16]
T2 CES-D		0.06	0.11	.605	[-0.15, 0.26]
T2 HADS-A		-0.00	0.18	.980	[-0.36, 0.35]
T1 Category fluency		0.49	0.08	<.001	[0.33, 0.64]
F(9,123)	7.01				
R^2	.339***				

Notes: CESD = Centre for Epidemiologic Studies Depression Scale; CR = cognitive reserve; CTT = Colour Trails Test; HADS-A = Hospital Anxiety and Depression Scale – anxiety subscale; INT = interaction term; T1 = Time 1; T2 = Time 2.
*** *p < .001*

Table 4.14: Moderation analysis for the interaction of age and CR on Letter Number Sequencing score at Time 2

Variable		*B*	*SE*	*p*	95% CI
(Constant)		12.47	1.68	<.001	[9.14, 15.80]
CR		0.99	1.25	.431	[-1.48, 3.45]
Age		-0.03	0.03	.280	[-0.08, 0.02]
INT Age*CR		-0.01	0.02	.734	[-0.05, 0.03]
Sex		0.07	0.09	.481	[-0.12, 0.25]
T1 CESD		-0.07	0.04	.105	[-0.14, 0.01]
T1 HADS-A		0.14	0.08	.091	[-0.02, 0.29]
T2 CES-D		0.03	0.05	.586	[-0.07, 0.12]
T2 HADS-A		-0.13	0.08	.129	[-0.29, 0.04]
T1 LNS		0.34	0.07	<.001	[0.20, 0.49]
F(9,123)	10.73				
R^2	.440***				

Notes: CESD = Centre for Epidemiologic Studies Depression Scale; CR = cognitive reserve; HADS-A = Hospital Anxiety and Depression Scale – anxiety subscale; INT = interaction term; LNS = WMS-III Letter Number Sequencing subtest; T1 = Time 1; T2 = Time 2.
*** *p < .001*

Table 4.15: Moderation analysis for the interaction of age and CR on visual reasoning score at Time 2

Variable		***B***	***SE***	***p***	**95% CI**
(Constant)		4.21	0.80	<.001	[2.63, 5.79]
CR		-0.60	0.57	.296	[-1.72, 0.53]
Age		-0.01	0.01	.535	[-0.03, 0.02]
INT Age*CR		0.01	0.01	.204	[-0.01, 0.03]
Sex		0.03	0.05	.556	[-0.06, 0.12]
T1 CESD		-0.03	0.02	.114	[-0.07, 0.01]
T1 HADS-A		0.02	0.04	.631	[-0.06, 0.09]
T2 CES-D		0.01	0.02	.712	[-0.03, 0.05]
T2 HADS-A		0.03	0.04	.407	[-0.05, 0.11]
T1 Visual reasoning		0.39	0.09	<.001	[-0.22, 0.56]
$F(9,124)$	5.80				
R^2	.296***				

Notes: CESD = Centre for Epidemiologic Studies Depression Scale; CR = cognitive reserve; HADS-A = Hospital Anxiety and Depression Scale – anxiety subscale; INT = interaction term; T1 = Time 1; T2 = Time 2.

****p < .001*

4.4 Discussion

This study aimed to investigate a potential moderating role for CR in the relationship between age and cognitive function, by testing the hypothesis that there would be a significant age by CR interaction effect on both baseline cognitive function and change in cognitive function over two years, in a large sample of generally healthy older adults. The cross-sectional analyses were an extension of the structural equation models presented in Chapter 3. These analyses did not support the hypothesis that CR moderates the relationship between age and cognitive function in older adults. There were no significant effects of age, CR, or the interaction between these variables on memory. For the executive function construct, there were significant first-order effects of age and CR in the expected directions (i.e. negative relationship with age; positive relationship with CR), but the latent age by CR interaction term did not have a significant effect on executive function at baseline. In order to test hypotheses related to change in cognitive function over two years, moderation analyses were conducted to investigate CR as a moderator in the relationship between age and Time 2 cognitive scores, while controlling for the Time 1 score and relevant covariates. The cognitive outcomes investigated in these analyses were individual cognitive measures that had been used as observed indicators of latent memory and executive function constructs in the cross-sectional models. Across the models, age had a significant negative effect on only two measures (Colour Trails 2 score and Colour Trails difference score). All of the models tested did not find a significant age by CR interaction effect, and therefore did not support the hypothesis that CR moderated the relationship between age and change in cognitive function over two years.

The findings of a positive main effect of CR on executive function at baseline were in line with previous research demonstrating a positive relationship between CR and cognitive function in late life, that varied in strength depending on the cognitive domain studied (Opdebeeck et al., 2015). The current study did not find any relationship between CR and change in cognitive function over two years; these results were in line with several previous studies that found no significant relationship between CR and rate of age-related cognitive decline (e.g. Gonzalez et al., 2013; Tucker-Drob et al., 2009; Zahodne et al., 2011; Zahodne et al., 2014). This study failed to support the findings of a previous study with similar methodology by Giogkaraki et al. (2013), that used SEM

to test whether CR moderated the cross-sectional relationship between age and cognitive function. In this previous study, age had a significant negative effect on two latent episodic memory and executive function constructs, and CR had a significant positive effect on both outcomes. The authors interpreted their findings as supporting a moderation effect for CR, because the effect of age on both cognitive outcomes, while still significant, was greatly reduced in magnitude when CR was added to the model, and the fit of the model was significantly worse if the direct paths of age on the two latent cognitive outcomes were removed (Giogkaraki et al., 2013). However, this previous study did not directly test a moderation effect using a latent variable interaction approach similar to that applied in the current study.

It is important to consider a number of factors when interpreting these findings. Firstly, it is perhaps unsurprising that a moderation effect of CR in the relationship between age and cognitive function was not supported, given that the effects of age on the cognitive outcomes studied were relatively small in magnitude in some cases, and non-significant in others. There was no significant relationship between age and episodic memory across all analyses presented. While there was a significant inverse relationship between age and executive function at baseline, age did not significantly impact change in the majority of these executive function measures over two years. These findings may be explained, at least in part, by the nature of the sample studied. Participants for this study had an average age of approximately 64 years, and were therefore a relatively young sample compared to those used in other previous studies (for example, participants in the study by Giogkaraki et al. (2013) had a mean age of 73 years; participants in the study by Marioni et al. (2012) had a mean age of 75 years; and participants in the study by Gonzalez et al. (2013) had a mean age of 74 years). The cut-off age of 50 and over for inclusion in the current sample was also lower than that used in several previous studies, many of which included participants who were aged 65 and over (e.g. Tucker-Drob et al., 2009; Zahodne et al., 2013). Furthermore, participants in the older age groups (70 years and over), for whom greater likelihood of decline in cognition might be expected, were under-represented relative to those aged under 69 years in the current sample.

The likelihood of detecting any effects of the predictors on cognitive decline may have been reduced in this study, because descriptive statistics for cognitive change scores

indicated that the sample studied displayed very little decline in cognitive measures over two years. Change from Time 1 to Time 2 was non-significant for most of the cognitive measures, in an unexpected direction for two memory measures (i.e. indicated improvement), and any declines that were observed were very small in magnitude. Again, this may be due to characteristics of the sample studied, such as the age profile or education levels of participants. As discussed in Chapter 3, in addition to being relatively young compared to samples in other cognitive ageing studies, the sample for the current study were highly educated, high-functioning, and would largely be considered to have high levels of CR. Although the evidence is mixed, some studies have provided evidence of a protective effect of CR against age-related cognitive decline (e.g. Manly et al., 2003; Marioni et al., 2012; Singh-Manoux et al., 2011). Therefore, the high levels of CR observed in the sample studied may have reduced the likelihood of detecting decline in cognition over two years among this group, in comparison to a sample that better reflected the general population and had a wider range of CR scores.

For the current study, follow-up after two years was the longest feasible interval within the time constraints of the project, but can be considered a relatively short follow-up duration in the context of other cognitive ageing studies. Samples with a relatively young, highly educated, high-performing profile, such as that included in the current study, may require a significantly longer duration of follow-up for the detection of cognitive decline.

This study had a number of methodological limitations. Replication of SEM analyses with additional samples provides evidence regarding the stability of the results (Schreiber et al., 2010), but was not possible within the practical constraints of this project. The sample size for the longitudinal dataset was not sufficiently large to permit use of SEM analyses, and the statistical methods used to investigate longitudinal research questions cannot accommodate latent variables with multiple observed indicators. It was therefore not possible to study the effects of age and CR on change in latent memory and executive function variables similar to those used in the cross-sectional models. Each of the cognitive measures used as observed indicators of these latent constructs were instead studied as a separate cognitive outcome for longitudinal analyses. While this is common practice, latent variables are considered preferable, as

they allow measurement error to be accounted for in the model (Buhi et al., 2007; Hoyle, 2011), and they may provide purer measures of the underlying construct that individual cognitive tests are designed to measure (Mitchell et al., 2012; Salthouse et al., 2003).

The current study provided some evidence for a positive relationship between CR and level of cognitive function in late life, but failed to support a relationship between CR and rate of decline in cognitive function, or a moderating role for CR in the relationship between age and cognitive function. Given that the sample in this study were relatively young, highly educated, and could largely be considered to have high levels of CR, further research using samples with a broader range of CR scores and an older age profile may be useful for determining whether CR moderates the effects of age on cognition in a sample more representative of the general population. Studies with significantly longer follow-up intervals than that used in the current study may be required for the detection of meaningful levels of age-related cognitive decline.

Chapter 5: Exploring methods to account for the effects of cognitive reserve on neuropsychological assessment

5.1 Introduction

Advanced age is the single greatest risk factor for Alzheimer's disease (AD) (Mangialasche et al., 2012; Travers, Lie, & Martin-Khan, 2015). This neurodegenerative disease is known to have a long preclinical phase during which neuropathology accumulates without clinical symptoms (Benke, 2011; Knopman & Caselli, 2012; Sperling et al., 2011). Identification of individuals with preclinical AD, before the onset of dementia, is a topic of considerable interest to both researchers and clinicians, although at present the concept is for research purposes only and not considered to have clinical or diagnostic utility (Knopman & Caselli, 2012; Rentz et al., 2004). These individuals represent an at-risk group for future cognitive decline, and can be considered a subpopulation that might particularly benefit from preventative interventions using a targeted population health approach (Jacobson et al., 2009; Travers et al., 2015). This preclinical phase may also represent an important window of opportunity for intervention with disease-modifying therapies as they become available, during which treatment efficacy could be maximised (Backman, Jones, Berger, Jonsson Laukka, & Small, 2005; Sperling et al., 2011). Research conducted with this preclinical group may be especially informative in terms of predictors of both cognitive decline and progression to dementia; they also represent a group that could be targeted in trials of potential neuroprotective therapies (Benke, 2011; Jacobson et al., 2009).

At present, definitive criteria for preclinical AD are lacking, although a framework for its definition has been proposed by a National Institute on Aging and the Alzheimer Association (NIA-AA) working group (Sperling et al., 2011). This preclinical disease state is typically inferred from the results of multiple measures that may include cognitive testing, functional ability assessments, neuroimaging, and CSF biomarkers (Benke, 2011; Sperling et al., 2011). Use of neuroimaging and CSF biomarkers to quantify pathologic neural change is currently at an early stage of investigation, and neuropsychological assessment of cognitive function therefore remains a widely accepted measure for identification of preclinical or prodromal AD (Rentz et al., 2007). Subtle cognitive deficits may be evident during this preclinical phase (Backman et al.,

2005; Knopman & Caselli, 2012; Sperling et al., 2011). A host of longitudinal observational studies have demonstrated that asymptomatic individuals who go on to develop dementia after a follow-up interval exhibit lower cognitive test scores at baseline, compared to those who do not develop dementia (Elias et al., 2000; Grober et al., 2008; Johnson, Storandt, Morris, & Galvin, 2009; Saxton et al., 2004; Wilson, Leurgans, Boyle, & Bennett, 2011). Deficits are most consistently observed in episodic memory and learning, with a number of studies suggesting that other domains such as executive function may also be affected (M. S. Albert, Moss, Tanzi, & Jones, 2001; Elias et al., 2000; Grober et al., 2008; Tierney, Yao, Kiss, & McDowell, 2005; Wilson et al., 2011). These cognitive deficits are below the level of clinical impairment, but greater than would be expected for normal ageing (see Figure 5.1), and may be difficult to distinguish from normal age-related change given the increased heterogeneity in cognitive function observed among older adults (M. S. Albert, 2002; Knopman & Caselli, 2012; Sperling et al., 2011). Figure 5.1 depicts a hypothetical model for a pathological-clinical continuum encompassing preclinical AD, MCI and AD as proposed by the NIA-AA working group (Sperling et al, 2011), but is likely to represent an over-simplification, given that considerable heterogeneity is observed in trajectories of cognitive decline and not all patients with mild cognitive impairment progress to clinical dementia.

Very sensitive measures of relevant cognitive domains, that can discriminate performance at the higher end of the distribution and that do not demonstrate ceiling effects, are required for detection of subtle, preclinical cognitive decline (Benke, 2011; Knopman & Caselli, 2012). Episodic memory measures are found to be particularly effective in differentiating individuals who will go on to develop AD from those with mild memory problems who will not progress to AD, with more mixed evidence relating to the discriminative power of tests that assess other cognitive domains (M. S. Albert et al., 2001; Backman et al., 2005). On the basis of the current literature, it appears that neuropsychological testing with appropriately sensitive measures is an effective method for identification of subtle cognitive changes associated with preclinical AD, although predictive power for future decline may be increased when cognitive test results are combined with other pertinent information as part of a multimodal assessment (e.g. functional status, genetic, or imaging data etc.) (Benke, 2011).

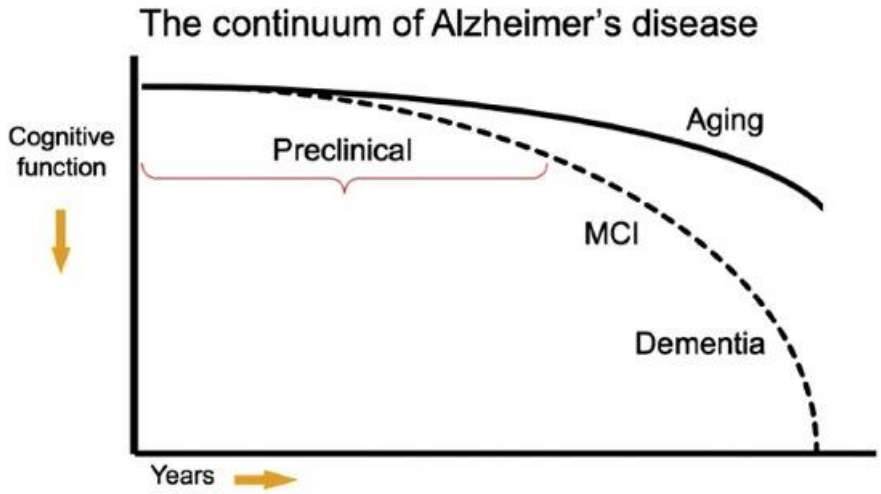

Figure 5.1: Cognitive decline in normal ageing and Alzheimer's disease

Note: Graph from Sperling et al (2011) representing a hypothetical trajectory of cognitive function in AD compared to normal ageing. Note that this graph is for illustrative purposes only and is an over-simplification; considerable inter-individual variability is observed in the rate and nature of cognitive decline associated with both normal ageing and neurodegenerative disease, and not all patients with mild cognitive impairment progress to dementia. Individuals with preclinical AD may exhibit subtle cognitive deficits that are not sufficiently severe to meet criteria for MCI or dementia, but are greater than would be expected for normal, non-pathological ageing.

Selection of neuropsychological methods with sufficient sensitivity to distinguish preclinical AD from normal age-related cognitive changes may be of particular concern when assessing individuals who have high levels of cognitive reserve (CR). Neuropsychological testing typically employs a standardized cut-off score approach, defining decline or clinical change on the basis of test scores that fall a certain number of standard deviations below the established mean for the population, or for a particular age group within the population, using published normative data (Rentz et al., 2004). However, well-educated, high-performing individuals with high levels of CR, who would be expected to typically score a number of standard deviations above the population mean on certain cognitive tests, may continue to perform within the normal range while experiencing a decline for them, relative to their premorbid ability (Petersen, 2004; Stern, 2012, 2013). This was acknowledged by the NIA-AA working group in their diagnostic framework, which notes that individuals with preclinical AD "may demonstrate evidence of decline from their own baseline (particularly if proxies of cognitive reserve are taken into consideration) even if they still perform within the 'normal' range on cognitive measures" (Sperling et al., 2011 p.289). As such, individuals with high CR present a particular challenge to neuropsychologists, since

their performance may mask subtle, disease-related cognitive deficits, and preclinical AD may therefore be more difficult to identify among this group (Sperling et al., 2011; Stern, 2013).

It has been suggested that measures which focus on intra-individual differences in cognitive performance, rather than comparison with group norms, may be a more sensitive approach that could assist in "unmasking" the effects of CR on neuropsychological test performance (Benke, 2011). One method that focuses on intra-individual variability is to identify subgroups within elderly cohorts that have asymmetric cognitive profiles, based on the degree of discrepancy between their performance in two cognitive domains (Jacobson et al., 2009). The assumption underlying this method is that an asymmetric profile may represent decline in certain cognitive domains relative to a premorbid level, and that individuals with this cognitive profile may therefore have a greater risk for AD compared to those with consistent performance across domains (Jacobson et al., 2009). The measures used to calculate an asymmetry index are selected to contrast one domain thought to be resilient to injury or neurodegeneration with a second domain with greater sensitivity to decline or impairment (Jacobson et al., 2009). There is some evidence to suggest that asymmetric cognitive profiles may be linked to preclinical AD. In a retrospective study, participants with AD at follow-up were found to have greater discrepancies between verbal and visuospatial abilities, and to be more likely to have an asymmetric cognitive profile at an assessment 1 to 2 years prior to their subsequent diagnosis of possible AD, when compared with a matched control group who did not develop AD (Jacobson et al., 2002). Studies comparing age- and education-matched groups of participants with or without the apolipoprotein E (ApoE) Ɛ4 allele, which infers genetic susceptibility to AD, have found that individuals in the ApoE Ɛ4+ group were significantly more likely to have an asymmetric cognitive profile than those without the genetic risk factor (Jacobson, Delis, Bondi, & Salmon, 2005; Jacobson, Delis, Lansing, et al., 2005).

Cognitive asymmetry indices contrasting measures of episodic memory and premorbid IQ are a potentially useful method for detecting declines in memory that may otherwise be masked by individuals with high CR when norm-referenced methods of neuropsychological assessment are used. A previous study using this asymmetry index to identify a subgroup of normally ageing individuals with an asymmetric cognitive

profile (defined by standardised scores for delayed verbal recall more than one standard deviation below standardised IQ score) found significant differences between consistent and asymmetric subgroups for measures of global cognitive status and episodic memory (with lower scores in the asymmetric group), although the groups did not significantly differ in measures of executive function (Dockree, Brennan, O'Sullivan, Robertson, & O'Connell, 2015). Using the same classification method, subgroups were also found to systematically differ in terms of behavioural and electrophysiological measures of memory function using event-related potentials (ERPs) (Dockree et al., 2015), and blood-based markers of inflammation that may indicate risk for neurodegeneration, which were increased in the asymmetric subgroup (Downer et al., 2013).

A second neuropsychological approach to detection of early memory changes masked by CR in high-performing individuals involves applying an adjustment for IQ to norms used to define memory impairment (Rentz et al., 2004; Rentz et al., 2007). This method was originally proposed by Rentz and colleagues, who found that participants with memory impairment at baseline according to IQ-adjusted norms were significantly more likely to show cognitive decline and to develop mild cognitive impairment (MCI) after a 3.5-year follow-up interval than those with normal memory at baseline (Rentz et al., 2004). A subsequent study of high-performing older adults (IQ > 120) by the same authors found that IQ-adjusted memory impairment at baseline was associated with a pattern of single-photon emission computed tomography (SPECT) perfusion abnormalities consistent with prodromal AD at baseline, and that participants with memory impairment were more likely to show cognitive and functional decline at a 3-year follow-up assessment than those with normal baseline memory performance (Rentz et al., 2007). These studies adjust for IQ as a proxy for CR rather than education, because the authors suggest that this measure provides an index of ability even when participants do not have the advantages of education, and may therefore be more widely applicable than norms adjusted for education (Rentz et al., 2007). In these previous studies, memory impairment defined by IQ-adjusted norms was significantly more sensitive in predicting progression to MCI when compared with education-adjusted norms, which the authors attributed to low levels of formal education among a large proportion of females with high IQ in their sample (Rentz et al., 2004).

The current study aimed to investigate whether the use of either (a) cognitive asymmetry scores, or (b) comparison with IQ-adjusted norms, were useful methods for identifying a subgroup of high-performing, normally ageing individuals who may be at risk for future cognitive decline. Participants were divided into subgroups with different cognitive profiles according to both classification methods, and analyses were then conducted to investigate whether either of these subgroup classification methods distinguished between participants in terms of baseline cognitive performance, subjective memory ratings, or change in cognitive function over two years.

Cognitive outcomes included measures of episodic memory, executive function, processing speed, and working memory. These measures were selected to include cognitive domains that are shown to decline during normal ageing (Anderson, 2008; Hedden & Gabrieli, 2004; Salthouse, 2004), that are thought to be affected during preclinical AD (Knopman & Caselli, 2012; Sperling et al., 2011; Twamley, Legendre-Ropacki, & Bondi, 2006), and for which significant performance differences have been found between subgroups with different cognitive profiles, using both of the classification methods studied (Dockree et al., 2015; Rentz et al., 2004).

Subjective memory outcome measures included ratings of overall memory performance and frequency of both prospective and retrospective memory failures. Subjective memory complaints are commonly reported in populations of community-dwelling older adults without any clinical condition known to cause memory impairment (Reid & MacLullich, 2006), and are regarded by many as one of the earliest symptoms of cognitive impairment (Juncos-Rabadán et al., 2014). A number of longitudinal studies have found that elderly individuals with subjective memory complaints at baseline were at a higher risk for subsequent cognitive decline and dementia, suggesting that subjective memory complaints may be an important predictor of future dementia (Abdulrab & Heun, 2008). However, research findings related to this topic are mixed, since other longitudinal studies have failed to find evidence for a relationship between subjective memory complaints at baseline and risk for cognitive decline at follow-up (e.g. Schofield et al., 1997). Prospective memory failures are less frequently studied than retrospective errors in elderly populations, but may have consequences that can be considered at least as – if not more – important as the ability to remember things from the past (Smith, Della Sala, Logie, & Maylor, 2000). Consequences of prospective

memory failures can range from minor frustrations as a result of, for example, forgetting to attend an appointment, to potentially serious consequences such as forgetting to take prescribed medications at the appropriate times (Crawford, Smith, Maylor, Della Sala, & Logie, 2003).

For the current study, it was hypothesised that there would be significant differences in baseline cognitive performance, subjective memory ratings, and change in cognitive function over two years between subgroups with (a) a "consistent" versus a "discrepant" (i.e. asymmetric) cognitive profile defined by cognitive asymmetry index scores and (b) a "memory-impaired" versus a "memory-stable" profile defined according to IQ-adjusted norms.

5.2 Methods

5.2.1 Participants

Participants for this study were a group of older adults taking part in an ongoing longitudinal study of cognitive function at the NEIL Memory Research Unit in Trinity College Dublin (Hannigan et al., 2015). Participant recruitment, inclusion/exclusion criteria, testing protocols, and procedures for this study are fully described in Chapter 3 (see pages 77 - 90). All study procedures were approved by the School of Psychology Research Ethics Committee at Trinity College (Appendix D) and written, informed consent was obtained from all participants (Appendix E).

Data from two samples of participants were used for the analyses presented in this chapter. Sample 1 consisted of all participants tested at baseline between June 2012 and September 2014, for whom complete data were available for measures relevant to the classification methods investigated in this chapter (National Adult Reading Test (NART) (Nelson, 1982) and Logical Memory II subtest of the Wechsler Memory Scale IV (WMS-IV) (Wechsler, 2009)). Given that one of the aims of this study was to investigate whether the subgroup classification methods under investigation were effective for identifying a group of individuals who may be at risk for future decline, but would not be detected using traditional norm-based approaches, the sample included only those participants whose baseline memory scores and performance on a short cognitive screening test (the Montreal Cognitive Assessment [MoCA] (Nasreddine et al., 2005)) were in the normal range according to published normative data (Wechsler, 2009) and cut-off scores (Luis et al., 2009) respectively. Sample 2 comprised a subset of participants from Sample 1 who completed a 2-year follow-up assessment between June 2014 and April 2015. The sample analysed depended on the nature of the data required to investigate the specific research question (i.e. measures collected at one time point only; cross-sectional or longitudinal data). Sample 1 was used for cross-sectional analyses of measures collected during baseline assessment. Sample 2 was used for cross-sectional analyses that included measures collected at Time 2 only, and for all longitudinal analyses.

Of the 697 participants who completed baseline assessment between June 2012 and September 2014, data from 43 participants were excluded from Sample 1 for the

following reasons: quality control (incorrect test administration) (n = 5); testing completed but taking an excluded medication (n = 12); diagnosis of diabetes (n = 8); diagnosis of Parkinson's disease (n = 4); incomplete baseline data for WMS Logical Memory II or NART (n = 14). Data were also excluded from these analyses for a further 58 participants with baseline WMS Logical Memory scores greater than 1.5SD below the population mean using age-adjusted normative data (Wechsler, 2009), and for an additional 47 participants with a baseline MoCA score below the cut-off score of 24 for impairment (Coen, Cahill, & Lawlor, 2011; Luis et al., 2009). The final sample for analysis therefore consisted of 549 participants (67% female, mean age = 63.85 years, SD = 6.7). Descriptive statistics for Sample 1 are presented in Table 5.1.

Table 5.1: Demographic characteristics of Samples 1 and 2

Variable	**Sample 1**	**Sample 2**
N	549	130
Age at baseline (mean, SD)	63.85 (6.7)	62.99 (7.6)
Sex (%)		
Female	67	58.5
Male	33	41.5
Years of education (mean, SD)	15.21 (3.4)	14.64 (3.3)
Highest level of education (%)		
Primary	2.7	4.6
Secondary	20	20.8
Tertiary	77.3	74.6
Self-rated health (%)		
Excellent	26.8	31
Very good	53.8	50
Good	16.8	15.1
Fair	2	3.2
Poor	0.6	0.7
Self-rated memory (%)		
Excellent	7.2	6.2
Very good	37	35.7
Good	43.3	48.8
Fair	11	8.5
Poor	1.5	0.8

The subset of Sample 1 eligible for inclusion in Sample 2 consisted of 154 participants who were due to complete a 2-year follow-up assessment between June 2014 and April 2015. Of the 154 eligible participants, 16 declined to take part in a follow-up

assessment, seven were not contactable at follow up, and one participant was deceased before follow-up assessment. This represents an attrition rate of 15.58%. Sample 2 therefore comprised 130 participants (58.5% female; mean age at baseline = 62.99 years; SD = 7.6). Descriptive statistics for Sample 2 are presented in Table 5.1.

5.2.2 Materials

The measures used for this study were administered to participants as part of a longer testing protocol which included an extended battery of cognitive tests, neuropsychological measures, self-report questionnaires, basic physical measures, and an electroencephalogram. A full list of measures included in the overall testing protocol is provided in Appendix F.

5.2.2.1 Subjective memory ratings

As part of a self-report questionnaire completed during both baseline and follow-up assessment, participants were asked to rate their own memory as *excellent*, *very good*, *good*, *fair* or *poor* in response to the question "How would you rate your day-to-day memory at the present time?". This item has been used in a number of large longitudinal studies to provide an overall subjective rating of memory, including the Irish Longitudinal Study of Ageing (TILDA, 2010).

In order to collect informant ratings of cognitive function, participants were also asked to have a spouse, partner, close friend, or relative complete a short questionnaire relating to the participants' memory. The short-form Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (Jorm, 1994) was included in this informant questionnaire at both assessment time points. This 16-item questionnaire measures cognitive decline from a premorbid level over a 10 year period. Each of the 16 items are scored on a five-point scale ranging from one (*much better*) to five (*much worse*), with an average score of three representing no change over the previous 10 years. The measure is widely used, well-validated, and has high internal consistency (coefficient alpha ranging from 0.93 - 0.97 across seven studies) and good test-retest reliability (0.75 over one year) (Jorm, 2004). A number of studies have also demonstrated that the measure is relatively unaffected by the subject's education or premorbid ability (e.g. H. Christensen & Jorm, 1992; Jorm, 1994; Jorm et al., 1996), or

by informant characteristics including age, education (Jorm et al., 1996), and length or type of relationship with the subject (Fuh et al., 1995).

A number of additional subjective memory measures were included in the testing protocol for the follow-up (Time 2) assessment, in order to allow more thorough investigation of subjective memory ratings/complaints. For the purposes of this study, cross-sectional differences between subgroups on these subjective memory ratings at Time 2 were investigated.

The Memory Assessment Clinics Questionnaire (MAC-Q) (Crook, Feher, & Larrabee, 1992) is a six-item scale that measures change in global memory performance and in five specific everyday activities related to memory, compared to a specified previous time point. The scale was initially developed to provide a brief, validated screening instrument for the subjective memory complaints criterion for Age-Associated Memory Impairment (AAMI), with relevant cut-off scores provided by the authors (Crook et al., 1992). The measure was shown to have concurrent validity with a longer, well-validated subjective memory impairment measure, and to have acceptable internal consistency (Cronbach's $\alpha = 0.57$) and test-retest reliability over 12 weeks (0.67) (Crook et al., 1992). The original scale asked about changes in each item since the participant was in high school (the US equivalent of secondary school under the Irish system), but subsequent studies have used shorter time frames, such as comparisons to 5 years and 10 years previously (Slavin et al., 2010). In the current study, each item asked about decline compared to ten years previously.

The Prospective and Retrospective Memory Questionnaire (PRMQ) (Smith et al., 2000) is a 16-item self-report questionnaire designed to measure the frequency with which a participant makes minor memory errors in everyday life. The scale provides scores reflecting frequencies of retrospective errors (i.e. failure to remember things from the past) and prospective errors (i.e. failure to remember intentions or to do something at the right time), as well as a total score. Using a large non-clinical sample of older adults, the scale was found to have high internal consistency (Cronbach's $\alpha = 0.89$ for the total scale; $\alpha = 0.80$ for both the Prospective and Retrospective scales), and demographic factors were not found to significantly influence participant ratings (Crawford et al., 2003). An informant-report version of the Prospective and

Retrospective Memory Questionnaire (Proxy PRMQ) was also included in the informant questionnaire to be completed by a close friend or relative at Time 2. In a validation study, Cronbach's alphas indicated high reliability for the Proxy PRMQ (total scale $\alpha = 0.92$; Prospective scale $\alpha = 0.87$; Retrospective scale $\alpha = 0.83$), and again, scores were not significantly influenced by demographic variables (Crawford, Henry, Ward, & Blake, 2006).

5.2.2.2 Cognitive measures

Premorbid IQ

Premorbid IQ was estimated using the NART, a reading list of 50 phonetically irregular words, with one point awarded for each correctly pronounced word. A table and formula provided in the test manual allow estimation of full scale IQ on the Wechsler Adult Intelligence Scale based on the number of errors the participant makes on the NART (Nelson, 1982). A detailed description of this measure, its reliability and validity, and the rationale for its use to estimate premorbid IQ, is provided in Chapter 3 (see pages 80 - 81).

Overall cognitive status

Overall cognitive status was estimated using the MoCA (Nasreddine et al., 2005), a short cognitive screening test used for the detection of MCI and early AD, which is fully described in Chapter 3 (see page 84). While the original publication (Nasreddine et al., 2005) recommended a cut-off score of less than 26 to indicate below-normal cognitive performance, more recent publications have shown that the test lacks specificity for cognitive impairment at this cut-off, and have recommended a more conservative cut-off score of 23 or less for impairment (Coen et al., 2011; Luis et al., 2009). Participants with scores of 23 or less at baseline were excluded from the analyses presented in this chapter.

Memory

Three memory measures were included in the current analyses: the Logical Memory I and II subtests of the WMS-IV (Wechsler, 2009) and the Free and Cued Selective Reminding Test (FCSRT) (Grober & Buschke, 1987). The WMS-IV Logical Memory I and II subtests (Wechsler, 2009) assess verbal memory under immediate and delayed free recall conditions respectively. These measures are described in detail in Chapter 3

(see page 85). The FCSRT (Grober & Buschke, 1987) measures episodic memory using controlled learning conditions that maximise recall by reinstating encoding conditions at retrieval and using cueing to prompt recall of items not retrieved by free recall. The test begins with a study phase, during which the participant is asked to identify and name each one of four pictures on a stimulus card that match a unique category cue provided by the researcher, and immediate cued recall is tested after each of the four items have been successfully named. The procedure is repeated using four stimulus cards, until a total of 16 items have been identified and retrieved from immediate recall. The study phase is followed by three trials of free recall for all 16 items followed by cued recall for items not retrieved, with 20 seconds of interference (counting backwards) between trials. Free recall across all three trials was included as an outcome measure for the current study. Three parallel forms of the test are available, and were administered in a counter-balanced order to participants in order to avoid practice effects at follow-up testing. The three alternate test forms have been shown to have good concurrent validity using ROC curve analyses, and to have similar levels of sensitivity and specificity for detecting memory impairment using cut-scores (Grober, Ocepek-Welikson, & Teresi, 2009). Cronbach's alpha values were high across the three parallel forms of the test (0.85 - 0.88), providing evidence for internal consistency of the measure (Grober et al., 2009).

Executive function and processing speed

Processing speed was measured using time to complete the Colour Trails Test (CTT) 1 (D'Elia et al., 1994). Scores for CTT 2 (D'Elia et al., 1994) and verbal fluency (animal naming task) were included in the current study as measures of executive function. Complete descriptions of each of these measures, including information related to reliability and validity, are provided in Chapter 3 (see pages 86 – 87).

Working memory

The Letter-Number Sequencing subtest of the Wechsler Memory Scale-III (WMS-III) (Wechsler, 1997b) was used to measure working memory for the current study. This measure is fully described in Chapter 3 (see page 86).

5.2.2.3 Demographic and psychosocial variables

For the current study, group differences for a number of demographic and psychosocial factors were analysed to investigate any potential confounding effects of age, sex, educational level, occupational complexity, and depressive or anxiety symptoms. Demographic measures were included in a self-report questionnaire completed by participants at both assessment time points. Lifelong occupational complexity was measured at Time 1 only, by asking participants to list each occupation held throughout their life and the number of years spent working in that occupation. As described in detail in Chapter 3 (see pages 81 - 83), each occupation was coded using the Standard Occupational Classification 2010 (Office for National Statistics, 2010) to have a complexity level ranging from 1-4, with higher scores indicating a greater degree of complexity. This complexity level was then multiplied by the number of years spent working in the occupation, and the resulting score for each of the participants' occupations was summed to create a total occupational complexity score.

Symptoms of depression or anxiety are known to negatively impact cognitive function in older adults (Beaudreau & O'Hara, 2008; H. Christensen, Griffiths, MacKinnon, & Jacomb, 1997; Murphy & O'Leary, 2010). The 20-item Centre for Epidemiologic Studies Depression scale (CES-D) (Radloff, 1977) was used to measure depressive symptoms at both assessment time points. The anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A) (Zigmond & Snaith, 1983) was also administered to participants at each assessment time point.

5.2.3 Participant classification

Samples were categorised into subgroups according to two separate classification methods, and analyses were repeated to investigate whether subgroup classification using either of these methods was significantly related to any of the outcomes of interest for this study. The first classification method (termed the "cognitive asymmetry classification" for the purposes of this thesis) categorised participants into two subgroups based on asymmetry scores that contrasted their memory performance with their estimated IQ. The second classification method (termed the "IQ-adjusted memory impairment classification" for the purposes of this thesis) used IQ-adjusted norms to

classify participants as either within or below the normal range for scores on a standardised memory test.

5.2.3.1 Cognitive asymmetry classification

For the cognitive asymmetry classification, participants were categorised as having either a "discrepant" or "consistent" profile, based on their memory performance relative to an estimate of their premorbid IQ. Scaled scores for delayed recall on a standardised story memory test (WMS-IV Logical Memory II) (Wechsler, 2009) and NART-estimated IQ scores (Nelson, 1982) were converted to z-scores. An asymmetry score was calculated for each participant by subtracting their Logical Memory II z-score from their NART IQ z-score, and thus represented the difference between these measures in standard deviation units. Participants were defined as discrepant if their Logical Memory II score fell more than 1.5 standard deviations below their NART-estimated IQ score. All other participants were classified as consistent. Using scores from three participants in this study, Table 5.2 illustrates how participants with identical IQ scores, or identical delayed recall scores, can fall into different subgroups.

Table 5.2: Sample cognitive asymmetry group classification calculations

ID	NART-IQ	IQ z-score	LM11 scaled score	LMII z-score	IQ z-score – LMII z-score
1	114.48	0.97	11	0.33	0.64 (Consistent)
2	114.48	0.97	7	-1.00	1.97 (Discrepant)
3	102.09	0.14	7	-1.00	1.14 (Consistent)

Note: LMII = Logical Memory II subtest of the Wechsler Memory Scale IV; NART-IQ = IQ estimated using the National Adult Reading Test

Using this cognitive asymmetry classification 147 (26.78%) participants from Sample 1 were classified as discrepant and 402 (73.22%) were classified as consistent. Pearson's chi-square analyses revealed no significant difference in sex between the consistent (n = 402, 279 female) and discrepant (n = 147, 89 female) groups, $\chi^2(1, N = 549) = 3.82$, $p > .05$. Welch's independent samples t-tests were used to test for group differences on potentially confounding variables. There was no significant difference between the consistent and discrepant groups in age, years of education, occupational complexity, or scores on depression (CES-D) and anxiety (HADS-A) scales (see Table 5.3). There was a significant difference between the subgroups in NART-estimated IQ ($t_{(362.73)} = -4.96$, $p = <.001$), with higher scores in the discrepant group.

Table 5.3: Results of Welch's t-tests and descriptive statistics for age, education, occupational complexity, NART IQ, depression, and anxiety for groups classified by cognitive asymmetry score (Sample 1)

	Group					
	Consistent (n = 402)	Discrepant (n = 147)	95% CI for Mean			
	Mean (SD)	**Mean (SD)**	**Difference**	***T***	***df***	***p***
Age	63.66 (6.6)	64.35 (7.2)	[-2.02, 0.65]	-1.01	240.92	.314
Education	15.21 (3.4)	15.20 (3.2)	[-0.60, 0.63]	0.05	280.03	.963
OCC	109.53 (49.5)	119.20 (52.1)	[-19.58, 0.25]	-1.92	238.71	.056
NART IQ	115.84 (5.1)	117.78 (3.6)	[-2.71, -1.17]	-4.96	352.73	<.001
Depression (CESD)	1.61 (0.9)	1.69 (0.9)	[-0.25, 0.09]	-0.92	240.28	.356
Anxiety (HADS-A)	1.15 (0.8)	1.26 (0.8)	[-0.25, 0.05]	-1.35	242.08	.178

Note: CES-D = Centre for Epidemiologic Studies Depression scale; HADS-A = Hospital Anxiety and Depression Scale – Anxiety subscale; NART IQ = IQ estimated using the National Adult Reading Test; OCC = occupational complexity

For Sample 2, the cognitive asymmetry classification yielded 29 (22.31%) discrepant and 101 (77.69%) consistent participants. Pearson's chi-square analyses revealed no significant difference in sex between the consistent (n = 101, 59 female) and discrepant (n = 29, 17 female) groups, $\chi^2(1, N = 130) = 0.000$, $p > .05$. There was no significant difference between the consistent and discrepant groups in age, years of education, occupational complexity, or scores on depression (CES-D) and anxiety (HADS-A) scales at both time points (see Table 5.4). There was a significant difference between the subgroups in NART-estimated IQ ($t_{(82.91)} = -3.71$, $p = .000$), with higher scores in the discrepant group.

Table 5.4: Results of Welch's t-tests and descriptive statistics for age, education, occupational complexity, NART IQ, depression, and anxiety for groups classified by cognitive asymmetry score (Sample 2)

	Group					
	Consistent (n = 101)	Discrepant (n = 29)	95% CI for Mean			
	Mean (SD)	**Mean (SD)**	**Difference**	***t***	***df***	***p***
Age	63.06 (7.9)	62.76 (6.4)	[-2.55, 3.16]	0.21	54.99	.834
Education	14.56 (3.5)	14.90 (2.7)	[-1.54, 0.87]	-0.56	58.62	.578
OCC	109.74 (51.9)	103.24 (54.7)	[-16.49, 29.48]	0.57	43.67	.572
NART IQ	115.86 (5.9)	119.01 (3.3)	[-4.85, -1.46]	-3.71	82.91	<.001
T1 Depression (CESD)	1.72 (0.9)	1.91 (0.8)	[-0.56, 0.17]	-1.07	44.47	.292
T1 Anxiety (HADS-A)	1.15 (0.8)	1.34 (0.8)	[-0.51, 0.14]	-1.17	48.20	.248
T2 Depression (CES-D)	1.54 (0.9)	1.74 (0.9)	[-0.60, 0.21]	-0.99	44.29	.328
T2 Anxiety (HADS-A)	1.28 (0.7)	1.40 (0.8)	[-0.45, 0.19]	-0.79	45.14	.431

Note: CES-D = Centre for Epidemiologic Studies Depression scale; HADS-A = Hospital Anxiety and Depression Scale – Anxiety subscale; NART IQ = IQ estimated using the National Adult Reading Test; OCC = occupational complexity; T1 = Time 1; T2 = Time 2

5.2.3.2 IQ-adjusted memory impairment classification

For the IQ-adjusted memory impairment classification, participants were categorised as either "stable" or "impaired" based on their score relative to IQ-adjusted norms for a delayed story recall test (WMS-IV Logical Memory II) (Wechsler, 2009). Consistent with the approach taken by Rentz et al (2004, 2007), a mean IQ value of 100, with a standard deviation of 15, for the population (based on the WAIS-R standardisation sample) was used to determine the adjustment of normative data required for each participant. IQ scores > 115 are 1 standard deviation above the population mean of 100, and IQ scores > 122.5 are approximately 1.5 standard deviations above the mean. The published normative mean for WMS-IV Logical Memory II scaled scores is 10 with a standard deviation of 3. This normative mean was therefore adjusted as follows:

- If a participant's NART-estimated IQ was less than 115, no adjustment was made.
- If NART-estimated IQ was ≥ 115 and < 122.5, the normative mean was adjusted upwards by 1 standard deviation (i.e. the adjusted normative mean was 13).
- If NART-estimated IQ was ≥ 122.5, the normative mean was adjusted upwards by 1.5 standard deviations (i.e. the adjusted normative mean was 14.5).

A z-score for Logical Memory II (scaled) was then calculated for each participant using the appropriate adjusted normative mean and published standard deviation. Participants were classified as "impaired" if their score for WMS-IV Logical Memory II fell more than 1.5 standard deviations below the new adjusted normative mean (i.e. adjusted z-score ≤ -1.5).

Using this IQ-adjusted memory impairment classification, 78 (14.21%) participants from Sample 1 were classified as impaired and 471 (85.79%) were classified as stable. Pearson's chi-square analyses revealed no significant difference in sex between the stable (n = 471, 323 female) and impaired (n = 78, 45 female) groups, $\chi^2(1, N = 549) = 3.59$, $p > .05$. Welch's independent samples t-tests were used to test for group differences on potentially confounding variables. There were no significant differences in age, years of education, or scores on depression (CES-D) and anxiety (HADS-A) scales (see Table 5.5). There was a significant difference between subgroups for NART-estimated IQ ($t_{(168.57)} = -9.81$, $p = < .001$); and for occupational complexity, with higher scores for both of these variables in the impaired group ($t_{(99.41)} = -2.65$, $p = .009$).

Table 5.5: Results of Welch's t-tests and descriptive statistics for age, education, occupational complexity, NART IQ, depression, and anxiety for groups classified by IQ-adjusted memory scores (Sample 1)

	Group					
	Stable (n = 471)	Impaired (n = 78)	95% CI for Mean			
	Mean (SD)	**Mean (SD)**	**Difference**	***t***	***df***	***p***
Age	63.70 (6.5)	64.76 (7.9)	[-2.93, 0.81]	-1.13	95.35	.263
Education	15.15 (3.4)	15.55 (3.2)	[-1.19, 0.39]	-1.01	107.08	.316
OCC	109.70 (49.8)	126.58 (51.7)	[-29.51, -4.26]	-2.65	99.41	.009
NART IQ	115.83 (4.9)	119.60 (2.7)	[-4.53, -3.01]	-9.81	168.57	<.001
Depression (CESD)	1.62 (0.9)	1.67 (0.8)	[-0.26, 0.17]	-0.43	95.92	.667
Anxiety (HADS-A)	1.18 (0.8)	1.20 (0.8)	[-0.21, 0.17]	-0.19	96.54	.848

Note: CES-D = Centre for Epidemiologic Studies Depression scale; HADS-A = Hospital Anxiety and Depression Scale – Anxiety subscale; NART IQ = IQ estimated using the National Adult Reading Test; OCC = occupational complexity

For Sample 2, the IQ-adjusted memory impairment classification yielded 20 (15.38%) impaired and 110 (84.62%) stable participants. Pearson's chi-square analyses revealed no significant difference in sex between the stable (n = 110, 66 female) and impaired (n = 20, 10 female) groups, $\chi^2(1, N = 130) = 0.697$, $p > .05$. There was no significant difference between the groups in age, years of education, occupational complexity, or scores on depression (CES-D) and anxiety (HADS-A) scales at either time point (see Table 5.6). There was a significant difference between subgroups in NART-estimated IQ ($t_{(53.31)} = -5.03$, $p = .000$), with higher scores in the impaired group.

Table 5.6: Results of Welch's t-tests and descriptive statistics for age, education, NART IQ, occupational complexity, depression and anxiety for groups classified by IQ-adjusted memory scores

	Group					
	Stable (n = 110)	Impaired (n = 20)	95% CI for Mean			
	Mean (SD)	**Mean (SD)**	**Difference**	***t***	***df***	***p***
Age	63.04 (7.7)	62.75 (6.8)	[-3.19, 3.76]	0.17	28.56	.867
Education	14.60 (3.4)	14.85 (3.0)	[-1.76, 1.25]	-0.35	28.78	.733
OCC	107.89 (53.1)	110.40 (49.7)	[-27.54, 22.51]	-0.21	27.58	.838
NART IQ	115.92 (5.7)	120.10 (2.8)	[-5.85, -2.52]	-5.03	55.31	<.001
T1 Depression (CESD)	1.76 (0.9)	1.76 (0.9)	[-0.44, 0.44]	-0.02	24.95	.986
T1 Anxiety (HADS-A)	1.17 (0.8)	1.28 (0.8)	[-0.51, 0.30]	-0.54	26.34	.592
T2 Depression (CES-D)	1.56 (0.9)	1.68 (0.9)	[-0.59, 0.36]	-0.51	26.11	.617
T2 Anxiety (HADS-A)	1.27 (0.7)	1.48 (0.7)	[-0.57, 0.16]	-1.13	26.87	.269

Note: CES-D = Centre for Epidemiologic Studies Depression scale; HADS-A = Hospital Anxiety and Depression Scale – Anxiety subscale; NART IQ = IQ estimated using the National Adult Reading Test; OCC = occupational complexity; T1 = Time 1; T2 = Time 2

5.2.4 Analytic strategy

Descriptive statistics and histograms were used to clean the data, screen for univariate outliers, test distributional assumptions, and determine the level of missing data. For methods requiring normally distributed data, variables with absolute skewness values greater than 1 (i.e. skewness lower than -1 or higher than +1) were considered to violate the normality assumption in a manner that was problematic for analysis, and these variables were transformed in an attempt to address this issue. If transformation was successful in improving the normality of the distribution, subsequent *t*-tests were conducted with the transformed data.

In order to test for cross-sectional differences between the groups in baseline subjective memory ratings, baseline cognitive performance, and subjective memory measures collected at Time 2 only, a series of independent *t*-tests were conducted. Welch's *t*-tests were used for all comparisons in order to include correction for any violations of the homogeneity of variance assumption (Field, Miles, & Field, 2012; Zimmerman, 2004). The Holm-Bonferroni method was used to correct for multiple comparisons. When multiple hypotheses are tested separately using basic statistical procedures such as *t*-tests with an accepted significance level of α (i.e. 0.05, 0.01, or 0.001), the probability of obtaining a significant result by chance increases as a function of the number of independent tests (R. A. Armstrong, 2014). The Bonferroni correction has been widely used to ameliorate this increased likelihood of Type I error due to multiple comparisons (R. A. Armstrong, 2014). Using the traditional Bonferroni correction for *n* number of null hypothesis tests at a significance level α, *p*-values for each hypothesis are compared with α/*n*, instead of with α (Aickin & Gensler, 1996). There is considerable debate in the scientific literature as to whether the Bonferroni correction should be used, and the method has been criticised for being overly-conservative, and for greatly increasing the likelihood of Type II error (R. A. Armstrong, 2014; Cohen, 2004). Step-wise Bonferroni methods such as that proposed by Holm (1979) are less conservative and now generally preferred to the traditional Bonferroni method, when correction is appropriate to the research question being studied (Aickin & Gensler, 1996; R. A. Armstrong, 2014). Using the Holm-Bonferroni correction for *n* hypothesis tests, *p*-values are placed in order of increasing size, and the smallest value tested for significance using normal Bonferroni correction (i.e. compared with α/*n*). If this

comparison is not significant, then no further testing is conducted, and all findings are considered non-significant (Cohen, 2004). If the smallest *p*-value is significant when compared with α/n, the next smallest *p*-value is compared with $\alpha/(n-1)$ to test for significance (Cohen, 2004). If this test is significant, the next smallest *p*-value is compared with $\alpha/(n-2)$, and then the next smallest with $\alpha/(n-3)$ and so on (Cohen, 2004). This process continues until a non-significant result is found, at which point testing stops and the remaining *p*-values are compared to the significance level at which the non-significant result was reached (Cohen, 2004).

Paired samples *t*-tests were used to investigate whether there was significant decline over two years in any of the cognitive outcomes studied. For any cognitive outcome that showed significant decline, conditional change models were then used to investigate whether classification as discrepant based on cognitive asymmetry score, or as memory-impaired based on comparison with IQ-adjusted norms, was a significant predictor of change in this outcome over two years. While many sophisticated analytic techniques for exploring trajectories of change over time in longitudinal data are now available – such as growth curve modelling, longitudinal multilevel modelling, and random-and fixed-effects pooled time series models – these techniques were developed for the analysis of three or more waves of data and were not considered appropriate for the two-wave panel data collected for this study. There is a lack of clear guidance in the methodological literature about how best to analyse change with data from two time points, and choice between the available methods must largely be guided by the nature of both the research question and the available data (Berrington, Smith, & Sturgis, 2006; Johnson, 2005).

Some authors have suggested investigating predictors of change for a particular outcome with two-wave panel data by using a simple change score (calculated by subtracting each participant's score for the outcome at Time 1 from their score at Time 2), as an outcome variable that is regressed on the predictors of interest (Berrington et al., 2006). However, a major limitation of these unconditional change score models is that change is assumed to be independent of the response at the first time point, given the predictor variables; therefore, they do not account for the "regression to the mean" effect (Berrington et al., 2006). Regression to the mean is an "almost universal" phenomenon in the analysis of change that results from random measurement error,

whereby relatively high or low observations are likely to be followed by a less extreme measurement that is closer to the subject's true mean at the next assessment point (Aickin, 2009; Allison, 1990). In most cases the phenomenon is a statistical artifact, although true regression to the mean is possible in some circumstances (Aickin, 2009). Regardless of its cause, failure to control for regression to the mean may produce biased results or result in natural variation in the data being interpreted as real change (A. G. Barnett, Van der Pols, & Dobson, 2005). A further source of potential bias in unconditional change models with two-wave panel data relates to the fact that scores for the outcome of interest at Time 1 are not included as a predictor in the model (Allison, 1990; Berrington et al., 2006). When panel data is collected as part of an observational, non-experimental study, participants are not randomly assigned to groups or levels of a predictor, and it is therefore possible that initial differences between groups in the outcomes of interest may bias effect estimates (Johnson, 2005). Conditional change models, which extend the unconditional change model to include the Time 1 measure of the outcome of interest as a predictor, allow control for regression to the mean and initial group differences in the outcome that may bias effect estimates in unconditional models (Berrington et al., 2006), and were therefore used in the current study. Following the approach recommended by Aickin (2009) change scores for each outcome of interest were regressed on predictors including the Time 1 score for that outcome, which was centred around the mean.

5.3 Results

5.3.1 Data cleaning and pre-processing

Descriptive statistics were conducted in order to screen for invalid or extreme scores that were indicative of data entry errors. Invalid scores were checked against paper records and corrected, or recoded to missing if the correct score could not be obtained from paper records.

Nine cases included in both Sample 1 and Sample 2 had baseline (Time 1) Colour Trails Test (CTT) difference scores (time to complete CTT2 minus time to complete CTT1) with a negative value. Using an approach consistent with data cleaning steps applied in Chapters 3 and 4, these negative values were considered to indicate invalid data, since CTT2 is designed to be a more complex task that should take longer than CTT1 to complete (D'Elia et al., 1994), and all baseline CTT data for these nine cases were therefore recoded to missing. Sample 2 contained one case with a negative Time 2 CTT difference score, and all Time 2 CTT data were therefore recoded to missing for this participant. Normative data published in the professional manual for the Colour Trails test (D'Elia et al., 1994) does not provide scores for CTT times less than 10 seconds or greater than 240 seconds, and as such, these values could be considered to represent the lower and upper limit of valid scores respectively. There were no CTT values less than 10 seconds in both the Sample 1 and Sample 2 dataset. In the Sample 1 dataset, eight cases contained baseline CTT scores greater than 240 seconds, and these scores were recoded to 240 (see Appendix H). In the Sample 2 dataset, there were no baseline CTT scores outside of the valid range, but one case had a Time 2 CTT2 score greater than 240, which was recoded to 240 for the present analysis (see Appendix H).

Table 5.7 details the percentage of data that were missing in Samples 1 and 2 for each variable relevant to the analyses. Missing data were handled by case-wise deletion for each of the analyses presented in this chapter.

Table 5.7: Number of missing observations

	Sample 1			Sample 2		
	Valid	Missing		Valid	Missing	
	N	N	%	N	N	%
Age	549	0	0	130	0	0
Sex	549	0	0	130	0	0
Education (years)	548	1	0.18	129	1	0.77
NART IQ	549	0	0	130	0	0
Occupational complexity	536	13	2.37	129	1	0.77
T1 CES-D	524	25	4.55	127	3	2.31
T1 HADS-A	528	21	3.83	126	4	3.08
T2 CESD	-	-	-	128	2	1.54
T2 HADS-A	-	-	-	127	3	2.31
T1 LMI immediate recall	543	6	1.09	129	1	0.77
T1 LMII delayed recall	549	0	0	130	0	0
T1 FCSRT free recall	549	0	0	130	0	0
T1 Category fluency	548	1	0.18	130	0	0
T1 Letter number sequencing	547	2	0.36	130	0	0
T1 CTT1 time	537	12	2.19	122	8	6.15
T1 CTT2 time	536	13	2.37	122	8	6.15
T1 MoCA total score	548	1	0.18	130	0	0
T1 Self-rated memory	545	4	0.73	129	1	0.77
T1 IQCODE total score	482	67	12.2	112	18	13.85
T2 LMI immediate recall	-	-	-	130	0	0
T2 LMII delayed recall	-	-	-	130	0	0
T2 FCSRT free recall	-	-	-	130	0	0
T2 Category fluency	-	-	-	130	0	0
T2 Letter number sequencing	-	-	-	130	0	0
T2 CTT1 time	-	-	-	128	2	1.54
T2 CTT2 time	-	-	-	128	2	1.54
T2 MoCA total score	-	-	-	130	0	0
T2 Self-rated memory	-	-	-	128	2	1.54
T2 IQCODE total score	-	-	-	112	18	13.85
T2 PRMQ total score	-	-	-	126	4	3.08
T2 PRMQ prospective score	-	-	-	126	4	3.08
T2 PRMQ retrospective score	-	-	-	128	2	1.54
T2 Proxy PRMQ total score	-	-	-	110	20	15.38
T2 Proxy PRMQ prospective score	-	-	-	115	15	11.54
T2 Proxy PRMQ retrospective score	-	-	-	110	20	15.38
T2 MAC-Q total score	-	-	-	128	2	1.54

Note: CES-D = Centre for Epidemiologic Studies Depression scale; CTT = Colour Trails Test; FCSRT = Free and Cued Selective Reminding Test; HADS-A = Hospital Anxiety and Depression Scale – Anxiety subscale; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; LMI = WMS-IV Logical Memory I subtest: LMII = WMS-IV Logical Memory II subtest; MAC-Q = Memory Assessment Clinics Questionnaire; MoCA = Montreal Cognitive Assessment; NART IQ = IQ estimated using the National Adult Reading Test; OCC = occupational complexity; PRMQ = Prospective and Retrospective Memory Questionnaire; T1 = Time 1; T2 = Time 2

For all variables included in analyses requiring normally distributed data (i.e. *t*-tests in the case of this chapter), distributional assumptions were checked using descriptive statistics and histograms. Distributional assumptions are not discussed for variables

included in the multiple regression analyses only, as this analytic method does not require variables to be normally distributed (Field et al., 2012). In Sample 1, the following variables had skewness and kurtosis values indicative of non-normality that was problematic for analysis: depressive symptoms (CES-D total score), anxiety (HADS-A total score), CTT1 score, CTT2 score, and IQCODE total score. Log transformation was effective in improving the normality of the distribution for each of these variables, with the exception of the IQCODE total score. For the IQCODE, log transformation did not improve the normality of the distribution, but the square root transformation was effective. Log transformed variables were therefore retained for subsequent analyses for all of the variables identified as non-normal apart from the IQCODE, for which the square root transformed variable was used. In Sample 2 the following variables were considered to violate the normality assumption to an extent that was problematic for analysis: depressive symptoms at Time 1 and Time 2 (CES-D), anxiety at Time 1 and Time 2 (HADS-A). Log transformation was effective in improving the normality of the distribution for each variable, and the log transformed variables were retained for subsequent analyses.

5.3.2 Cross-sectional differences in baseline subjective memory ratings

5.3.2.1 Cognitive asymmetry classification

Welch's *t*-tests with Holm-Bonferroni correction for multiple comparisons were used to investigate whether there were significant differences between consistent and discrepant groups in subjective ratings of memory at baseline. There was no significant difference between the groups in self-rated memory ($t_{(247.26)} = -1.70$, $p = .627$). There was also no significant difference in informant memory ratings (IQCODE – square root transformed scores) between consistent and discrepant groups ($t_{(258.36)} = 0.63$, $p = 1$).

5.3.2.2 IQ-adjusted memory impairment classification

Welch's *t*-tests with Holm-Bonferroni correction for multiple comparisons were used to investigate whether there were significant differences in subjective ratings of memory between stable and impaired groups. There was no significant difference between the groups in self-rated memory ($t_{(102.63)} = -1.04$, $p = 1$). There was also no significant difference in informant memory ratings (IQCODE – square root transformed scores) between stable and impaired groups ($t_{(108.45)} = 0.72$, $p = 1$).

5.3.3 Cross-sectional differences in baseline cognitive performance

5.3.3.1 Cognitive asymmetry classification

Welch's *t*-tests with Holm-Bonferroni correction for multiple comparisons were used to investigate whether there were significant differences between consistent and discrepant groups in objective measures of cognitive performance at Time 1. Participants in the discrepant group had significantly lower scores for Logical Memory I immediate recall ($t_{(307.05)} = 15.59$, $p = < .001$), Logical Memory II delayed recall ($t_{(474.33)} = 27.75$, $p = < .001$), and FCSRT free recall ($t_{(231.85)} = 4.10$, $p = < .001$). There were no significant differences between the groups for the remaining cognitive measures (see Table 5.8).

Table 5.8: Results of Welch's t-tests with Holm-Bonferroni adjusted p-values and descriptive statistics for cognitive performance measures: groups classified by cognitive asymmetry score (Sample 1)

	Group					
	Consistent (n = 402)	Discrepant (n = 147)	**95% CI for Mean**			
	Mean (SD)	**Mean (SD)**	**Difference**	***t***	***df***	***p***
MoCA	27.71 (1.71)	27.44 (1.72)	[-0.05, 0.60]	1.65	257.92	.627
LMI immediate recall	11.33 (2.01)	8.64 (1.70)	[2.35, 3.03]	15.59	307.05	<.001
LMII delayed recall	11.36 (1.95)	7.76 (1.04)	[3.34, 3.85]	27.75	474.33	<.001
FCSRT free recall	35.66 (5.21)	33.37 (5.98)	[1.19, 3.39]	4.10	231.85	<.001
Category fluency	22.77 (5.47)	22.16 (6.47)	[-0.57, 1.79]	1.02	226.72	1.000
LNS	11.18 (2.80)	11.13 (2.33)	[-0.42, 0.51]	0.19	302.71	1.000
CTT1 time[1]	3.83 (0.36)	3.87 (0.37)	[-0.10, 0.04]	-0.96	242.60	1.000
CTT2 time[1]	4.54 (0.31)	4.55 (0.33)	[-0.07, 0.05]	-0.27	228.43	1.000

Note: CTT = Colour Trails Test; FCSRT = Free and Cued Selective Reminding Test; LMI = WMS-IV Logical Memory I subtest; LMII = WMS-IV Logical Memory II subtest; LNS = WMS-III Letter Number Sequencing subtest; MoCA = Montreal Cognitive Assessment
[1] Log transformed variable

5.3.3.2 IQ-adjusted memory impairment classification

Welch's *t*-tests with Holm-Bonferroni correction for multiple comparisons were used to investigate whether there were significant differences between stable and impaired groups in objective measures of cognitive performance at Time 1. Participants in the impaired group had significantly lower scores for Logical Memory I immediate recall ($t_{(125.10)} = 10.91$, $p = .000$), and Logical Memory II delayed recall ($t_{(216.97)} = 20.81$, $p = .000$). There were no significant differences between the groups for the remaining cognitive measures (see Table 5.9).

Table 5.9: Results of Welch's t-tests with Holm-Bonferroni adjusted p-values and descriptive statistics for cognitive performance measures: groups classified by IQ-adjusted logical memory scores (Sample 1)

	Group					
	Stable (n = 471)	Impaired (n = 78)	95% CI for Mean			
	Mean (SD)	**Mean (SD)**	**Difference**	***t***	***df***	***p***
MoCA	27.62 (1.73)	27.74 (1.65)	[-0.53, 0.28]	-0.62	107.13	1.000
LMI immediate recall	10.94 (2.18)	8.59 (1.68)	[1.92, 2.77]	10.91	125.10	<.001
LMII delayed recall	10.85 (2.21)	7.63 (1.03)	[2.92, 3.53]	20.81	216.97	<.001
FCSRT free recall	35.24 (5.32)	33.87 (6.51)	[-0.18, 2.91]	1.76	94.76	.574
Category fluency	22.56 (5.53)	22.88 (7.01)	[-1.98, 1.33]	-0.39	93.53	1.000
LNS	11.08 (2.77)	11.68 (1.99)	[-1.12, -0.09]	-2.30	126.90	.183
CTT1 time[1]	3.84 (0.36)	3.87 (0.37)	[-0.12, 0.06]	-0.64	97.25	1.000
CTT2 time[1]	4.55 (0.31)	4.53 (0.34)	[-0.07, 0.10]	0.40	94.86	1.000

Note: CTT = Colour Trails Test; FCSRT = Free and Cued Selective Reminding Test; LMI = WMS-IV Logical Memory I subtest; LMII = WMS-IV Logical Memory II subtest; LNS = WMS-III Letter Number Sequencing subtest; MoCA = Montreal Cognitive Assessment
[1] Log transformed variable

5.3.4 Cross-sectional differences in subjective memory measures collected at Time 2

5.3.4.1 Cognitive asymmetry classification

Using Welch's *t*-tests with Holm-Bonferroni correction for multiple comparisons, no significant differences between consistent and discrepant groups were found for subjective memory measures collected at Time 2 only (see Table 5.10).

Table 5.10: Results of Welch's t-tests with Holm-Bonferroni adjusted p-values and descriptive statistics for Time 2 subjective memory measures: groups classified by cognitive asymmetry score (Sample 2)

	Group					
	Consistent (n = 101)	Discrepant (n = 29)	95% CI for Mean			
	Mean (SD)	**Mean (SD)**	**Difference**	***t***	***df***	***p***
PRMQ total	34.52 (7.95)	35.37 (8.06)	[-4.26, 2.56]	-0.52	45.53	1.000
PRMQ retrospective	16.06 (3.90)	16.28 (4.23)	[-1.98, 1.55]	-0.25	42.97	1.000
PRMQ prospective	18.49 (4.56)	19.10 (4.41)	[-2.50, 1.28]	-0.65	47.37	1.000
MAC-Q total	23.24 (3.18)	23.59 (2.90)	[-1.60, 0.91]	-0.55	49.42	1.000
P-PRMQ total	30.45 (7.79)	31.52 (8.82)	[-5.04, 2.89]	-0.55	35.74	1.000
P-PRMQ retrospective	14.26 (3.93)	15.04 (4.77)	[-2.91, 1.34]	-0.75	34.14	1.000
P-PRMQ prospective	16.23 (4.35)	16.48 (4.38)	[-2.25, 1.75]	-0.25	38.17	1.000

Note: MAC-Q = Memory Assessment Clinics Questionnaire; PRMQ = Prospective and Retrospective Memory Questionnaire; P-PRMQ = Proxy Prospective and Retrospective Memory Questionnaire

5.3.4.2 IQ-adjusted memory impairment classification

Using Welch's *t*-tests with Holm-Bonferroni correction for multiple comparisons, no significant differences between stable and impaired groups were found for subjective memory measures collected at Time 2 only (see Table 5.11).

Table 5.11: Results of Welch's t-tests with Holm-Bonferroni adjusted p-values and descriptive statistics for Time 2 subjective memory measures: groups classified by IQ-adjusted logical memory scores (Sample 2)

	Group					
	Stable (n = 110)	Impaired (n = 20)	**95% CI for Mean**			
	Mean (SD)	**Mean (SD)**	**Difference**	***t***	***df***	***p***
PRMQ total	34.42 (7.97)	36.30 (7.87)	[-5.84, 3.06]	-0.98	26.89	1.000
PRMQ retrospective	15.97 (3.92)	16.85 (4.22)	[-2.97, 1.21]	-0.86	25.42	1.000
PRMQ prospective	18.48 (4.55)	19.45 (4.36)	[-3.16, 1.23]	-0.91	27.41	1.000
MAC-Q total	23.30 (3.19)	23.45 (2.70)	[-1.54, 1.23]	-0.23	29.68	1.000
P-PRMQ total	30.97 (7.86)	29.18 (8.86)	[-2.99, 6.57]	0.78	20.87	1.000
P-PRMQ retrospective	14.51 (4.04)	14.06 (4.70)	[-2.08, 2.97]	0.38	20.55	1.000
P-PRMQ prospective	16.49 (4.32)	15.12 (4.40)	[-1.02, 3.76]	1.19	21.69	1.000

Note: MAC-Q = Memory Assessment Clinics Questionnaire; PRMQ = Prospective and Retrospective Memory Questionnaire; P-PRMQ = Proxy Prospective and Retrospective Memory Questionnaire

5.3.5 Effect of subgroup classification on change in cognitive performance over two years

5.3.5.1 Longitudinal changes in cognitive function

Change scores were first calculated for each cognitive outcome variable by subtracting each participant's Time 1 score from their Time 2 score. Descriptive statistics for these change scores are provided in Table 5.12 below. As a preliminary analysis step, Pearson's correlations were used to investigate whether there was a relationship between age and change in cognitive function over two years. There was a significant negative relationship between age and MoCA change scores (r = -0.183; p = .037). There were no significant correlations between age and change scores for all other cognitive outcomes studied (see Table 5.12).

Table 5.12: Descriptive statistics and correlations with age for cognitive change scores

Variable	N	Min	Max	Mean	SD	Age r^1
MoCA change	130	-12	3	-1.08	2.5	-0.183*
LMI immediate recall change	129	-9	6	0.27	2.8	0.115
LMII delayed recall change	130	-7	6	0.39	2.4	0.007
FSCRT free recall change	130	-14	13	1.15	5.5	0.126
LNS change	130	-8	10	-0.58	2.5	0.120
Category fluency change	130	-13	14	-0.82	5.3	0.081
CTT1 change	120	-37	29	-3.53	12.9	-0.01
CTT2 change	129	-61	52	0.5	19.2	0.039

Note: CTT = Colour Trails Test; LMI = WMS-IV Logical Memory I subtest: LMII = WMS-IV Logical Memory II subtest; LNS = WMS-III Letter Number Sequencing subtest; MoCA = Montreal Cognitive Assessment
[1] Pearson's correlation coefficient
**p < .05*

Paired-samples *t*-tests were used to investigate whether there was a significant decline in any of the cognitive outcomes studied over two years. There was a significant decline in MoCA total score (paired $t_{(129)}$ = -4.87, p = <.001) and WMS-III Letter Number Sequencing (paired $t_{(129)}$ = -2.62, p = .009). There was no significant change in WMS Logical Memory I immediate recall (paired $t_{(128)}$ = 1.12, p = .266); WMS Logical Memory II delayed recall (paired $t_{(129)}$ = 1.85, p = .067); category fluency (paired $t_{(129)}$ = -1.76, p = .081); and CTT2 scores (paired $t_{(119)}$ = 0.29, p = .776). Performance increased significantly for FCSRT free recall (paired $t_{(129)}$ = 2.40, p = .018) and CTT1 (paired $t_{(119)}$ = -2.98, p = .004). Since only the MoCA and WMS-III Letter Number Sequencing subtest showed significant decline over two years, multiple regression analyses were used to investigate whether discrepant or impaired cognitive profile classifications were predictors of decline for these two measures only.

5.3.5.2 Cognitive asymmetry classification

Multiple regression analyses were performed to test whether a discrepant cognitive profile classification at Time 1 (based on cognitive asymmetry scores) predicted change scores for MoCA or the WMS-III Letter Number Sequencing subtest, while controlling for age, sex, education, depression, anxiety, and the Time 1 score for the outcome of interest. Summary results for each model are presented in Table 5.13 and Table 5.14. Discrepant classification based on cognitive asymmetry score was not a significant predictor of decline in either MoCA or Letter Number Sequencing scores. Age was a significant predictor of change in MoCA scores, but not Letter Number Sequencing

scores. Education was a significant predictor of change scores for both the MoCA and the Letter Number Sequencing test; and Time 1 scores also explained a significant proportion of variance in change scores for each of the outcomes studied.

Table 5.13: Multiple regression results for effect of discrepant cognitive profile (cognitive asymmetry) on change in MoCA, controlling for covariates

	B	***SE***	**β**	***t***	***p***
(Constant)	1.20	2.25		0.53	.596
Cognitive asymmetry (discrepant)	0.07	0.50	0.12	0.15	.883
T1 MoCA score	-0.44	0.13	-0.29	-3.39	<.001
Age	-0.08	0.03	-0.22	-2.61	.010
Sex (male)	0.23	0.43	0.05	0.53	.595
Education	0.14	0.06	0.18	2.16	.033
Depression (T2 CES-D)	0.02	0.05	0.05	0.40	.689
Anxiety (T2 HADS-A)	0.07	0.09	0.09	0.80	.425
$F_{(7, 119)}$	3.733**				
R^2	0.180				

Note: CES-D = Centre for Epidemiologic Studies Depression scale; HADS-A = Hospital Anxiety and Depression Scale – Anxiety subscale; MoCA = Montreal Cognitive Assessment; T1 = Time 1; T2 = Time 2
***p < .01*

Table 5.14: Multiple regression results for effect of discrepant cognitive profile (cognitive asymmetry) on change in Letter Number Sequencing, controlling for covariates

	B	***SE***	**β**	***t***	***p***
(Constant)	-0.21	1.98		-0.11	.914
Cognitive asymmetry (discrepant)	0.65	0.43	0.11	1.48	.140
T1 LNS score	-0.59	0.07	-0.66	-8.33	<.001
Age	-0.04	0.03	-0.10	-1.34	.182
Sex (male)	0.29	0.38	0.06	0.77	.442
Education	0.12	0.06	0.16	2.12	.036
Depression (T2 CES-D)	0.00	0.04	0.01	0.10	.920
Anxiety (T2 HADS-A)	-0.05	0.08	-0.06	-0.66	.508
$F_{(7, 119)}$	10.81***				
R^2	0.389				

Note: CES-D = Centre for Epidemiologic Studies Depression scale; HADS-A = Hospital Anxiety and Depression Scale – Anxiety subscale; LNS = WMS-III Letter Number Sequencing subtest; T1 = Time 1; T2 = Time 2
****p < .001*

5.3.5.3 IQ-adjusted memory impairment classification

Multiple regression analyses were performed to test whether classification as memory impaired at Time 1 (based on comparison with IQ-adjusted norms for WMS-IV Logical Memory II) predicted decline in MoCA and WMS-III Letter Number Sequencing

scores, while controlling for age, sex, education, depression, anxiety, and the Time 1 score for the relevant outcome variable. Summary results for each model are presented in Table 5.15 and Table 5.16. Memory impairment based on IQ-adjusted norms was not a significant predictor of decline in either of the cognitive outcome measures. Age was a significant predictor of change in MoCA, but not Letter Number Sequencing. Education was a significant predictor of change both of the cognitive outcomes studied. Time 1 scores also explained a significant proportion of the variance in change scores for each of the outcomes studied.

Table 5.15: Multiple regression results for effect of IQ-adjusted memory impairment on change in MoCA, controlling for covariates

	B	***SE***	**β**	***t***	***p***
(Constant)	1.18	2.24		0.53	.600
IQ-adjusted memory impairment	0.56	0.58	0.08	0.96	.339
T1 MoCA score	-0.45	0.13	-0.30	-3.48	<.001
Age	-0.08	0.03	-0.23	-2.64	.009
Sex (male)	0.19	0.44	0.04	0.43	.665
Education	0.14	0.06	0.19	2.23	.028
Depression (T2 CES-D)	0.02	0.05	0.05	0.45	.652
Anxiety (T2 HADS-A)	0.06	0.09	0.07	0.37	.502
$F_{(7, 119)}$	3.89***				
R^2	0.186				

Note: CES-D = Centre for Epidemiologic Studies Depression scale; HADS-A = Hospital Anxiety and Depression Scale – Anxiety subscale; MoCA = Montreal Cognitive Assessment; T1 = Time 1; T2 = Time 2
****p < .001*

Table 5.16: Multiple regression results for effect of IQ-adjusted memory impairment on change in Letter Number Sequencing, controlling for covariates

	B	***SE***	**β**	***t***	***p***
(Constant)	-0.15	1.97		-0.08	.941
IQ adjusted memory impairment	0.98	0.50	0.14	1.96	.053
T1 LNS score	-0.58	0.07	-0.65	-8.30	<.001
Age	-0.04	0.03	-0.11	-1.36	.177
Sex (male)	0.22	0.38	0.04	0.58	.564
Education	0.12	0.06	0.16	2.13	.036
Depression (T2 CES-D)	0.01	0.04	0.03	0.30	.765
Anxiety (T2 HADS-A)	-0.07	0.08	-0.09	-0.89	.375
$F_{(7, 119)}$	11.18***				
R^2	0.397				

Note: CES-D = Centre for Epidemiologic Studies Depression scale; HADS-A = Hospital Anxiety and Depression Scale – Anxiety subscale; LNS = WMS-III Letter Number Sequencing subtest; T1 = Time 1; T2 = Time 2
****p < .001*

5.3.6 Supplementary analyses

As noted in Section 5.2.3, there was a significant difference in IQ scores between subgroups classified using both methods, with higher IQ scores in the discrepant compared to the consistent group using the cognitive asymmetry classification, and in the impaired compared to the stable group using the IQ-adjusted memory impairment classification. For a subset of the overall sample that included only those participants with high IQ (> 120), there were no significant differences in IQ between subgroups using either classification method. In order to ensure that any results found in the overall sample were not due to confounding effects of initial group differences in IQ, all analyses were repeated using data from this subset with high IQ (for whom there were no initial subgroup differences in IQ). The pattern of results was largely unchanged when analyses were repeated with this subset, and the results of these supplementary analyses are therefore not presented in this chapter.

Given that risk for cognitive decline increases with advancing age, and in light of the fact that the overall sample studied was relatively young, all analyses were also repeated with participants aged 65 and over only. A similar pattern of results to those from the overall sample were also found when analyses were restricted to include only participants aged 65 and over, and these supplementary analyses are therefore not presented in this chapter.

5.4 Discussion

In this chapter, participants were divided into subgroups with different cognitive profiles, using two classification methods that attempt to account for the effects of CR on neuropsychological assessment. All participants completed a battery of neuropsychological tests and subjective memory measures at baseline and after a follow-up interval of two years, in order to investigate whether the classification methods were effective in identifying a subgroup of older adults with subtle cognitive deficits at baseline, who were at greater risk of subsequent cognitive decline. The "cognitive asymmetry classification" method categorised participants into "consistent" or "discrepant" subgroups based on the degree of asymmetry between their performance on a standardised episodic memory test and their NART-estimated premorbid IQ. The "IQ-adjusted memory impairment classification" method categorised participants into "stable" or "impaired" groups based on their score for a standardised episodic memory test relative to normative values that were adjusted for their NART-estimated premorbid IQ.

Both methods distinguished between individuals in terms of memory performance at baseline; scores for several memory measures at Time 1 were significantly lower in the discrepant and impaired subgroups compared to their consistent and stable counterparts. There were no significant differences between subgroups for baseline performance on measures of overall cognitive function, executive function, processing speed, and working memory. There were no significant cross-sectional differences between either set of subgroups for subjective memory measures, and the hypothesis that individuals classified as discrepant or impaired would be more likely to exhibit subjective memory complaints was therefore not supported. Multiple regression analyses were conducted to investigate whether participants who were classified as discrepant or impaired at baseline were at an increased risk of cognitive decline over two years. Predictors of decline were investigated for MoCA total scores (Nasreddine et al., 2005) and WMS-III Letter Number Sequencing (Wechsler, 1997b) scores only, because these were the only cognitive outcome measures for which significant decline was observed over the follow-up interval (i.e. for which Time 2 scores were found to be significantly lower than Time 1 scores using paired samples *t*-tests). Subgroup classification using either method was not a significant predictor of change in these outcome measures over two

years, and the hypothesis that individuals in the discrepant or impaired groups would show greater decline in cognitive function at follow-up was therefore not supported.

The findings related to cross-sectional differences in baseline cognitive performance and subjective memory ratings were consistent with behavioural results from a previous study that used the cognitive asymmetry method to categorise a small sample of older adults into "low-performing" and "high-performing" subgroups, that equate to the "discrepant" and "consistent" subgroups studied for this chapter (Dockree et al., 2015). This previous study also found that memory scores were significantly lower in the low-performing (i.e. discrepant group), and found no significant differences between the subgroups for performance on executive function measures or for subjective memory ratings (Dockree et al., 2015). The current study did not replicate the findings of previous studies using the IQ-adjusted memory impairment classification method, in which individuals with baseline memory impairment according to IQ-adjusted norms were significantly more likely to show cognitive decline at follow-up assessment (Rentz et al., 2004; Rentz et al., 2007). In these previous studies, the duration of follow-up was somewhat longer (between 3 and 3.5 years, compared to 2 years in the current study), and participant samples had an older age profile than those in the current study (mean age 69.3 - 70.5 years compared to mean age of 63 - 63.9 years in the current study); these factors may have improved the likelihood of detecting declines in cognitive function, which increase with advancing age.

As discussed in Chapter 4, both the nature of the sample studied and characteristics of the study design may have had an impact on the findings presented in this thesis. The average age of participants for this study was relatively young compared to those in other similar studies; older age groups (70 years and over), who could be considered more likely to exhibit age-related declines in cognitive function, were also under-represented in this sample. However, the findings were largely unchanged when analyses were repeated with participants aged 65 and over only. Participants were also very highly educated and high-functioning, displaying above-average levels of performance across cognitive measures. Furthermore, declines in cognitive outcome measures over the follow-up interval were either very small in magnitude or non-significant, and it is therefore perhaps unsurprising that this study failed to detect significant effects of the predictors on cognitive decline. The follow-up interval of two

years, selected for practical reasons, is a relatively short duration in the context of other cognitive ageing studies, and a longer follow-up window may have been required to detect significant cognitive decline, particularly given the high-performing, highly educated, and relatively young sample studied. Further research with extended follow-up intervals, and using samples of older adults with a greater range of education and baseline cognitive function, may therefore be helpful in establishing the utility of the subgroup classification methods studied for predicting risk of future cognitive decline or preclinical AD.

There was a low prevalence of subjective memory complaints in the sample studied, and participants' subjective ratings of memory performance were relatively high and were also restricted in range. The narrow range of scores for subjective memory measures may have reduced the likelihood of detecting any group differences for these measures. Since the classification methods investigated in this chapter are designed to identify individuals who are performing at a level that is within the normal range but represents a decline for them, these methods may have greater utility when accompanied by evidence of subjective memory complaints. It may therefore be useful to test the hypotheses investigated in this chapter using samples with different characteristics, for example, those attending primary care or a memory clinic with subjective memory complaints, but performing within the normal range for the population.

The subgroup classification methods employed in this study have been investigated in a limited number of studies to date, with relatively small sample sizes and relatively short follow-up durations. Therefore, the extent to which cognitive asymmetry or IQ-adjusted memory impairment are typically observed in a normally ageing population is currently poorly understood, and it is not possible to comment on how the proportion of participants in the current study with a discrepant/impaired profile relates to what would be expected in the general population. Further research using these classification methods with larger and more representative samples is required. Further longitudinal data is also required to understand the predictive value and the potential clinical relevance of these classification methods in terms of subsequent progression to pathological declines in cognition.

While there were significant differences in IQ between the subgroups using both classification methods, the overall pattern of results did not change when analyses were repeated with a subset of the sample for whom there were no differences in IQ between subgroups (all those with IQ >120). Initial group differences in IQ therefore did not appear to significantly affect the results of the current study. It is possible that individuals with higher IQ scores are more likely to be classified as discrepant or impaired using the classification methods studied, although it should be noted that no significant differences in IQ were found between subgroups in previous studies using these methods (Dockree et al, 2015; Downer et al, 2013; Rentz et al, 2004; Rentz et al 2007). Further studies using these classification methods using large samples of participants with IQ-score distributions that are more representative of the general population may be useful in determining whether asymmetric cognitive profiles are more likely to occur in participants with higher IQ.

There is considerable evidence to suggest individuals who go on to develop AD may experience subtle declines, that are below the level of clinical impairment and are difficult to distinguish from normal age-related changes in cognition, many years before they are diagnosed with dementia (Elias et al., 2000; Knopman & Caselli, 2012). In order to detect subtle cognitive deficits associated with preclinical AD, sensitive methods of neuropsychological assessment that account for CR or premorbid function are required, because deficits may be masked by individuals with high CR when their test scores are simply compared with normative values for the population (Petersen, 2004; Sperling et al., 2011; Stern, 2013). Further research is required to establish definitive criteria and methods for identification of individuals with preclinical AD, who could be an "at-risk" group of particular interest for research trials of potential preventative, neuroprotective, and disease-modifying treatments or interventions (Backman et al., 2005; Jacobson et al., 2009; Sperling et al., 2011). The classification methods presented in this chapter provide potential strategies to account for the effects of CR on neuropsychological testing, by considering each individual's test performance relative to their premorbid levels of functioning, and as such represent two potential approaches for identifying subtle cognitive deficits that may be associated with increased risk for future cognitive decline. In the current study, individuals classified into "potentially at-risk" subgroups (i.e. classified as discrepant based on cognitive asymmetry scores or classified as impaired based on IQ-adjusted norms for a

standardised memory test) did not exhibit greater levels of cognitive decline over two years. Further research with more diverse samples is required to determine whether either of these classification methods are useful for identifying individuals at risk for future decline or preclinical AD, who would not be identified as such using traditional norm-referenced methods of neuropsychological assessment.

The classification methods studied may also be useful for future research investigating correlates of "successful ageing" and factors that reduce risk of age-related cognitive decline or promote the preservation of cognitive function in late life (Dockree et al., 2015). Since the classification methods studied are based on dissociations between one cognitive domain expected to remain relatively stable across the lifespan (i.e. IQ) and a second domain with known vulnerability to decline with advancing age (i.e. episodic memory), they could alternatively be used to identify a subgroup whose memory performance is at a level consistent with, or greater than, their premorbid function; this subgroup could represent "successful agers" who are avoiding typical age-related declines in episodic memory.

Chapter 6: General Discussion

6.1 Summary of findings

This thesis began with a number of aims:

- To evaluate the construct validity of a multiple-indicator, latent variable model of cognitive reserve (CR).
- To investigate the effects of CR on cognitive performance at baseline, on and decline in cognitive function over two years, in a cohort of generally healthy older adults; and to test for moderating effects of CR in relationships between age and each of these cognitive outcomes.
- To classify participants into subgroups using two methods based on intra-individual differences in cognitive performance; and to investigate differences between these subgroups in terms of baseline cognitive performance, subjective memory ratings, and cognitive decline over two years.

This chapter summarises the main findings of each study and raises further points for discussion with respect to each. The findings will be considered in the context of previous empirical research and their implications in light of the literature discussed in Chapter 1. Some important limitations of the current studies will also be highlighted. Potential questions for future consideration, arising from the current research, will then be discussed.

In Chapter 2, a systematic review of the literature revealed considerable heterogeneity in the methods used to measure CR for studies investigating the relationship of this construct to cognitive outcomes associated with normal, non-pathological ageing. A range of proxy indicators were used, either in isolation or in various combinations, to represent CR, including education, occupational complexity, multilingualism/ bilingualism, IQ, reading ability/literacy, socioeconomic status, and participation in mentally stimulating leisure activities. Education was the most commonly used proxy indicator, and was included as either the sole indicator of CR, or as one of several indicators, in 22 or the 35 reviewed articles. In studies using the same variable(s) to represent CR, further heterogeneity resulted from the use of different methods to operationalise or assess the indicator in question. The literature reviewed in Chapter 2

largely supported a positive relationship between CR and level of cognitive function among older adults. However, evidence for a relationship between CR and rate of age-related cognitive decline was less consistent, since some of the reviewed studies demonstrated an inverse relationship between these variables, but other studies failed to find a significant effect of CR on rate of age-related decline.

In Chapter 3, a series of structural equation models were employed to investigate the convergent and discriminant validity of a latent CR construct with measures of education, occupational complexity, mentally stimulating leisure activities, reading ability, and premorbid IQ as observed indicators. This study aimed to extend models from previous construct validity studies (Mitchell et al., 2012; Siedlecki et al., 2009), by evaluating a latent CR construct with a wider range of observed indicators, to more closely reflect the range of variables thought to contribute to CR across the lifespan. The findings strongly supported the convergent validity of the hypothesised CR construct, since each of the observed indicators loaded significantly on this latent construct across all models. Inter-factor correlations between latent CR and episodic memory constructs were non-significant in all models, providing consistent support for discriminant validity. There was evidence of some overlap between CR and executive function constructs, but relationships between these constructs remained significantly less than 1.0 across each of the models; these results therefore provide at least partial additional support for discriminant validity of the hypothesised CR construct.

In Chapter 4, the structural equation models presented in Chapter 3 were extended in order to investigate the effects of age, CR, and the interaction between age and CR on cognitive function at baseline. Moderation analyses were then used to investigate the effects of CR on the relationship between age and decline in cognitive function over two years. In models investigating cognitive function at baseline, age had a significant negative effect on executive function and no significant effect on memory; CR had a significant positive effect on executive function and no significant effect on memory. The interaction between age and CR had no significant effect on memory or executive function at baseline. Moderation analyses of the longitudinal dataset indicated that the interaction between age and CR had no significant effect on change in each of the cognitive measures over two years. The findings of this study therefore did not support

the hypothesis that CR moderates relationships between age and cognitive function, or between age and rate of cognitive decline.

In Chapter 5, participants were classified into subgroups with different cognitive profiles using two methods that attempted to account for the effects of CR on neuropsychological test performance. The first method involved classifying participants into "consistent" or "discrepant" subgroups based on the degree of asymmetry between their performance on a standardised episodic memory test and an estimate of their IQ; the second method involved classifying participants into "stable" or "impaired" groups based on their score for a standardised episodic memory test relative to normative values that were adjusted for their estimated IQ. A series of *t*-tests and multiple regressions were then used to investigate whether either of these classification methods were effective in distinguishing participants in terms of baseline cognitive performance, subjective memory ratings, or rate of change in cognitive function over two years. Participants classified as "discrepant" or "impaired" were hypothesised to exhibit poorer cognitive performance at baseline, to have lower scores for subjective memory measures, and to show greater levels of age-related decline in cognitive measures over two years. It is important to underscore that all participants in the study performed within the normal range for their age according to published normative data. Participants in the "discrepant" or "impaired" groups were only classified as such based on their memory performance relative to an estimate of their IQ (as an indicator of CR); this chapter proposed that these methods of "benchmarking" participants' memory performance relative to IQ may be effective in identifying subtle memory changes that are masked by traditional norm-referenced methods of neuropsychological assessment, particularly in high-functioning individuals with high levels of CR. Scores for several baseline memory measures were significantly lower in "discrepant" and "impaired" groups compared to their "consistent" and "stable" counterparts; there were no significant differences between subgroups for baseline performance in other cognitive domains. There were no significant differences between subgroups for subjective memory measures using either classification method. Significant decline over two years was observed in the sample as a whole for only two measures (MoCA and WMS-III Letter-Number Sequencing subtest); subgroup classification using either method was not a significant predictor of change in these measures over two years. Therefore, while these classification methods were effective in distinguishing between participants in

terms of baseline memory performance, the findings of this study did not support the hypotheses that individuals classified as "discrepant" or "impaired" would have significantly poorer subjective memory ratings or would show greater declines in cognitive function than the "consistent" or "stable" groups over the follow-up interval.

6.2 Implications

The findings presented in this thesis highlight the need for a more consistent, standardised, and comprehensive approach to measurement of CR. The heterogeneity in proxy indicators used to measure CR observed in Chapter 2 is in line with findings of previous reviews that reported inconsistent measurement of CR in studies investigating the construct in relation to outcomes associated with Alzheimer's disease (AD) (Harrison et al., 2015), and in relation to cross-sectional measures of cognitive function in older adults (Opdebeeck et al., 2015). This heterogeneity in measures used to represent CR may limit the comparability of findings across studies, and raises concerns related to the validity of the construct (Jones et al., 2011; Satz et al., 2011).

A considerable proportion of studies reviewed in Chapter 2 used a single variable to represent CR; the proxy indicator used in the majority of these studies was education. However, findings from several previous studies demonstrating the independent and synergistic contributions of several CR proxies to late-life cognitive function (e.g. Dekhtyar et al., 2015; Kavé et al., 2008; Richards & Sacker, 2003) suggest that education alone, or any other single proxy indicator, may not fully capture CR. Furthermore, relationships between any single proxy indicator and cognitive performance may be explained by alternative mechanisms or pathways linked to that specific indicator, rather than by the hypothesised CR processes (Jones et al., 2011). Other studies reviewed in Chapter 2 included several indicators of CR, but investigated the effects of each indicator in parallel rather than in combination, and the limitations associated with single-indicator measurement approaches therefore also apply to these studies. Five of the included studies used latent variable analysis to combine several CR indicators, but the observed indicators of these latent constructs did not reflect the full range of variables thought to contribute to CR, and used as single proxies in the extant literature. The findings presented in Chapter 2, along with previous reviews (e.g. Harrison et al., 2015; Opdebeeck et al., 2015), demonstrate a lack of consensus

about how to measure CR, and highlight the need for theoretical and methodological work to promote a more standardised approach to measuring and operationalising the construct.

The multiple-indicator, latent variable approach to measurement of CR employed in this thesis contributes to a growing body of literature investigating the relationship of latent CR constructs that combine several proxy indicators, to age- and disease-related cognitive outcomes (e.g. Brickman et al., 2011; Giogkaraki et al., 2013; Lojo-Seoane et al., 2014; Scarmeas et al., 2004). These latent variable measures aim to quantify the combined effects of a range of intellectually enriching exposures hypothesised to contribute to CR across the lifespan (Pettigrew et al., 2013; Stern, 2012), and therefore may provide a more theoretically valid measure of the construct (Jones et al., 2011; Satz et al., 2011). The multiple-indicator model of CR tested in Chapters 3 and 4 extended models used in previous studies by including a wider range of CR proxies as observed indicators of the latent construct. This thesis also aimed to address a gap in the literature by empirically testing the construct validity of this model, since previous studies have either been based on a priori groupings of indicators and implicit assumptions about construct validity (Satz et al., 2011), or have evaluated the construct validity of models with a limited range of observed indicators, that did not include some key variables related to CR (e.g. occupational complexity, mentally stimulating activities) (e.g. Mitchell et al., 2012; Siedlecki et al., 2009).

The findings presented in Chapter 3 replicate and extend those of Siedlecki et al. (2009), who used the same methodology to demonstrate the convergent and discriminant validity of a latent CR construct with education and performance on two vocabulary tests as observed indicators. In this previous study, convergent validity was supported across all four models, and discriminant validity was partially supported, but failed the most demanding test in Model D; results of this final model indicated that CR and executive function variables were highly related and that these latent constructs were not distinct from one another in terms of individual differences (Siedlecki et al., 2009). For the models presented in Chapter 3, relationships between latent CR and executive function constructs remained significantly less than 1.0, even in Model D, and the current study therefore provided more consistent support for convergent and discriminant validity of CR. As noted in Chapter 3, executive function is typically

measured by tasks involving abilities such as strategy selection and mental flexibility, which are very similar to the skills and processes hypothesised to underlie CR. It is therefore perhaps unsurprising that the constructs of CR and executive function were found to overlap in Chapter 3 and in previous studies. These findings, along with those of previous construct validity evaluations (e.g. Lojo-Seoane et al., 2014; Mitchell et al., 2012; Siedlecki et al., 2009), suggest that it is meaningful to refer to and investigate CR as a distinct construct, and support the use of multiple-indicator, latent variable models of CR. An important implication for future research is that studies aiming to investigate CR might benefit from including a range of proxy indicator measures in their protocols, to allow researchers to study the combined effects of these CR indicators, using analytic strategies similar to those employed in this thesis.

The findings presented in Chapter 4 add to a body of literature demonstrating a positive relationship between CR and level of cognitive function in older adults (see Opdebeeck et al. (2015) for a review), although positive effects of CR observed in the current study were limited to executive function, and the construct had no significant effect on memory. CR also had no significant effects on decline in cognitive measures over two years, and the current study therefore contributes to mixed findings relating to the potential for CR to mitigate age-related cognitive decline (e.g. H. Christensen et al., 2009; Marioni et al., 2012; Tucker-Drob et al., 2009; Wilson et al., 2013).

While CR was positively related to level of executive function in Chapter 4, the interaction between age and CR had no significant effects on the cognitive outcomes studied, and CR therefore did not appear to moderate the negative relationship between age and executive function. CR also had no significant effect on age-related cognitive decline over two years in this study. It is therefore unclear whether positive effects of CR on cognitive performance in older adults reflect lifelong differences in cognitive ability, or whether CR can modify the negative influence of ageing on cognitive function. Similarly, it is important to understand the temporal order of relationships between CR and late-life cognitive outcomes, which cannot be determined from many of the epidemiological, observational, and cross-sectional studies quoted to support the CR hypothesis (J. Barnett & Sahakian, 2008). For instance, positive relationships between mentally stimulating leisure activities and late-life cognitive outcomes have been reported (e.g. Helzner et al., 2007; Scarmeas et al., 2001; Wilson et al., 2005), and

could indicate that these stimulating activities contribute to CR and protect against cognitive decline, but it is also plausible that premorbid cognitive ability influences choice of activities (J. Barnett & Sahakian, 2008), or that declining cognitive function causes individuals to reduce their engagement in mentally challenging leisure activities. Longitudinal studies may be useful in this regard, but require very long follow-up durations and repeated measures of activities associated with CR; it is also important to acknowledge that potential confounding due to additional, unmeasured factors cannot be ruled out in these observational studies (La Rue, 2010).

The question of whether CR can modify the effects of age on cognitive function has important implications for the development of interventions aimed at preventing decline and promoting successful cognitive ageing. Both innate characteristics and a series of intellectually enriching life experiences are hypothesised to contribute to CR (J. Barnett & Sahakian, 2008; Stern, 2012). If late-life cognitive outcomes can be modified by the life experiences associated with CR, psychological and behavioural interventions aiming to impart reserve by encouraging engagement in intellectually enriching activities could help to slow, prevent, or delay age-related cognitive decline. As noted by Yaakov Stern (2013), while epidemiological evidence suggests many of the "ingredients", the exact "recipe" for an effective intervention to boost CR remains unknown. In the context of public health policy recommendations for an increased focus on risk reduction and primary prevention of dementia via modifiable risk factors (Cleary & McAvoy, 2015; Lincoln et al., 2014; World Health Organization, 2012), research that aims to elucidate the neural or cognitive mechanisms underlying the effects of CR may help to identify some optimal targets for intervention (Anstey, 2014; Stern, 2013). Empirical evaluation of multi-modal interventions to promote CR across the lifespan is likely to be complex and costly; large-scale, multi-centre, randomised controlled trials with long follow up durations would provide the strongest evidence, but would obviously require considerable resources and also present a range of practical and ethical challenges (Cleary & McAvoy, 2015; Henderson, 2014; Stern, 2013). However, it has been noted that in the absence of definitive evidence that cognitively stimulating or social activities can preserve cognitive function in healthy older adults, or prevent/delay dementia, general recommendations related to increasing engagement in these activities are associated with very minimal risks of harm (La Rue, 2010; Stern, 2013).

When traditional methods of norm-referenced neuropsychological assessment are used, subtle cognitive deficits may be masked by high-functioning individuals with high levels of CR, who may continue to perform within the normal range for the population while experiencing considerable decline relative to their own premorbid levels of function (Petersen, 2004; Sperling et al., 2011; Stern, 2013). The subgroup classification methods investigated in Chapter 5 represent two potential strategies to account for the effects of CR on neuropsychological assessment; these methods focus on intra-individual differences in cognitive performance and "benchmark" memory scores relative to IQ (Dockree et al., 2015; Jacobson et al., 2009; Rentz et al., 2004). In Chapter 5, these classification methods distinguished between participants in terms of baseline memory performance, but subgroups did not differ in terms of subjective memory ratings, and classification as "discrepant" or "impaired" was not a significant predictor of cognitive decline over two years. Therefore, in the current study, participants classified as "discrepant" or "impaired" at baseline did not appear to be at increased risk for subsequent cognitive decline. This chapter therefore failed to replicate previous findings of an increased risk for subsequent cognitive decline among individuals classified as "impaired" at baseline using IQ-adjusted norms (Rentz et al., 2004; Rentz et al., 2007). However, since the sample in the current study were relatively young, and exhibited very little decline in cognitive measures over two years, it is possible that a much longer follow-up duration may have been required to investigate whether these subgroups differed in terms of rate of age-related decline. Further research with more heterogeneous samples and longer follow-up durations may help to determine the efficacy of these methods. If these methods prove useful for detecting subtle memory deficits with clinical relevance, they could be used by both researchers and clinicians, in conjunction with neuroimaging or CSF biomarkers, to characterise preclinical AD and to identify "at risk" groups who could be targeted in trials of potential preventative or neuroprotective therapies (Backman et al., 2005; Jacobson et al., 2009; Sperling et al., 2011).

6.3 Limitations

Perhaps the most obvious limitation of this work is one that was highlighted in each of the empirical chapters – that the sample studied were self-selecting, and that the

majority of participants were relatively young, very highly educated and had above-average levels of cognitive function. It is almost certain that the sample studied was subject to volunteer (self-selection) bias, which occurs when individuals who volunteer for a study differ from those who do not volunteer in characteristics relevant to the research question (Tripepi, Jager, Dekker, & Zoccali, 2010). This type of bias threatens the internal validity of a study if the characteristics that distinguish volunteers and non-volunteers are related to the independent variable, or are related to the outcome through alternative pathways (Tripepi et al., 2010). This methodological limitation is common in cognitive ageing studies, many of which use self-selecting, volunteer samples of generally healthy older adults. It has been suggested that these volunteer participants may be distinguished from the population as a whole by the very fact that they chose to take part in cognitive ageing research; studies comparing randomly recruited and convenience samples of cognitively normal older adults have found that participants recruited through convenience sampling were younger (Brodaty et al., 2014; Whitwell et al., 2012), more highly educated (Brodaty et al., 2014; Ganguli, Lytle, Reynolds, & Dodge, 1998; Whitwell et al., 2012), and had higher levels of cognitive performance (Brodaty et al., 2014) than randomly selected, population-based samples. Participants recruited to cognitive ageing studies through convenience sampling have also been shown to be more likely to have a family history of AD than population-based samples (Brodaty et al., 2014; Whitwell et al., 2012); it has been suggested that those with a family history may be more likely to volunteer for research due to increased motivation and personal interest in prevention of cognitive decline (Brodaty et al., 2014).

Self-selection bias due to convenience sampling in the current studies may account for the restricted range of scores observed for both CR variables and cognitive tests, which may in turn have reduced the likelihood of detecting significant relationships between CR and the outcomes of interest. The narrow range of variation in CR indicator variables may also have limited the fit of structural equation models tested in Chapters 3 and 4 (Mitchell et al., 2012), although the majority of fit statistics remained within an acceptable range in these analyses. Most importantly, this methodological limitation of the current studies may seriously reduce the generalisability of the results observed. Future studies aiming to investigate the relationship between CR and age-related cognitive outcomes must include careful consideration of the most appropriate methods for sample selection and participant recruitment. Volunteer samples can be considered

relatively easy to recruit from a practical perspective; methods based on random selection may require allocation of greater resources to participant recruitment, but may have the advantage of producing more representative samples and increasing confidence in the generalisability of subsequent study findings. While some bias in study samples may be unavoidable, it is important that researchers are cognisant of the implications of sampling methods when interpreting their findings, and that they take steps to minimise sources of bias wherever possible.

A number of limitations that are common to all longitudinal designs apply to the two-wave panel data analysed in the current studies. Attrition is inevitable in longitudinal studies, and since older adults who are older, frailer, have lower baseline cognitive scores, or have a greater number of comorbidities may be less likely to return for follow-up (Chatfield, Brayne, & Matthews, 2005; Launer, Wind, & Deeg, 1994; Van Beijsterveldt et al., 2002), selective attrition can bias results and reduce the representativeness of the sample (Barry, 2005; Deng, Hillygus, Reiter, Si, & Zheng, 2013). However, a relatively low attrition rate of approximately 14.5% was achieved for the two-wave data presented in this thesis. The high retention rate may have reduced the potential for selective attrition to bias the findings.

Secondly, the issue of reliability across measurement waves is one that is common to longitudinal studies. As the same measures are repeated over waves of data, it is possible that either measurement error or practice effects may cause fluctuations in scores that would confound the associations investigated through longitudinal analyses (Aickin, 2009; A. G. Barnett et al., 2005). In order to reduce this source of bias, conditional change models that attempt to minimise the effects of regression to the mean by controlling for baseline performance were employed for all longitudinal analyses. Parallel versions of cognitive tests, where available, were administered to participants in a counter-balanced order across testing waves, in order to minimise practice effects specific to these measures.

This thesis aimed to investigate effects of CR on age-related cognitive decline, but participants in the current study exhibited relatively little, if any, decline in cognitive measures over two years. Given the characteristics of the sample studied, a significantly longer follow-up interval may be required to observe meaningful levels of cognitive

decline, but this was not possible within the practical constraints of the current studies. However, future research with additional waves of data from the project may allow for detection of greater levels of cognitive decline in some participants, and provide further insight into the nature of relationships between age, CR, and the rate of this decline.

The sample size of the longitudinal dataset analysed for the current studies was not sufficient for structural equation modelling, which is a large-sample technique, requiring a minimum of 200 participants or 10 participants per parameter to be freely estimated in the model (Hoyle, 2011; Nachtigall et al., 2003; Schreiber et al., 2010). The latent variable model of CR analysed with the cross-sectional data could therefore not be applied to the two-wave panel data analysed for research questions that required a longitudinal design. This can be considered an important limitation of multiple-indicator, latent variable models of CR in general, since practical constraints may not always allow researchers to collect data from the type of sample sizes required to use this measurement approach. In the current studies, it was possible to extract a factor score for each participant from the cross-sectional models, to use in subsequent analyses that could not accommodate latent variables with multiple observed indicators. However, it should be acknowledged that it would have been preferable to also investigate the longitudinal research questions using latent variable models.

6.4 Future directions

Cognitive reserve is a relatively new concept and this is an area of research with many unanswered questions. The findings presented in this thesis provided empirical support for the construct validity of CR, using a multiple-indicator model that combined a range of commonly used proxy variables as observed indicators of the latent CR construct. An important first step would be, of course, to replicate the findings of these construct validity analyses. Replication of findings using the same model in different samples is an important step for establishing construct validity (Raykov & Marcoulides, 2000). Previous evidence for construct validity of a more narrowly defined model of CR (Siedlecki et al., 2009) was derived from analyses with a primary sample and two replication samples. It would therefore be useful to take a similar approach and repeat the analyses presented in Chapter 3 with additional samples of older adults. This latent variable, multiple-indicator model of CR could also be used in future studies aiming to

investigate the effects of CR on outcomes associated with AD or other clinical conditions.

The question of whether relationships between CR and cognitive function in generally healthy older adults reflect lifelong differences in cognitive ability, or are evidence of CR moderating relationships between age and cognitive decline, remains open to investigation. A more consistent approach to measurement of CR using multiple-indicator models, along with standardisation of other aspects of study design (such as follow-up durations, cognitive outcome measures, and sample characteristics) may increase comparability of findings and help to clarify the nature of these relationships.

Similarly, the mechanisms that might underlie any protective effects of CR against age-related cognitive decline remain poorly understood. Neuroimaging studies have provided preliminary evidence for the proposed mechanisms of neural reserve and neural compensation (e.g. Holtzer et al., 2009; Steffener et al., 2014; Steffener & Stern, 2012; Zarahn, Rakitin, Abela, Flynn, & Stern, 2007), but further research is required to fully understand the neural implementation of CR. At a behavioural level, it has been suggested that variance in the selection, use, and adaptation of cognitive strategies may be an important aspect of these individual differences in task processing, and a small experimental study has provided some preliminary support for this hypothesis (Barulli et al., 2013). Further experimental studies with larger samples of participants would be useful for investigating whether strategy selection, or other cognitive processes, are related to CR and can moderate relationships between age and cognitive function.

6.5 Conclusions

The findings presented in this thesis provide support for construct validity of CR, highlight the importance of consistent and comprehensive measurement of CR across studies, and demonstrate the utility of latent variable modelling techniques for combining several proxy variables in a multiple-indicator model of CR. Efforts to harmonise the measurement of CR across future studies will increase confidence in the validity of the construct and aid comparability of empirical findings. There are significant gaps in current knowledge related to CR, and this theoretical concept provides a useful framework for generating and testing hypotheses related to inter-

individual variability in cognitive ageing, and factors associated with successful ageing and preservation of cognitive function across the lifespan. Research that aims to elucidate the neural and cognitive mechanisms underlying CR may have important implications for large-scale, population-level, behavioural or public health interventions to promote brain health and successful cognitive ageing. However, it is important to gain a better understanding of whether the effects of CR observed in epidemiological studies simply reflect lifelong differences in cognitive abilities, or if this construct can truly modify the negative effects of ageing or neuropathological disease on cognitive function.

References

Abdulrab, K., & Heun, R. (2008). Subjective Memory Impairment. A review of its definitions indicates the need for a comprehensive set of standardised and validated criteria. *European Psychiatry, 23*(5), 321-330.

Adam, S., Bonsang, E., Grotz, C., & Perelman, S. (2013). Occupational activity and cognitive reserve: implications in terms of prevention of cognitive aging and Alzheimer's disease. *Clinical Interventions in Aging, 8*, 377.

Adler, N. E., & Newman, K. (2002). Socioeconomic disparities in health: pathways and policies. *Health Affairs, 21*(2), 60-76.

Aickin, M. (2009). Dealing with change: using the conditional change model for clinical research. *The Permanente Journal, 13*(2), 80-84.

Aickin, M., & Gensler, H. (1996). Adjusting for multiple testing when reporting research results: the Bonferroni vs Holm methods. *American Journal of Public Health, 86*(5), 726-728.

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

Albert, M. S., Moss, M. B., Tanzi, R., & Jones, K. (2001). Preclinical prediction of AD using neuropsychological tests. *Journal of the International Neuropsychological Society, 7*(05), 631-639.

Albert, S. M., Glied, S., Andrews, H., Stern, Y., & Mayeux, R. (2002). Primary care expenditures before the onset of Alzheimer's disease. *Neurology, 59*(4), 573-578.

Alexander, G. E., Furey, M. L., Grady, C. L., Pietrini, P., Brady, D. R., Mentis, M. J., & Schapiro, M. B. (1997). Association of premorbid intellectual function with cerebral metabolism in Alzheimer's disease: implications for the cognitive reserve hypothesis. *American Journal of Psychiatry, 154*(2), 165-172.

Algina, J., & Moulder, B. C. (2001). A note on estimating the Joreskog-Yang model for latent variable interaction using LISREL 8.3. *Structural Equation Modeling, 8*, 40-52.

Allison, P. D. (1990). Change scores as dependent variables in regression analysis. *Sociological Methodology, 20*, 93-114.

Andel, R., Crowe, M., Pedersen, N. L., Mortimer, J., Crimmins, E., Johansson, B., & Gatz, M. (2005). Complexity of work and risk of Alzheimer's disease: a

population-based study of Swedish twins. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 60*(5), P251-P258.

Andel, R., Vigen, C., Mack, W. J., Clark, L. J., & Gatz, M. (2006). The effect of education and occupational complexity on rate of cognitive decline in Alzheimer's patients. *Journal of the International Neuropsychological Society, 12*, 147-152.

Anderson, E. (2008). Cognitive change in old age. In R. Jacoby, C. Oppenheimer, T. Dening, & A. Thomas (Eds.), *Oxford Textbook of Old Age Psychiatry*. New York: Oxford University Press.

Anstey, K. (2014). Optimising cognitive development over the life course and preventing cognitive decline: Introducing the Cognitive Health Environment Life Course Model (CHELM). *International Journal of Behavioural Development, 38*(1), 1-10.

Apolinario, D., Brucki, S. M. D., de Lucena Ferretti, R. E., Farfel, J. M., Magaldi, R. M., Busse, A. L., & Jacob-Filho, W. (2013). Estimating premorbid cognitive abilities in low-educated populations. *PLoS ONE, 8*(3), e60084.

Arenaza-Urquijo, E. M., Molinuevo, J.-L., Sala-Llonch, R., Sole-Padulles, C., Balasa, M., Bosch, B., . . . Sanchez-Valle, R. (2013). Cognitive reserve proxies relate to gray matter loss in cognitively healthy elderly with abnormal cerebrospinal fluid amyloid-beta levels. *Journal of Alzheimer's Disease, 35*, 715-726.

Armstrong, M. J., Nagile, G., Duff-Canning, S., Meaney, C., Gille, D., Eslinger, P. J., . . . Marras, C. (2012). Role of education and IQ in cognitive reserve in Parkinson's disease and mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders Extra, 2*, 343-352.

Armstrong, R. A. (2014). When to use the Bonferroni correction. *Ophthalmic and Physiological Optics, 34*(5), 502-508.

Ashendorf, L., Jefferson, A. L., Green, R. C., & Stern, R. A. (2009). Test–retest stability on the WRAT-3 reading subtest in geriatric cognitive evaluations. *Journal of Clinical and Experimental Neuropsychology, 31*(5), 605-610.

Backman, L., Jones, S., Berger, A.-K., Jonsson Laukka, E., & Small, B. J. (2005). Cognitive impairment in preclinical Alzheimer's disease: a meta-analysis. *Neuropsychology, 19*(4), 520-531.

Bäckman, L., Lindenberger, U., Li, S.-C., & Nyberg, L. (2010). Linking cognitive aging to alterations in dopamine neurotransmitter functioning: recent data and future avenues. *Neuroscience & Biobehavioral Reviews, 34*(5), 670-677.

Barker-Collo, S., Bartle, H., Clarke, A., van Toledo, A., Vykopal, H., & Willets, A. (2008). Accuracy of the National Adult Reading Test and Spot the Word estimates of premorbid intelligence in a non-clinical New-Zealand sample. *New Zealand Journal of Psychology, 37*(3), 53-61.

Barnett, A. G., Van der Pols, J. C., & Dobson, A. J. (2005). Regression to the mean: what it is and how to deal with it. *International Journal of Epidemiology, 34*, 215-220.

Barnett, J., & Sahakian, B. (2008). *Foresight Mental Capital and Wellbeing Project. State-of-science review SR-E4: Cognitive reserve and mental capital*. London: The Government Office for Science.

Barry, A. E. (2005). How attrition impacts the internal and external validity of longitudinal research. *The Journal of School Health, 75*(7), 267-270.

Barulli, D., Rakitin, B. C., Lemaire, P., & Stern, Y. (2013). The influence of cognitive reserve on strategy selection in normal aging. *Journal of the International Neuropsychological Society, 19*, 1-4.

Barulli, D., & Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. *Trends in Cognitive Sciences, 17*(10), 502-509.

Bastin, C., Yakushev, I., Bahri, M. A., Fellgiebel, A., Eustache, F., Landeau, B., . . . Chételat, G. (2012). Cognitive reserve impacts on inter-individual variability in resting-state cerebral metabolism in normal aging. *NeuroImage, 63*(2), 713-722.

Basu, R. (2012). Education and dementia risk: results from the Aging Demographics and Memory study. *Research on Aging, 35*, 7-31.

Beardsall, L., & Brayne, C. (1990). Estimation of verbal intelligence in an elderly community: A prediction analysis using a shortened NART. *British Journal of Clinical Psychology, 29*, 83-90.

Beaudreau, S. A., & O'Hara, R. (2008). Late-life anxiety and cognitive impairment: a review. *The American Journal of Geriatric Psychiatry, 16*(10), 790-803.

Benke, T. (2011). The role of neuropsychology in prodromal dementia. *Neurodegenerative Disease Management, 1*(4), 323-333.

Bennett, D. A., Schneider, J. A., Tang, Y., Arnold, S. E., & Wilson, R. S. (2006). The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study. *Lancet Neurology, 5*, 406-412.

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

Bentler, P. M. (1990). Comparative fit indexes in structural models. *Psychological bulletin, 107*(2), 238.

Berrington, A., Smith, P., & Sturgis, P. (2006). *An overview of methods for the analysis of panel data*: ESRC National Centre for Research Methods.

Bird, C. M., Papadopoulou, K., Ricciardelli, P., Rossor, M. N., & Cipolotti, L. (2004). Monitoring cognitive changes: Psychometric properties of six cognitive tests. *British Journal of Clinical Psychology, 43*(2), 197-210.

Borsboom, D. (2005). *Measuring the mind: Conceptual issues in contemporary psychometrics*. New York: Cambridge University Press.

Bowen, N. K., & Guo, S. (2012). *Structural Equation Modeling*. New York: Oxford University Press.

Brickman, A. M., Habeck, C., Zarahn, E., Flynn, J., & Stern, Y. (2007). Structural MRI covariance patterns associated with normal aging and neuropsychological functioning. *Neurobiology of Aging, 28*(2), 284-295.

Brickman, A. M., Paul, R. H., Cohen, R. A., Williams, L. M., MacGregor, K. L., Jefferson, A. L., . . . Gordon, E. (2005). Category and letter verbal fluency across the adult lifespan: relationship to EEG theta power. *Archives of Clinical Neuropsychology, 20*(5), 561-573.

Brickman, A. M., Siedlecki, K. L., Muraskin, J., Manly, J., Luchsinger, J. A., Yeung, L., . . . Stern, Y. (2011). White matter hyperintensities and cognition: testing the reserve hypotheses. *Neurobiology of Aging, 32*(9), 1588-1598.

Brickman, A. M., Zimmerman, M. E., Paul, R. H., Grieve, S. M., Tate, D. F., Cohen, R. A., . . . Gordon, E. (2006). Regional white matter and neuropsychological functioning across the adult lifespan. *Biological Psychiatry, 60*(5), 444-453.

Brodaty, H., Mothakunnel, A., de Vel-Palumbo, M., Ames, D., Ellis, K. A., Reppermund, S., . . . Crawford, J. (2014). Influence of population versus

convenience sampling on sample characteristics in studies of cognitive aging. *Annals of Epidemiology, 24*(1), 63-71.

Buckner, R. L. (2004). Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron, 44*, 195-208.

Bucur, B., Madden, D. J., Spaniol, J., Provenzale, J. M., Cabeza, R., White, L. E., & Huettel, S. A. (2008). Age-related slowing of memory retrieval: contributions of perceptual speed and cerebral white matter integrity. *Neurobiology of Aging, 29*(7), 1070-1079.

Buhi, E. R., Goodson, P., & Neilands, T. B. (2007). Structural equation modeling: a primer for health behaviour researchers. *American Journal of Health Behavior, 31*(1), 74-85.

Burke, D. M., & Shafto, M. A. (2004). Aging and language production. *Current Directions in Psychological Science, 13*(1), 21-24.

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

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *NeuroImage, 17*(3), 1394-1402.

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

Calvo, N., Garcia, A.M., Manoiloff, L. and Ibanez, A. (2016). Bilingualism and cognitive reserve: a critical overview and a plea for methodological innovations. *Frontiers in Aging Neuroscience, 7*, 249.

Central Statistics Office. (2012). *Census 2011: Profile 2: Older and Younger*. Dublin: Stationery Office.

Central Statistics Office, & Northern Ireland Statistics & Research Agency. (2011). *Census 2011 Ireland and Northern Ireland*. Dublin: Central Statistics Office.

Centre for Ageing Research and Development in Ireland (CARDI). (2014). *A Picture of Ageing Research in Ireland, North and South 2014*. Dublin/Belfast: CARDI.

Chatfield, M. D., Brayne, C., & Matthews, F. E. (2005). A systematic literature review of attrition between waves in longitudinal studies in the elderly shows a

consistent pattern of dropout between differing studies. *Journal of Clinical Epidemiology, 58*, 13-19.

Chertkow, H., Feldman, H. H., Jacova, C., & Massoud, F. (2013). Definitions of dementia and predementia states in Alzheimer's disease and vascular cognitive impairment: consensus from the Canadian conference on diagnosis of dementia. *Alzheimer's Research & Therapy, 5* (Suppl. 1), S2.

Chibnall, J. T., & Eastwood, R. (1998). Postsecondary education and dementia risk in older Jesuit priests. *International Psychogeriatrics, 10*(4), 359-368.

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

Christensen, H., Anstey, K. J., Leach, L. S., & Mackinnon, A. J. (2008). Intelligence, education, and the brain reserve hypothesis. In F. I. Craik & T. A. Salthouse (Eds.), *The Handbook of Aging and Cognition* (3 ed., pp. 133-188). Mahwah, NJ: Lawrence Erlbaum Associates.

Christensen, H., Anstey, K. J., Parslow, R. A., Maller, J., Mackinnon, A., & Sachdev, P. (2007). The brain reserve hypothesis, brain atrophy and aging. *Gerontology, 53*(2), 82-95.

Christensen, H., Batterham, P. J., Mackinnon, A. J., Anstey, K., Wen, W., & Sachdev, P. (2009). Education, atrophy and cognitive change in an epidemiological sample in early old age. *American Journal of Geriatric Psychiatry, 17*(3), 218-226.

Christensen, H., Griffiths, K., MacKinnon, A., & Jacomb, P. (1997). A quantitative review of cognitive deficits in depression and Alzheimer-type dementia. *Journal of the International Neuropsychological Society, 3*(06), 631-651.

Christensen, H., & Jorm, A. F. (1992). Short report: Effect of premorbid intelligence on the Mini-Mental State and IQCODE. *International Journal of Geriatric Psychiatry, 7*(3), 159-160.

Christensen, K. J., Moye, J., Armson, R. R., & Kern, T. M. (1992). Health screening and random recruitment for cognitive ageing research. *Psychology and Ageing, 7*(2), 204-208.

Cleary, O., & McAvoy, H. (2015). *Brain health and dementia prevention in Ireland - a discussion paper*. Dublin, Ireland: Institute of Public Health in Ireland and the Alzheimer Society of Ireland.

Coen, R. F., Cahill, R., & Lawlor, B. A. (2011). Things to watch out for when using the Montreal cognitive assessment (MoCA). *International Journal of Geriatric Psychiatry, 26*, 106-108.

Cohen, B. H. (2004). *Explaining Psychological Statistics* (2 ed.). New Jersey: John Wiley & Sons.

Conroy, R. M., Golden, J., Jeffares, I., O'Neill, D., & McGee, H. (2010). Boredom-proneness, loneliness, social engagement and depression and their association with cognitive function in older people: a population study. *Psychology, Health and Medicine, 15*(4), 463-473.

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

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

Craik, F. I., Bialystok, E., & Freedman, M. (2010). Delaying the onset of Alzheimer disease Bilingualism as a form of cognitive reserve. *Neurology, 75*(19), 1726-1729.

Crane, P. K., Gruhl, J. C., Erosheva, E. A., Gibbons, L. E., McCurry, S. M., Rhoads, K., . . . White, L. (2010). Use of spoken and written Japanese did not protect Japanese-American men from cognitive decline in late life. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 65*(6), 654-666.

Crawford, J. R., Deary, I. J., Starr, J., & Whalley, L. J. (2001). The NART as an index of prior intellectual functioning: a retrospective validity study covering a 66 year interval. *Psychological Medicine, 31*, 451-458.

Crawford, J. R., Henry, J. D., Ward, A. L., & Blake, J. (2006). The Prospective and Retrospective Memory Questionnaire (PRMQ): Latent structure, normative data and discrepancy analysis for proxy-ratings. *British Journal of Clinical Psychology, 45*, 83-104.

Crawford, J. R., Parker, D., Allan, K., Jack, A., & Morrison, F. (1991). The Short NART: Cross-validation, relationship to IQ and some practical considerations. *British Journal of Clinical Psychology, 29*, 435-436.

Crawford, J. R., Parker, D., Stewart, L., Besson, J., & Lacey, G. (1989). Prediction of WAIS IQ with the National Adult Reading Test: Cross-validation and extension. *British Journal of Clinical Psychology, 28*(3), 267-273.

Crawford, J. R., Smith, G., Maylor, E. A., Della Sala, S., & Logie, R. H. (2003). The Prospective and Retrospective Memory Questionnaire (PRMQ): Normative data and latent structure in a large non-clinical sample. *Memory, 11*(3), 261-274.

Crook, T. H., Feher, E. P., & Larrabee, G. J. (1992). Assessment of memory complaint in age-associated memory impairment: the MAC-Q. *International Psychogeriatrics, 4*(02), 165-176.

Crystal, H., Dickson, D., Fuld, P., Masur, D., Scott, R., Mehler, M., & et al. (1988). Clinico-pathologic studies in dementia: Nondemented subjects with pathologically confirmed Alzheimer's disease. *Neurology, 38*, 1682-1687.

Czernochowski, D., Fabiani, M., & Friedman, D. (2008). Use it or lose it? SES mitigates age-related decline in a recency/recognition task. *Neurobiology of Aging, 29*(6), 945-958.

D'Elia, L. F., Satz, P., Lyons Uchiyama, C., & White, T. (1994). *Colour Trails Test: Professional Manual*. Florida, USA: PAR.

D'Elia, L. F., Satz, P., Uchiyama, C. L., & White, T. (1996). *Colour Trails Test*. Odessa, FL: PAR.

Daffner, K. R. (2010). Promoting successful cognitive aging: A comprehensive review. *Journal of Alzheimer's Disease, 19*(4), 1101-1122.

de Frias, C. M., Lövdén, M., Lindenberger, U., & Nilsson, L.-G. (2007). Revisiting the dedifferentiation hypothesis with longitudinal multi-cohort data. *Intelligence, 35*(4), 381-392.

Deary, I. J., Corley, J., Gow, A. J., Harris, S. E., Houlihan, L. M., Marioni, R. E., . . . Starr, J. M. (2009). Age-associated cognitive decline. *British Medical Bulletin, 92*, 135-152.

Deary, I. J., & Gow, A. J. (2008). *Foresight Mental Capital and Wellbeing Project. State-of-science review E14: Determinants of Normal Cognitive Ageing: Implications for Mental Capital*. London: The Government Office for Science.

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

Deng, Y., Hillygus, D. S., Reiter, J. P., Si, Y., & Zheng, S. (2013). Handling attrition in longitudinal studies: The case for refreshment samples. *Statistical Science, 28*(2), 238-256.

Dennis, N. A., & Cabeza, R. (2008). Neuroimaging of healthy cognitive aging. In F. I. Craik & T. A. Salthouse (Eds.), *The Handbook of Aging and Cognition* (3rd ed., pp. 1-54). Mawah, NJ: Erlbaum.

Depp, C. A., Harmell, A., & Vahia, I. V. (2012). Successful cognitive aging. *Current Topics in Behavioral Neurosciences, 10*, 35-50.

Dockree, P. M., Brennan, S., O'Sullivan, M., Robertson, I. H., & O'Connell, R. G. (2015). Characterising neural signatures of successful aging: electrophysiological correlates of preserved episodic memory in older age. *Brain and Cognition, 97*, 40-50.

Downer, E. J., Jones, R. S., McDonald, C. L., Greco, E., Brennan, S., Connor, T. J., . . . Lynch, M. A. (2013). Identifying early inflammatory changes in monocyte-derived macrophages from a population with IQ-discrepant episodic memory. *PLoS ONE, 8*(5), e63194.

Dubois, B., Feldman, H. H., Jacova, C., Cummings, J., DeKosky, S. T., Barberger-Gateau, P., . . . Scheltens, P. (2010). Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurology, 9*, 1118-1127.

Dubois, B., Feldman, H. H., Jacova, C., DeKosky, S. T., Barberger-Gateau, P., Cummings, J., . . . Scheltens, P. (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurology, 6*, 734-746.

Elias, M. F., Beiser, A., Wolf, P. A., Au, R., White, R. F., & D'Agostino, R. B. (2000). The preclinical phase of Alzheimer disease: a 22-year prospective study of the Framingham Cohort. *Archives of Neurology, 57*(6), 808-813.

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., . . . White, S. M. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences, 108*(7), 3017-3022.

Farias, S. T., Chand, V., Bonnici, L., Baynes, K., Harvey, D., Mungas, D., . . . Reed, B. R. (2012). Idea density measured in late life predicts subsequent cognitive trajectories: implications for the measurement of cognitive reserve. *The Journals*

of Gerontology, Series B: Psychological Sciences and Social Sciences, 67(6), 677-686.

Field, A., Miles, J., & Field, Z. (2012). *Discovering Statistics Using R*. London: SAGE Publications Ltd.

Finkel, D., Pedersen, N. L., Plomin, R., & McClearn, G. E. (1998). Longitudinal and cross-sectional twin data on cognitive abilities in adulthood: the Swedish Adoption/Twin Study of Aging. *Developmental Psychology, 34*(6), 1400.

Foley, J. M., Ettenhofer, M. L., Kim, M. S., Behdin, N., Castellon, S. A., & Hinkin, C. H. (2012). Cognitive reserve as a protective factor in older HIV-positive patients at risk for cognitive decline. *Applied Neuropsychology: Adult, 19*, 16-25.

Foubert-Samier, A., Catheline, G., Amieva, H., Dilharreguy, B., Helmer, C., Allard, M., & Dartigues, J. (2012). Education, occupation, leisure activities and brain reserve: a population-based study. *Neurobiology of Aging, 33*, 423.e415-423.e425.

Fratiglioni, L., & Wang, H. (2007). Brain reserve hypothesis in dementia. *Journal of Alzheimer's Disease, 12*, 11-22.

Fritsch, T., Larsen, J. D., & Smyth, K. A. (2007). The role of adolescent IQ and gender in the use of cognitive support for remembering in aging. *Aging, Neuropsychology, and Cognition, 14*(4), 394-416.

Fuh, J.-L., Teng, E. L., Lin, K.-N., Larson, E. B., Wang, S.-J., Liu, C.-Y., . . . Liu, H.-C. (1995). The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) as a screening tool for dementia for a predominantly illiterate Chinese population. *Neurology, 45*(1), 92-96.

Ganguli, M., Lytle, M. E., Reynolds, M. D., & Dodge, H. H. (1998). Random versus volunteer selection for a community-based study. *Journal of Gerontology: Medical Sciences, 53A*(1), M39-M46.

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

Giordano, N., Tikhonoff, V., Palatini, P., Bascelli, A., Boschetti, G., De Lazzari, F., . . . Piccoli, A. (2012). Cognitive functions and cognitive reserve in relation to blood pressure components in a population-based cohort aged 53 to 94 years. *International Journal of Hypertension, 2012*, 1-8.

Glymour, M. M., Weuve, J., Fay, M. E., Glass, T., & Berkman, L. F. (2008). Social ties and cognitive recovery after stroke: does social integration promote cognitive resilience? *Neuroepidemiology, 31*, 10-20.

Gold, B. T., Johnson, N. F., & Powell, D. K. (2013). Lifelong bilingualism contributes to cognitive reserve against white matter integrity declines in aging. *Neuropsychologia, 51*, 2841-2846.

Gold, J. M., Carpenter, C., Randolph, C., Goldberg, T. E., & Weinberger, D. R. (1997). Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. *Archives of General Psychiatry, 54*(2), 159-165.

Gonzalez, H. M., Tarraf, W., Bowen, M. E., Johnson-Jennings, M. D., & Fisher, G. G. (2013). What do parents have to do with my cognitive reserve? Life course perspectives on twelve-year cognitive decline. *Neuroepidemiology, 41*, 101-109.

Gooding, L. F., Abner, E. L., Jicha, G. A., Kryscio, R. J., & Schmitt, F. A. (2014). Musical training and late-life cognition. *American Journal of Alzheimer's Disease and Other Dementias, 29*(4), 333-343.

Gordon, L. T., Soldan, A., Thomas, A., & Stern, Y. (2012). Effect of repetition lag on priming of unfamiliar visual objects in young and older adults. *Psychology and Aging, 28*(1), 219-231.

Grady, C. L., Randy McIntosh, A., Horwitz, B., & Rapoport, S. I. (2000). Age-related changes in the neural correlates of degraded and nondegraded face processing. *Cognitive Neuropsychology, 17*(1-3), 165-186.

Graves, A. B., Mortimer, J., Larson, E., Wenzlow, A., Bowen, J., & McCormick, W. (1996). Head circumference as a measure of cognitive reserve. Association with severity of impairment in Alzheimer's disease. *The British Journal of Psychiatry, 169*(1), 86-92.

Graves, A. B., Mortimer, J. A., Bowen, J., McCormick, W. C., McCurry, S. M., Schellenberg, G. D., & Larson, E. (2001). Head circumference and incident Alzheimer's disease: Modification by apolipoprotein E. *Neurology, 57*(8), 1453-1460.

Green, R. E., Colella, B., Christensen, B., Johns, K., Frasca, D., Bayley, M., & Monette, G. (2008). Examining moderators of cognitive recovery trajectories after moderate to severe traumatic brain injury. *Archives of Physical Medicine and Rehabilitation, 89*(2), S16-S23.

Grober, E., & Buschke, H. (1987). Genuine memory deficits in dementia. *Developmental Neuropsychology, 3*, 13-36.

Grober, E., Hall, C. B., Lipton, R. B., Zonderman, A. B., Resnick, S. M., & Kawas, C. (2008). Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer's disease. *Journal of the International Neuropsychological Society, 14*(02), 266-278.

Grober, E., Ocepek-Welikson, K., & Teresi, J. A. (2009). The free and cued selective reminding test: evidence of psychometric adequacy. *Psychology Science Quarterly, 51*(3), 266-282.

Gunning-Dixon, F. M., Brickman, A. M., Cheng, J. C., & Alexopoulos, G. S. (2009). Aging of cerebral white matter: a review of MRI findings. *International Journal of Geriatric Psychiatry, 24*(2), 109-117.

Habeck, C. G., Hilton, H. J., Zarahn, E., Flynn, J., Moeller, J. R., & Stern, Y. (2003). Relation of cognitive reserve and task performance to expression of regional covariance networks in an event-related fMRI study of nonverbal memory. *NeuroImage, 20*, 1723-1733.

Habib, R., Nyberg, L., & Nilsson, L.-G. (2007). Cognitive and non-cognitive factors contributing to the longitudinal identification of successful older adults in the Betula study. *Aging, Neuropsychology, and Cognition, 14*(3), 257-273.

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

Hannigan, C., Coen, R. F., Lawlor, B. A., Robertson, I. H., & Brennan, S. (2015). The NEIL Memory Research Unit: psychological, biological, physiological and lifestyle factors associated with healthy ageing: study protocol. *BMC Psychology, 3*(1), 20-34.

Harrison, S. L., Sajjad, A., Bramer, W. M., Ikrawm, M. A., Tiemeier, H., & Stephan, B. C. M. (2015). Exploring strategies to operationalize cognitive reserve: a systematic review of reviews. *Journal of Clinical and Experimental Neuropsychology, 37*(3), 253-264.

Hayes, A. F. (2012). PROCESS: A versatile computational tool for observed variable mediation, moderation and conditional process modeling [White paper]. Retrieved April, 2014, from http://www.afhayes.com/public/process2012.pdf

Hedden, T., & Gabrieli, J. D. (2004). Insights into the ageing mind: a view from cognitive neuroscience. *Nature Reviews Neuroscience, 5*(2), 87-96.

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

Henderson, V. W. (2014). Three midlife strategies to prevent cognitive impairment due to Alzheimer's disease. *Climacteric, 17*(Suppl. 2), 38-46.

Holm, S. (1979). A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics, 6*, 65-70.

Holtzer, R., Rakitin, B. C., Steffener, J., Flynn, J., Kumar, A., & Stern, Y. (2009). Age effects on load-dependent brain activations in working memory for novel material. *Brain Research, 1249*, 148-161.

Honaker, J., King, G., & Blackwell, M. (2011). Amelia II: A program for missing data. *Journal of Statistical Software, 45*(7), 1-47.

Horn, J. L., & Cattell, R. B. (1967). Age differences in fluid and crystallised intelligence. *Acta Psychologica, 26*(2), 107-129.

House, J. S., Robbins, C., & Metzner, H. L. (1982). The association of social relationships and activities with mortality: prospective evidence from the Tecumseh community health study. *American Journal of Epidemiology, 116*(1), 123-140.

Hoyle, R. H. (2011). *Structural Equation Modeling for Social and Personality Psychology*. London: SAGE Publications Ltd.

Hu, L., & Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling: A Multidisciplinary Journal, 6*(1), 1-55.

Hultsch, D. F., Hertzog, C., Small, B. J., & Dixon, R. A. (1999). Use it or lose it: Engaged lifestyle as a buffer of cognitive decline in aging? *Psychology and Aging, 14*(2), 245-263.

Hultsch, D. F., Hertzog, C., Small, B. J., McDonald-Miszczak, L., & Dixon, R. A. (1992). Short-term longitudinal change in cognitive performance in later life. *Psychology and Aging, 7*(4), 571.

Ince, P. G. (2001). Pathological correlates of late-onset dementia in a multicenter community-based population in England and Wales. *Lancet, 357*, 169-175.

Jacobson, M. W., Delis, D. C., Bondi, M. W., & Salmon, D. P. (2002). Do neuropsychological tests detect preclinical Alzheimer's disease: Individual-test versus cognitive-discrepancy score analyses. *Neuropsychology, 16*(2), 132.

Jacobson, M. W., Delis, D. C., Bondi, M. W., & Salmon, D. P. (2005). Asymmetry in auditory and spatial attention span in normal elderly genetically at risk for Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology, 27*(2), 240-253.

Jacobson, M. W., Delis, D. C., Lansing, A., Houston, W., Olsen, R., Wetter, S., . . . Salmon, D. P. (2005). Asymmetries in global-local processing ability in elderly people with the Apolipoprotein E-ε4 allele. *Neuropsychology, 19*(6), 822.

Jacobson, M. W., McEvoy, L. K., Dale, A., & Fennema-Notestine, C. (2009). Cognitive phenotypes, brain morphometry and the detection of cognitive decline in preclinical AD. *Behavioural Neurology, 21*, 29-37.

Jagust, W., & Mormino, E. C. (2011). Lifespan brain activity, beta amyloid, and Alzheimer's disease. *Trends in Cognitive Sciences, 15*(11), 520-526.

Johnson, D. K. (2005). Two-wave panel analysis: comparing statistical methods for studying the effects of transitions. *Journal of Marriage and Family, 67*(4), 1061-1075.

Johnson, D. K., Storandt, M., Morris, J. C., & Galvin, J. E. (2009). Longitudinal study of the transition from healthy aging to Alzheimer disease. *Archives of Neurology, 66*(10), 1254-1259.

Jones, R. N., Fong, T. G., Metzger, E., Tulebaev, S., Yang, F. M., Alsop, D. C., . . . Inouye, S. K. (2010). Aging, brain disease, and reserve: implications for delirium. *The American Journal of Geriatric Psychiatry, 18*(2), 117.

Jones, R. N., Manly, J., Glymour, M. M., Rentz, A. l., & Stern, Y. (2011). Conceptual and measurement challenges in research on cognitive reserve. *Journal of the International Neuropsychological Society, 17*, 593-601.

Joreskog, K. G., & Yang, F. M. (1996). Nonlinear structural equation models: The Kenny-Judd model with interaction effect. In G. A. Marcoulides & R. E. Schumacker (Eds.), *Advanced Structural Equation Modeling: Issues and Techniques* (pp. 57-88). Mahwah, NJ: Erlbaum.

Jorm, A. F. (1994). A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): development and validation. *Psychological Medicine, 24*(1), 145-153.

Jorm, A. F. (2004). The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): A review. *International Psychogeriatrics, 16*(3), 275-293.

Jorm, A. F., Broe, G., Creasey, H., Sulway, M., Dent, O., Fairley, M., . . . Tennant, C. (1996). Further data on the validity of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). *International Journal of Geriatric Psychiatry, 11*(2), 131-139.

Juncos-Rabadán, O., Pereiro, A. X., Facal, D., Lojo, C., Caamaño, J. A., Sueiro, J., . . . Eiroa, P. (2014). Prevalence and correlates of mild cognitive impairment in adults aged over 50 years with subjective cognitive complaints in primary care centers. *Geriatrics & Gerontology International, 14*(3), 667-673.

Kaplan, R. F., Cohen, R. A., Moscufo, N., Guttman, C., Chasman, J., Buttaro, M., . . . Wolfson, L. (2009). Demographic and biological influences on cognitive reserve. *Journal of Clinical and Experimental Neuropsychology, 31*(7), 868-876.

Karp, A., Andel, R., Parker, M. G., Wang, H., Winblad, B., & Fratiglioni, L. (2009). Mentally stimulating activities at work during midlife and dementia risk after age 75: follow up study from the Kungsholmen project. *American Journal of Geriatric Psychiatry, 17*(3), 227-236.

Katzman, R., Aronson, M., Fuld, P., Kawas, C., Brown, T., Morgenstern, H., . . . Ooi, W. L. (1989). Development of dementing illnesses in an 80-year-old volunteer cohort. *Annals of Neurology, 25*, 317-324.

Kavé, G., Eyal, N., Shorek, A., & Cohen-Mansfield, J. (2008). Multilingualism and cognitive state in the oldest old. *Psychology and Aging, 23*(1), 70.

Kearney, P., Cronin, H., O'Regan, C., Kamiya, Y., Savva, G. M., Whelan, B. J., & Kenny, R. A. (2011). Cohort profile: The Irish Longitudinal Study on Ageing. *International Journal of Epidemiology, 40*, 877-884.

Kehoe, E. G., Farrell, D., Metzler-Baddeley, C., Lawlor, B. A., Kenny, R. A., Lyons, D., . . . Bokde, A. L. (2015). Fornix white matter is correlated with resting-state functional connectivity of the thalamus and hippocampus in healthy aging but not in mild cognitive impairment–a preliminary study. *Frontiers in Aging Neuroscience, 7*(10), 1-10.

Keller, J. N. (2006). Age-related neuropathology, cognitive decline, and Alzheimer's disease. *Ageing Research Reviews, 5*(1), 1-13.

Kenny, D. A., & Judd, C. M. (1984). Estimating the nonlinear and interactive effects of latent variables. *Psychological Bulletin, 96*, 201-210.

Kenny, R. A., Coen, R. F., Frewen, J., Donoghue, O., Cronin, H., & Savva, G. M. (2013). Normative values of cognitive and physical function in older adults: findings from The Irish Longitudinal Study on Ageing. *JAGS, 61*(S2), S279-S290.

Kenny, R. A., Whelan, B. J., Cronin, H., Kamiya, Y., Kearney, P., O'Regan, C., & Ziegel, M. (2010). *The Design of the Irish Longitudinal Study on Ageing*. Dublin, Ireland: Trinity College Dublin.

Kensinger, E. A., & Corkin, S. (2009). Cognition in aging and age related disease. In P. R. Hof & C. V. Mobbs (Eds.), *Handbook of the neuroscience of aging* (pp. 249-256). London, UK: Elsevier Press.

Kesler, S. R., Adams, H. F., Blasey, C. M., & Bigler, E. D. (2003). Premorbid intellectual functioning, education, and brain size in traumatic brain injury: an investigation of the cognitive reserve hypothesis. *Applied Neuropsychology, 10*(3), 153-162.

Kirkwood, T., Bond, J., May, C., McKeith, I., Teh, M., & Foresight Mental Capital and Wellbeing Project. (2008). *Foresight capital through life: Future challenges*. London: The Government Office for Science.

Kliegel, M., Moor, C., & Rott, C. (2004). Cognitive status and development in the oldest old: a longitudinal analysis from the Heidelberg Centenarian Study. *Archives of Gerontology and Geriatrics, 39*(2), 143-156.

Kline, R. (2010). *Principles and Practice of Structural Equation Modeling* (3 ed.). New York: The Guilford Press.

Knopman, D., & Caselli, R. J. (2012). Appraisal of cognition in preclinical Alzheimer's disease: a conceptual review. *Neurodegenerative Disease Management, 2*(2), 183-195.

Kontis, D., Huddy, V., Reeder, C., Landau, S., & Wykes, T. (2013). Effects of age and cognitive reserve on cognitive remediation therapy outcome in patients with schizophrenia. *The American Journal of Geriatric Psychiatry, 21*(3), 218-230.

Korkmaz, S., Goksuluk, D., & Zararsiz, G. (2014). MVN: An R Package for Assessing Multivariate Normality. *The R Journal, 6*(2), 151-162.

Krasean, L. E. (2014). *Word reading ability, occupational complexity, and neuropsychological functioning in a clinical older adult population.*

(Unpublished doctoral dissertation), University of Windsor, Windsor, Ontario, Canada.

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

La Rue, A. (2010). Healthy brain aging: role of cognitive reserve, cognitive stimulation, and cognitive exercises. *Clinics in Geriatric Medicine, 26*(1), 99-111.

Launer, L. J., Wind, A. W., & Deeg, D. J. (1994). Nonresponse pattern and bias in a community-based cross-sectional study of cognitive functioning among the elderly. *American Journal of Epidemiology, 139*(8), 803-812.

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

Lei, P. W., & Wu, Q. (2007). Introduction to structural equation modeling: Issues and practical considerations. *Educational Measurement: Issues and Practice, 26*(3), 33-43.

Leon, I., García-García, J., & Roldan-Tapia, L. (2014). Estimating cognitive reserve in healthy adults using the Cognitive Reserve Scale. *PLoS ONE, 9*(7), e102632.

Leon, I., Garcia, J., & Roldan-Tapia, L. (2011). [Development of the scale of cognitive reserve in Spanish population: a pilot study]. *Revista de neurologia, 52*(11), 653-660.

Levi, Y., Rassovsky, Y., Agranov, E., Sela-Kaufman, M., & Vakil, E. (2013). Cognitive reserve components as expressed in traumatic brain injury. *Journal of the International Neuropsychological Society, 19*, 664-671.

Lincoln, P., Fenton, K., Alessi, C., Prince, M., Brayne, C., Wortmann, M., . . . Mwatsama, M. (2014). The Blackfriars Consensus on brain health and dementia. *The Lancet, 383*(9931), 1805-1806.

Lindenberger, U., & Baltes, P. B. (1997). Intellectual functioning in old and very old age: cross sectional results from the Berlin Aging Study. *Psychology and Aging, 12*(3), 410-432.

Link, B., & Phelan, J. (1995). Social conditions as fundamental causes of disease. *Journal of Health and Social Behavior, 35*, 80-94.

Lojo-Seoane, C., Facal, D., Guardia-Olmos, J., & Juncos-Rabadán, O. (2014). Structural model for estimating the influence of cognitive reserve on cognitive performance in adults with subjective memory complaints. *Archives of Clinical Neuropsychology, 29*(3), 245-255.

Lonie, J. A., Tierney, K. M., & Ebmeier, K. P. (2009). Screening for mild cognitive impairment: a systematic review. *International Journal of Geriatric Psychiatry, 24*(9), 902-915.

Lövdén, M., Bodammer, N. C., Kühn, S., Kaufmann, J., Schütze, H., Tempelmann, C., . . . Lindenberger, U. (2010). Experience-dependent plasticity of white-matter microstructure extends into old age. *Neuropsychologia, 48*(13), 3878-3883.

Lövdén, M., Ghisletta, P., & Lindenberger, U. (2005). Social participation attenuates decline in perceptual speed in old and very old age. *Psychology and Aging, 20*(3), 423.

Lövdén, M., Wenger, E., Mårtensson, J., Lindenberger, U., & Bäckman, L. (2013). Structural brain plasticity in adult learning and development. *Neuroscience & Biobehavioral Reviews, 37*(9), 2296-2310.

Lowe, D. A., & Rogers, S. A. (2011). Estimating premorbid intelligence among older adults: The utility of the AMNART. *Journal of Aging Research, 2011*(428123), 1-7.

Luis, C. A., Keegan, A. P., & Mullan, M. (2009). Cross validation of the Montreal Cognitive Assessment in community dwelling older adults residing in the Southeastern US. *International Journal of Geriatric Psychiatry, 24*, 197-201.

Lyman, G. H., & Kuderer, N. M. (2005). The strengths and limitations of meta-analyses based on aggregate data. *BMC Medical Research Methodology, 5*(1), 14.

MacCallum, R. C., & Austin, J. T. (2000). Applications of structural equation modeling in psychological research. *Annual Review of Psychology, 51*, 201-226.

Madden, D. J., Turkington, T. G., Provenzale, J. M., Denny, L. L., Hawk, T. C., Gottlob, L. R., & Coleman, R. E. (1999). Adult age differences in the functional neuroanatomy of verbal recognition. *Human Brain Mapping, 7*, 115-135.

Mangialasche, F., Kivipelto, M., Solomon, A., & Fratiglioni, L. (2012). Dementia prevention: current epidemiological evidence and future perspective. *Alzheimer's Research & Therapy, 4*(6), 1-8.

Manly, J., Jacobs, D. M., Touradji, P., Small, S. A., & Stern, Y. (2002). Reading level attenuates differences in neuropsychological test performance between African

American and White elders. *Journal of the International Neuropsychological Society, 8*, 341-348.

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

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

Marioni, R. E., Van den Hout, A., Valenzuela, M. J., Brayne, C., Matthews, F. E., & MRC Cognitive Function and Ageing Study. (2012). Active cognitive lifestyle associates with cognitive recovery and a reduced risk of cognitive decline. *Journal of Alzheimer's Disease, 28*, 223-230.

Marsh, H. W., Wen, Z., & Hau, K.-T. (2004). Structural equation models of latent interactions: evaluation of alternative estimation strategies and indicator construction. *Psychological Methods, 9*(3), 275-300.

Mårtensson, J., Eriksson, J., Bodammer, N. C., Lindgren, M., Johansson, M., Nyberg, L., & Lövdén, M. (2012). Growth of language-related brain areas after foreign language learning. *NeuroImage, 63*(1), 240-244.

McGill, P. (2010). *Illustrating Ageing in Ireland North & South: Key facts and figures*. Belfast: Centre for Ageing Research and Development in Ireland.

McGinnis, D. (2012). Susceptibility to distraction during reading in young, young-old, and old-old adults. *Experimental Aging Research, 38*(4), 370-393.

Mecklin, C. J., & Mundfrom, D. J. (2004). An appraisal and bibliography of test for multivariate normality. *International Statistical Review, 72*(1), 123-138.

Mehta, K. M., Stewart, A. L., Langa, K. M., Yaffe, K., Moody-Ayers, S., Williams, B. A., & Covinsky, K. E. (2009). 'Below average' self-assessed school performance and Alzheimer's disease in the Aging, Demographics and Memory Study. *Alzheimer's & Dementia, 5*(5), 380-387.

Meng, X., & D'Arcy, C. (2012). Education and dementia in the context of the cognitive reserve hypothesis: a systematic review with meta-analyses and qualitative analyses. *PLoS ONE, 7*(6), e38268.

Mitchell, M. B., Shaughnessy, L. W., Shirk, S. D., Yang, F. M., & Atri, A. (2012). Neuropsychological test performance and cognitive reserve in healthy aging and

the Alzheimer's disease spectrum: a theoretically driven factor analysis. *Journal of the International Neuropsychological Society, 18*, 1071-1080.

Mitrushina, M. M., Boone, K. B., Razani, J., & D'Elia, L. F. (2005). *Handbook of Normative Data for Neuropsychological Assessment* (2 ed.). New York: McGraw Hill.

Molinuevo, J. L., Ripolles, P., Simó, M., Lladó, A., Olives, J., Balasa, M., . . . Rami, L. (2014). White matter changes in preclinical Alzheimer's disease: a magnetic resonance imaging-diffusion tensor imaging study on cognitively normal older people with positive amyloid β protein 42 levels. *Neurobiology of Aging, 35*(12), 2671-2680.

Morgan, E. E., Woods, S. P., Smith, C., Weber, E., Cobb Scott, J., & Grant, I. (2012). Lower cognitive reserve among individuals with syndromic HIV-associated neurocognitive disorders (HAND). *AIDS Behaviour, 16*, 2279-2285.

Morris, J. C., Storandt, M., McKeel, D. W., Rubin, E. H., Price, J. L., Grant, E. A., & et al. (1996). Cerebral amyloid deposition and diffuse plaques in "normal" aging: Evidence for presymptomatic and very mild Alzheimer's disease. *Neurology, 46*, 707-719.

Mortimer, J. A., Snowdon, D. A., & Markesbery, W. R. (2003). Head circumference, education and risk of dementia: findings from the Nun Study. *Journal of Clinical and Experimental Neuropsychology, 25*(5), 671-679.

Mueller, R. O., & Hancock, G. R. (2008). Best practices in structural equation modeling. In J. Osborne (Ed.), *Best Practices in Quantitative Methods* (pp. 488-508). Thousand Oaks, CA: SAGE.

Murphy, M., & O'Leary, E. (2010). Depression, cognitive reserve and memory performance in older adults. *International Journal of Geriatric Psychiatry, 25*, 665-671.

Murray, A. D., Staff, R. T., McNeil, C. J., Salarirad, S., Ahearn, T. S., Mustafa, N., & Whalley, L. J. (2011). The balance between cognitive reserve and brain imaging biomarkers of cerebrovascular and Alzheimer's diseases. *Brain, 134*, 3687-3696.

Nachtigall, C., Kroehne, U., Funke, F., & Steyer, R. (2003). (Why) should we use SEM? Pros and cons of structural equation modeling. *Methods of Psychological Research Online, 8*(2), 1-22.

Nagel, I. E., Preuschhof, C., Li, S., Nyberg, L., Backman, L., Lindenberger, U., & Heekeren, H. R. (2009). Performance level modulates adult age differences in brain activation during spatial working memory. *PNAS, 106*(52), 22552-22557.

Nagel, I. E., Preuschhof, C., Li, S., Nyberg, L., Backman, L., Lindenberger, U., & Heekeren, H. R. (2011). Load modulation of BOLD response and connectivity predicts working memory performance in younger and older adults. *Journal of Cognitive Neuroscience, 23*(8), 2030-2045.

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., . . . Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *JAGS, 53*(4), 695-699.

Nebes, R. D., Meltzer, C. C., Whyte, E. M., Scanlon, J. M., Halligan, E. M., Saxton, J. A., . . . DeKosky, S. T. (2006). The relation of white matter hyperintensities to cognitive performance in the normal old: education matters. *Aging, Neuropsychology and Cognition: A Journal on Normal and Dysfunctional Development, 13*(3-4), 326-340.

Nelson, H. E. (1982). *National Adult Reading Test (NART): Test Manual*. Windsor, Berks: NFER-Nelson.

Nucci, M., Mapelli, D., & Mondini, S. (2012). Cognitive Reserve Index Questionnaire (CRIq): a new instrument for measuring cognitive reserve. *Ageing Clinical and Experimental Research, 24*(3), 218-226.

Nyberg, L., Lovdén, M., Riklund, K., Lindenberger, U., & Backman, L. (2012). Memory aging and brain maintenance. *Trends in Cognitive Sciences, 16*(5), 292-305.

Office for National Statistics. ONS Occupation Code Search Tool. Retrieved 11 August, 2015, from http://www.neighbourhood.statistics.gov.uk/HTMLDocs/dev3/ONS_SOC_occupation_coding_tool.html

Office for National Statistics. (2010). *Standard Occupational Classification 2010 Volume 1: Structure and descriptions of unit groups*. United Kingdom: Palgrave Macmillan.

Ojala-Oksala, J., Jokinen, H., Kopsi, V., Lehtonen, K., Luukkonen, L., Paukkunen, A., . . . Oksala, N. (2012). Educational history is an independent predictor of cognitive deficits and long-term survival in postacute patients with mild to moderate ischemic stroke. *Stroke, 43*, 2931-2935.

Opdebeeck, C., Martyr, A., & Clare, L. (2015). Cognitive reserve and cognitive function in healthy older people: a meta-analysis. *Aging, Neuropsychology and Cognition: A Journal on Normal and Dysfunctional Development*, Advance online publication.

Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: aging and neurocognitive scaffolding. *Annual Review of Psychology, 60*, 173-196.

Perls, T. (2004). Centenarians who avoid dementia. *Trends in Neurosciences, 27*(10), 633-636.

Perneczky, R., Drzezga, A., Diehl-Schmid, J., Schmid, G., Wohlschlager, A., Kars, S., . . . Kurz, A. (2006). Schooling mediates brain reserve in Alzheimer's disease: findings of fluoro-deoxy-glucose-positron emission tomography. *Journal of Neurology, Neurosurgery & Psychiatry, 77*, 1060-1063.

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine, 256*(3), 183-194.

Petrosini, L., De Bartolo, P., Foti, F., Gelfo, F., Cutuli, D., Leggio, M. G., & Mandolesi, L. (2009). On whether the environmental enrichment may provide cognitive and brain reserves. *Brain Research Reviews, 61*, 221-239.

Pettigrew, C., Soldan, A., Shanshan, L., Lu, Y., Wang, M., Selnes, O. A., . . . BIOCARD, R. T. t. (2013). Relationship of cognitive reserve and APOE status to the emergence of clinical symptoms in preclinical Alzheimer's disease. *Cognitive Neuroscience, 4*(3-4), 136-142.

Pinter, D., Enzinger, C., & Fazekas, F. (2015). Cerebral small vessel disease, cognitive reserve and cognitive dysfunction. *Journal of Neurology*, 1-9.

Plassman, B. L., Langa, K. M., Fisher, G. G., Heeringa, S. G., Weir, D. R., Ofstedal, M. B., . . . Rodgers, W. L. (2008). Prevalence of cognitive impairment without dementia in the United States. *Annals of Internal Medicine, 148*(6), 427-434.

Pornprasertmanit, S., Miller, P., Schoemann, A., & Rosseel, Y. (2014). semTools: Useful tools for structural equation modeling (Version R package version 0.4-6). Retrieved from http://CRAN.R-project.org/package=semTools

Price, J. L., & Morris, J. C. (1999). Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. *Annals of Neurology, 45*, 358-368.

Prull, M. W., Crandell Dawes, L. L., McLeish Martin, A., Rosenberg, H. F., & Light, L. L. (2006). Recollection and familiarity in recognition memory: adult age

differences and neuropsychological test correlates. *Psychology and Aging, 21*(1), 107-118.

Puccioni, O., & Vallesi, A. (2012a). Conflict resolution and adaptation in normal aging: The role of verbal intelligence and cognitive reserve. *Psychology and Aging, 27*(4), 1018.

Puccioni, O., & Vallesi, A. (2012b). High cognitive reserve is associated with a reduced age-related deficit in spatial conflict resolution. *Frontiers in Human Neuroscience, 6*, 327.

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

R Core Team. (2015). R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing. Retrieved from http://www.R-project.org/

Radloff, L. S. (1977). The CES-D scale: a self-report depression scale for research in the general population. *Applied Psychological Measurement, 1*, 385-401.

Raiha, I., Kaprio, J., Koskenvuo, M., Rajala, T., & Sourander, L. (1998). Environmental differences in twin pairs discordant for Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry, 65*, 785-787.

Rami, L., Valls-Pedret, C., Bartres-Faz, D., Caprile, C., Solé-Padullés, C., Castellvi, M., . . . Molinuevo, J. L. (2011). [Cognitive reserve questionnaire. Scores obtained in a healthy elderly population and in one with Alzheimer's disease]. *Revista de Neurologia, 52*(4), 195-201.

Raykov, T., & Marcoulides, G. A. (2000). *A First Course in Structural Equation Modeling*. London: Lawrence Erlbaum Associates.

Raz, N. (2000). Aging of the brain and its impact on cognitive performance: integration of structural and functional findings. In F. I. Craik & T. A. Salthouse (Eds.), *The Handbook of Aging and Cognition* (2nd ed.). Mahaw, NJ: Erblaum.

Raz, N., Gunning-Dixon, F. M., Head, D., Dupuis, J. H., & Acker, J. D. (1998). Neuroanatomical correlates of cognitive aging: evidence from structural magnetic resonance imaging. *Neuropsychology, 12*, 95-114.

Raz, N., & Rodrigue, K. M. (2006). Differential aging of the brain: patterns, cognitive correlates and modifiers. *Neuroscience & Biobehavioral Reviews, 30*(6), 730-748.

Reed, B. R., Mungas, D., Tomaszewski Farias, S., Harvey, D., Beckett, L., Widaman, K., . . . DeCarli, C. (2010). Measuring cognitive reserve based on the decomposition of episodic memory variance. *Brain, 133*, 2196-2209.

Reid, L. M., & MacLullich, A. M. J. (2006). Subjective memory complaints and cognitive impairment in older people. *Dementia and Geriatric Cognitive Disorders Extra, 22*, 471-485.

Reitz, C., Brayne, C., & Mayeux, R. (2011). Epidemiology of Alzheimer disease. *Nature Reviews Neurology, 7*(3), 137-152.

Rentz, D. M., Huh, T. J., Faust, R. R., Budson, A. E., Scinto, L. F. M., Sperling, R. A., & Daffner, K. R. (2004). Use of IQ-adjusted norms to predict progressive cognitive decline in highly intelligent older individuals. *Neuropsychology, 18*(1), 38-49.

Rentz, D. M., Huh, T. J., Sardinha, L. M., Moran, E. K., Becker, J. A., Daffner, K. R., . . . Johnson, K. A. (2007). Intelligence quotient-adjusted memory impairment is associated with abnormal single photon emission computed tomography perfusion. *Journal of the International Neuropsychological Society, 13*(5), 821-831.

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

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

Reuter-Lorenz, P. A., & Park, D. C. (2014). How does it STAC up? Revisiting the scaffolding theory of aging and cognition. *Neuropsychology Review, 24*(3), 355-370.

Richards, M., & Sacker, A. (2003). Lifetime antecedents of cognitive reserve. *Journal of Clinical and Experimental Neuropsychology, 25*(5), 614-624.

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

Rieckmann, A., Karlsson, S., Karlsson, P., Brehmer, Y., Fischer, H., Farde, L., . . . Bäckman, L. (2011). Dopamine D1 receptor associations within and between

dopaminergic pathways in younger and elderly adults: links to cognitive performance. *Cerebral Cortex*, bhq266.

Ritchie, S. J., Bates, T. C., Der, G., Starr, J. M., & Deary, I. J. (2013). Education is associated with higher later life IQ scores, but not with faster cognitive processing speed. *Psychology and Aging*, *28*(2), 515.

Robertson, I. H. (2014). A right hemisphere role in cognitive reserve. *Neurobiology of aging*, *35*, 1375-1385.

Rog, L. A., & Fink, J. W. (2013). Mild Cognitive Impairment and Normal Aging. In L. D. Ravdin & H. L. Katzen (Eds.), *Handbook on the Neuropsychology of Aging and Dementia*. New York: Springer.

Ropacki, M. T., & Elias, J. W. (2003). Preliminary examination of cognitive reserve theory in closed head injury. *Archives of Clinical Neuropsychology*, *18*, 643-654.

Rosseel, Y. (2012). lavaan: an R package for structural equation modeling. *Journal of Statistical Software*, *48*(2), 1-36.

Roth, M., Huppert, G. A., Mountjoy, C. Q., & Tym, E. (1998). *CAMDEX-R: The Cambridge Examination for Mental Disorders of the Elderly*. Cambridge: Cambridge University Press.

Rowe, J. W., & Kahn, R. L. (1997). Successful aging. *The Gerontologist*, *27*(4), 433-440.

Rubin, D. L. (1987). *Multiple Imputation for Nonresponse in Surveys*. New Jersey: John Wiley & Sons.

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

Salthouse, T. A. (2004). What and when of cognitive aging. *Current Directions in Psychological Science*, *13*(4), 140-144.

Salthouse, T. A. (2009). When does age-related cognitive decline begin? *Neurobiology of Aging*, *30*, 507-514.

Salthouse, T. A. (2012). Consequences of age-related cognitive declines. *Annual review of Psychology*, *63*, 201.

Salthouse, T. A., Atkinson, T. M., & Berish, D. E. (2003). Executive functioning as a potential mediator of age-related cognitive decline in normal adults. *Journal of Experimental Psychology: General*, *132*(4), 566-594.

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

Salthouse, T. A., & Davis, H. P. (2006). Organization of cognitive abilities and neuropsychological variables across the lifespan. *Developmental Review, 26*(1), 31-54.

Sanchez, J. L., Torrellas, C., Martin, J., & Barrera, I. (2011). Study of sociodemographic variables linked to lifestyle and their possible influence on cognitive reserve. *Journal of Clinical and Experimental Neuropsychology, 33*(8), 874-891.

Sartori, A. C., Vance, D. E., Slater, L. Z., & Crowe, M. (2012). The impact of inflammation on cognitive function in older adults: Implications for health care practice and research. *The Journal of Neuroscience Nursing, 44*(4), 206.

Satorra, A., & Bentler, P. M. (1994). Corrections to test statistics and standard errors in covariance structure analysis. In A. von Eye & C. C. Clogg (Eds.), *Latent variables analysis: Applications for developmental research* (pp. 399-419). Thousand Oaks, CA: Sage.

Satz, P. (1993). Brain reserve capacity on symptom onset after brain injury: a formulation and review of evidence for threshold theory. *Neuropsychology, 7*(3), 273.

Satz, P., Cole, M. A., Hardy, D. J., & Rassovsky, Y. (2011). Brain and cognitive reserve: Mediator (s) and construct validity, a critique. *Journal of Clinical and Experimental Neuropsychology, 33*(1), 121-130.

Savva, G. M., Wharton, S. B., Ince, P. G., Forster, G., Matthews, F. E., & Brayne, C. (2009). Age, neuropathology and dementia. *The New England Journal of Medicine, 360*, 2302-2309.

Saxton, J., Lopez, O. L., Ratcliff, G., Dulberg, C., Fried, L., Carlson, M., . . . Kuller, L. (2004). Preclinical Alzheimer disease: Neuropsychological test performance 1.5 to 8 years prior to onset. *Neurology, 63*(12), 2341-2347.

Scarmeas, N., Levy, G., Tang, M. X., Manly, J., & Stern, Y. (2001). Influence of leisure activity on the incidence of Alzheimer's disease. *Neurology, 57*, 2236-2242.

Scarmeas, N., Zarahn, E., Anderson, K. E., Habeck, C. G., Hilton, J., Flynn, J., . . . Stern, Y. (2003). Association of life activities with cerebral blood flow in Alzheimer disease. *Archives of Neurology, 60*, 359-365.

Scarmeas, N., Zarahn, E., Anderson, K. E., Honig, L. S., Park, A., Hilton, J., . . . Stern, Y. (2004). Cognitive reserve-mediated modulation of positron emission tomographic activations during memory tasks in Alzheimer disease. *Archives of Neurology, 61*(1), 73-78.

Schafer, J. L., & Olsen, M. K. (1998). Multiple imputation for multivariate missing-data problems: a data analysts perspective. *Multivariate Behavioral Research, 33*(4), 545-571.

Schaie, K. H. (1996). *Intellectual Development in Adulthood: The Seattle Longitudinal Study*. Cambridge: Cambridge University Press.

Schaie, K. H., & Willis, S. L. (2010). The Seattle Longitudinal Study of Adult Cognitive Development. *ISSBD Bull, 57*(1), 24-29.

Scheller, E., Minkova, L., Leitner, M., & Kloppel, S. (2014). Attempted and successful compensation in preclinical and early manifest neurodegeneration - a review of task fMRI studies. *Frontiers in Psychiatry, 5*, 132.

Schmand, B., Geerlings, M. G., Jonker, C., & Lindeboom, J. (1998). Reading ability as an estimate of premorbid intelligence: does if remain stable in emergent dementia? *Journal of Clinical and Experimental Neuropsychology, 20*(1), 42-51.

Schmand, B., Smit, J. H., Geerlings, M. G., & Lindeboom, J. (1997). The effects of intelligence and education on the development of dementia: a test of the brain reserve hypothesis. *Psychological Medicine, 27*, 1337-1344.

Schmitt, F., Davis, D., Wekstein, D., Smith, C., Ashford, J., & Markesbery, W. (2000). "Preclinical" AD revisited: Neuropathology of cognitively normal older adults. *Neurology, 55*(3), 370-376.

Schofield, P. W., Marder, K. S., Dooneief, G., Jacobs, D. M., Sano, M., & Stern, Y. (1997). Association of subjective memory complaints with subsequent cognitive decline in community-dwelling elderly individuals with baseline cognitive impairment. *American Journal of Psychiatry, 154*, 609-615.

Schooler, C., Mulatu, M. S., & Oates, G. (1999). The continuing effects of substantively complex work on the intellectual functioning of older workers. *Psychology and Aging, 14*(3), 483.

Schreiber, J. B., Amaury, N., Stage, F. K., Barlow, E. A., & King, J. (2010). Reporting structural equation modeling and confirmatory factor analysis results: a review. *The Journal of Education Research, 99*(6), 323-338.

Siedlecki, K. L., Salthouse, T. A., & Berish, D. E. (2005). Is there anything special about the aging of source memory? *Psychology and Aging, 20*(1), 19.

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

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

Slavin, M. J., Brodaty, H., Kochan, N. A., Crawford, J. D., Trollor, J. N., Draper, B., & Sachdev, P. S. (2010). Prevalence and predictors of "subjective cognitive complaints" in the Sydney Memory and Ageing Study. *The American Journal of Geriatric Psychiatry, 18*(8), 701-710.

Small, B. J., Dixon, R. A., McArdle, J. J., & Grimm, K. J. (2012). Do changes in lifestyle engagement moderate cognitive decline in normal aging? Evidence from the Victoria Longitudinal Study. *Neuropsychology, 26*(2), 144.

Smith, G., Della Sala, S., Logie, R. H., & Maylor, E. A. (2000). Prospective and retrospective memory in normal ageing and dementia: a questionnaire study. *Memory, 8*(5), 311-321.

Sobral, M., Pestana, M. H., & Paúl, C. (2014). Measures of cognitive reserve in Alzheimer's disease. *Trends in Psychiatry and Psychotherapy, 36*(3), 160-168.

Soldan, A., Pettigrew, C., Shanshan, L., Wang, M., Moghekar, A., Selnes, O. A., . . . Team, t. B. R. (2013). Relationship of cognitive reserve and cerebrospinal fluid biomarkers to the emergence of clinical symptoms in preclinical Alzheimer's disease. *Neurobiology of Aging, 34*, 2827-2834.

Sole-Padulles, C., Bartres-Faz, D., Junque, C., Vendrell, P., Rami, L., Clemente, I. C., . . . Molinuevo, J. L. (2009). Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer's disease. *Neurobiology of Aging, 30*(7), 1114-1124.

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., . . . Montine, T. J. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia, 7*(3), 280-292.

Staff, R. T., Murray, A. D., Deary, I. J., & Whalley, L. J. (2004). What provides cerebral reserve? *Brain, 127,* 1191-1199.

Starr, J. M., & Lonie, J. (2008). Estimated pre-morbid IQ effects on cognitive and functional outcomes in Alzheimer disease: a longitudinal study in a treated cohort. *BMC Psychiatry, 8*(1), 27-34.

Steffener, J., Barulli, D., Habeck, C. G., & Stern, Y. (2014). Neuroimaging explanations of age-related differences in task performance. *Frontiers in Aging Neuroscience, 6*.

Steffener, J., & Stern, Y. (2012). Exploring the neural basis of cognitive reserve in aging. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1822*(3), 467-473.

Steiger, J. H., & Lind, J. C. (1980). *Statistically based tests for the number of common factors*. Paper presented at the Annual Meeting of the Psychometric Society, Iowa City, IA.

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

Stern, Y. (2003). The concept of cognitive reserve: a catalyst for research. *Journal of Clinical and Experimental Neuropsychology, 25*(5), 589-593.

Stern, Y. (2007). The concept of cognitive reserve: A catalyst for research. In Y. Stern (Ed.), *Cognitive Reserve: Theory and Applications*. New York: Taylor & Francis.

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

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology, 11*(11), 1006-1012.

Stern, Y. (2013). Cognitive reserve: implications for assessment and intervention. *Folia Phoniatrica et Logopaedica, 65*(2), 49-54.

Stern, Y., Albert, S., Tang, M. X., & Tsai, W. Y. (1999). Rate of memory decline in AD is related to education and occupation: cognitive reserve? *Neurology, 53*(9), 1942-1947.

Stern, Y., Alexander, G. E., Prohovnik, I., & Mayeux, R. (1992). Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer's disease. *Annals of Neurology, 32*(3), 371-375.

Stern, Y., Alexander, G. E., Prohovnik, I., Stricks, L., Link, B., Lennon, M. C., & Mayeux, R. (1995). Relationship between lifetime occupation and parietal flow: implications for a reserve against Alzheimer's disease pathology. *Neurology, 45*(1), 55-60.

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

Sterne, J. A., White, I. R., Carlin, J. B., Spratt, M., Royston, P., Kenward, M. G., . . . Carpenter, J. R. (2009). Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *British Medical Journal, 338*, b2393.

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). *A Compendium of Neuropsychological Tests: Administration, Norms and Commentary* (3 ed.). New York, NY: Oxford University Press.

Sumowski, J. F., Chiaravalloti, N., Wylie, G., & Deluca, J. (2009). Cognitive reserve moderates the negative effect of brain atrophy on cognitive efficiency in multiple sclerosis. *Journal of the International Neuropsychological Society, 15*, 606-612.

Sumowski, J. F., Wylie, G., Gonnella, A., Chiaravalloti, N., & Deluca, J. (2010). Premorbid cognitive leisure independently contributes to cognitive reserve in multiple sclerosis. *Neurology, 7*(5), 1428-1431.

The Psychological Corporation. (2002). *WAIS-III/WMS-III Technical Manual*. San Antonio, Texas: The Psychological Corporation.

Thomas, A. (2008). Clinical aspects of dementia: Alzheimer's disease. In R. Jacoby, C. Oppenheimer, T. Dening, & A. Thomas (Eds.), *Oxford Textbook of Old Age Psychiatry*. New York: Oxford University Press.

Tierney, M. C., Yao, C., Kiss, A., & McDowell, I. (2005). Neuropsychological tests accurately predict incident Alzheimer disease after 5 and 10 years. *Neurology, 64*(11), 1853-1859.

TILDA. (2009). *Self completion questionnaire in confidence*. Dublin, Ireland: The Irish Longitudinal Study on Ageing.

TILDA. (2010). *The Design of the Irish Longitudinal Study on Ageing*. Dublin, Ireland: Trinity College Dublin.

Tisserand, D. J., & Jolles, J. (2003). On the involvement of prefrontal networks in cognitive ageing. *Cortex, 39*(4), 1107-1128.

Tombaugh, T. N., Kozak, J., & Rees, L. (1999). Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Archives of Clinical Neuropsychology, 14*(2), 167-177.

Travers, C., Lie, D., & Martin-Khan, M. (2015). Dementia and the population health approach: promise, pitfalls and progress. An Australian perspective. *Reviews in Clinical Gerontology, 25*, 60-71.

Trinity College Dublin. (2009). *Trinity College Dublin Policy on Good Research Practice*. Dublin, Ireland: Trinity College.

Tripepi, G., Jager, K. J., Dekker, F. W., & Zoccali, C. (2010). Selection bias and information bias in clinical research. *Nephron Clinical Practice, 115*(2), c94-c99.

Tucker-Drob, E. M., Johnson, K. E., & Jones, R. N. (2009). The cognitive reserve hypothesis: a longitudinal examination of age-associated declines in reasoning and processing speed. *Developmental Psychology, 45*(2), 431-446.

Tucker, A. M., & Stern, Y. (2011). Cognitive Reserve in Aging. *Current Alzheimer Research, 8*(4), 354-360.

Twamley, E. W., Legendre-Ropacki, S. A., & Bondi, M. W. (2006). Neuropsychological and neuroimaging changes in preclinical Alzheimer's disease. *Journal of the International Neuropsychological Society, 12*, 707-735.

United Nations Department of Economic and Social Affairs Population Division. (2009). *World Population Ageing 2009*. New York: United Nations.

Valenzuela, M. J. (2008). Brain reserve and the prevention of dementia. *Current Opinion in Psychiatry, 21*, 296-302.

Valenzuela, M. J., & Sachdev, P. (2006a). Brain reserve and cognitive decline: a non-parametric systematic review. *Psychological Medicine, 36*(08), 1065-1073.

Valenzuela, M. J., & Sachdev, P. (2006b). Brain reserve and dementia: a systematic review. *Psychological Medicine, 36*(4), 441-454.

Valenzuela, M. J., & Sachdev, P. (2007). Assessment of complex mental activity across the lifespan: development of the Lifetime of Experiences Questionnaire (LEQ). *Psychological Medicine, 37*(7), 1015-1026.

Valenzuela, M. J., Sachdev, P., Wen, W., Chen, X., & Brodaty, H. (2008). Lifespan mental activity predicts diminished rate of hippocampal atrophy. *PLoS ONE, 3*(7), e2598.

Van Beijsterveldt, C., Van Boxtel, M., Bosma, H., Houx, P., Buntinx, F., & Jolles, J. (2002). Predictors of attrition in a longitudinal cognitive aging study:: The Maastricht Aging Study (MAAS). *Journal of Clinical Epidemiology, 55*(3), 216-223.

Van Burren, S. (2013). Multiple Imputation - calculating effect size and reporting results [Reply]. from http://stats.stackexchange.com/questions/50055/multiple-imputation-calculating-effect-size-and-reporting-results

Van der Linden, M., Hupet, M., Feyereisen, P., Schelstraete, M.-A., Bestgen, Y., Bruyer, R., . . . Seron, X. (1999). Cognitive mediators of age-related differences in language comprehension and verbal memory performance. *Aging, Neuropsychology, and Cognition, 6*(1), 32-55.

Van Gerven, P. W., Van Boxtel, M. P., Ausems, E. E., Bekers, O., & Jolles, J. (2012). Do apolipoprotein E genotype and educational attainment predict the rate of cognitive decline in normal aging? A 12-year follow-up of the Maastricht Aging Study. *Neuropsychology, 26*(4), 459.

Van Gerven, P. W., Willemien, A. M., & Jolles, J. (2007). Education does not protect against age-related decline of switching focal attention in working memory. *Brain and Cognition, 64*, 158-163.

Vemuri, P., Weigand, S. D., Przybelski, S. A., Knopman, D. S., Smith, G. E., Trojanowski, J. Q., . . . Bernstein, M. A. (2011). Cognitive reserve and Alzheimer's disease biomarkers are independent determinants of cognition. *Brain, 134*, 1479-1492.

Von Hippel, P. T. (2009). How to impute interactions, squares, and other transformed variables. *Sociological Methodology, 39*(1), 265-291.

Vuoksimaa, E., Panizzon, M. S., Chen, C., Eyler, L. T., Fennema-Notestine, C., Fiecas, M. J. A., . . . Kremen, W. S. (2013). Cognitive reserve moderates the association between hippocampal volume and episodic memory in middle age. *Neuropsychologia, 51*, 1124-1131.

Wager, T. D., & Smith, E. E. (2003). Neuroimaging studies of working memory: a meta-analysis. *Cognitive, Affective, & Behavioral Neuroscience, 3*(4), 255-274.

Ward, D. D., Summers, M. J., Saunders, N. L., & Vickers, J. C. (2014). Modelling cognitive reserve in healthy middle-aged and older adults: the Tasmanian Healthy Brain Project. *International Psychogeriatrics, 1*, 1-11.

Watson, A., & Joyce, E. (2015). Cognitive reserve and neuropsychiatric disorders. *Current Opinion in Behavioral Sciences, 4*, 142-146.

Wechsler, D. (1997a). *WAIS-III: Administration and scoring manual*. San Antonio, Texas: Psychological Corporation.

Wechsler, D. (1997b). *Wechsler Memory Scale - Third Edition*. San Antonio, TX: The Psychological Corporation.

Wechsler, D. (2009). *Wechsler Memory Scale - Fourth Edition (WMS-IV) technical and interpretive manual*. San Antonio, TX: Pearson.

Weston, R., & Gore, P. A. (2006). A brief guide to structural equation modeling. *The Counseling Psychologist, 34*(5), 719-751.

Whalley, L., Starr, J., Athawes, R., Hunter, D., Pattie, A., & Deary, I. (2000). Childhood mental ability and dementia. *Neurology, 55*(10), 1455-1459.

Whitwell, J. L., Wiste, H. J., Weigand, S. D., Rocca, W. A., Knopman, D. S., Roberts, R. O., . . . Initiative, A. D. N. (2012). Comparison of imaging biomarkers in the Alzheimer disease neuroimaging initiative and the Mayo Clinic Study of Aging. *Archives of Neurology, 69*(5), 614-622.

Wilkenson, G. S. (1993). *The Wide Range Achievement Test Administration Manual*: Wide Range Inc.

Wilson, R. S., Barnes, L. L., Krueger, K. R., Hoganson, G., Bienias, J. L., & Bennett, D. A. (2005). Early and late life cognitive activity and cognitive systems in old age. *Journal of the International Neuropsychological Society, 11*, 400-407.

Wilson, R. S., Boyle, P. A., Yu, L., Barnes, L. L., Schneider, J. A., & Bennett, D. A. (2013). Life-span cognitive activity, neuropathologic burden, and cognitive ageing. *Neurology, 81*, 1-8.

Wilson, R. S., Leurgans, S. E., Boyle, P. A., & Bennett, D. A. (2011). Cognitive decline in prodromal Alzheimer disease and mild cognitive impairment. *Archives of Neurology, 68*(3), 351-356.

World Health Organization. (2012). *Dementia: a public health priority*: World Health Organization.

Yaffe, K., Fiocco, A., Lindquist, K., Vittinghoff, E., Simonsick, E., Newman, A., . . . Ayonayon, H. (2009). Predictors of maintaining cognitive function in older adults The Health ABC Study. *Neurology, 72*(23), 2029-2035.

Yankner, B. A., Lu, T., & Loerch, P. (2008). The aging brain. *Annual Review of Pathology: Mechanisms of Disease, 3*, 41-66.

Zahodne, L. B., Glymour, M. M., Sparks, C., Bontempo, D., Dixon, R. A., MacDonald, S. W., & Manly, J. J. (2011). Education does not slow cognitive decline with aging: 12-year evidence from the Victoria Longitudinal Study. *Journal of the International Neuropsychological Society, 17*(06), 1039-1046.

Zahodne, L. B., Manly, J., Brickman, A. M., Siedlecki, K. L., DeCarli, C., & Stern, Y. (2013). Quantifying cognitive reserve in older adults by decomposing episodic memory variance: replication and extension. *Journal of the International Neuropsychological Society, 19*, 1-9.

Zahodne, L. B., Schofield, P. W., Farrell, M. T., Stern, Y., & Manly, J. J. (2014). Bilingualism does not alter cognitive decline or dementia risk among Spanish-speaking immigrants. *Neuropsychology, 28*(2), 238.

Zarahn, E., Rakitin, B., Abela, D., Flynn, J., & Stern, Y. (2007). Age-related changes in brain activation during a delayed item recognition task. *Neurobiology of Aging, 28*(5), 784-798.

Zelinski, E. M., & Burnight, K. P. (1997). Sixteen-year longitudinal and time lag changes in memory and cognition in older adults. *Psychology and Aging, 12*(3), 503.

Zigmond, A. S., & Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica, 67*, 361-370.

Zimmerman, D. W. (2004). A note on preliminary tests of equality of variances. *British Journal of Mathematical and Statistical Psychology, 57*(1), 173-181.

Appendix A: Excluded articles tables

Articles excluded based on full text	
Citation	***Reason for Exclusion***
Ansado et al (2013) Coping with task demand in aging using neural compensation and neural reserve triggers primarily intra-hemispheric-based neurofunctional reorganisation. *Neuroscience Research, 75*(4), 295	Outcome (investigating possible mechanisms using neuroimaging outcome measures)
Arenaza-Urquijo et al (2013) Relationships between years of education and grey matter volume, metabolism and functional connectivity in healthy elders. *Neuroimage, 83*, 3450	Outcome (investigating possible mechanisms using neuroimaging measures)
Arenaza-Urquijo et al (2011) Specific anatomic associations between white matter integrity and cognitive reserve in normal and cognitively impaired elders. *The American Journal of Geriatric Psychiatry*, *19*(1), 33	Outcome (investigating potential mechanisms using neuroimaging measures)
Bartres-Faz et al (2009) Interactions of cognitive reserve with regional brain anatomy and brain function during a working memory task in healthy elders. *Biological Psychology*, *80*(2), 256	Outcome (investigating potential mechanisms using neuroimaging measures)
Bastin et al (2012) Cognitive reserve impacts on inter-individual variability in resting state cerebral metabolism in normal aging. *Neuroimage*, *63*(2), 713	Outcome (neuroimaging outcome measure)
Batterham et al (2011) The effect of education on the onset and rate of terminal decline. *Psychology and Aging*, *26*(2), 339	Outcome (terminal decline related to pathological processes distinct from normal, age-related decline)
Bosch et al (2010) Cognitive reserve modulates task-induced activations and deactivations in healthy elders, amnestic mild cognitive impairment and mild Alzheimer's disease. Cortex, 46(4), 451	Outcome (investigating potential mechanisms using neuroimaging outcome measures)
Boyle et al (2008) Processing resources reduce the effect of Alzheimer pathology on other cognitive systems. *Neurology*, *70*(17), 1534	Did not measure a CR indicator (investigating relationship certain cognitive functions on other cognitive domains)
Corral et al (2006) Cognitive reserve, age and neuropsychological performance in healthy participants. *Developmental Neuropsychology*, *29*(3), 479	Sample (includes participants outside of specified age range)
Elcombe et al (2013) Clinical and cognitive correlates of structural hippocampal change in "at-risk" older adults. *Journal of Geriatric Psychiatry and Neurology*, *27*(2), 67	Intervention study (cognitive training)
Elkins et al (2006) Education and the cognitive decline associated with MRI defined brain infarct. *Neurology*, *67*(3), 435	Outcome (cognitive impairment related to stroke pathology)
Farfel et al (2013) Very low levels of education and cognitive reserve: a clinicopathologic study. *Neurology*, *81*(7), 650	Sample (includes normal cognition, mild and severe dementia analysed as single group)

Farias et al (2012) Idea density measured in late life predicts subsequent cognitive trajectories: implications for the measurement of cognitive reserve. *J Gerontol. B Psychol. Sci. Soc Sci., 67*(6), 677	Sample (includes normal cognition, MCI and AD analysed as a single group)
Fyffe et al (2011) Explaining differences in episodic memory performance among older African Americans and Whites: the roles of factors related to cognitive reserve. *Journal of the International Neuropsychological Society, 17*(4), 625	Outcome (investigating effect of race on episodic memory rather than normal ageing)
Garrett et al (2012) Intraindividual reaction time variability is malleable: feedback- and education-related reductions in variability with age. *Frontiers in Human Neuroscience, 6*, 101	Outcome (investigating effect of education on experimental task-specific benefit from feedback)
Garret et al (2010) Everyday memory compensation: the impact of cognitive reserve, subjective memory and stress. *Psychology and Aging, 25*(1), 74	Outcome (Self-report use of compensation strategies rather than objectively measured cognitive outcome)
Gold et al (2013) Lifelong bilingualism contributes to cognitive reserve against white matter integrity declines in aging. *Neuropsychologia, 51*(13), 2841	Outcome (neuroimaging outcome measure)
Holtzer et al (2012) The protective effects of executive functions and episodic memory on gait speed decline in aging defined in the context of cognitive reserve. *Journal of the American Geriatrics Society, 60*(11), 2093	Outcome (non-cognitive: impaired mobility as defined by decline in gait speed)
Huang & Zhou (2013) Effects of education on cognition at older ages: evidence from China's Great Famine. *Social Science & Medicine, 98*, 54	Sample (incudes participants outside age range)
Jefferson et al (2011) A life course model of cognitive activities, socioeconomic status, education, reading ability and cognition. *Journal of the American Geriatrics Society, 59*(8), 1403	Sample (includes participants with MCI/possible dementia)
Lam et al (2009) Modality of physical exercise and cognitive function in Hong Kong older Chinese community. *International Journal of Geriatric Psychiatry, 24*(1), 48	Normal cognition and dementia patients in one sample; did not investigate effects of CR indicator
Lee et al (2006) The relation of education and income to cognitive function among professional women. *Neuroepidemiology, 26*(2), 93	Outcome (risk of clinical cognitive impairment)
Mitchell et al (2012) Neuropsychological test performance and cognitive reserve in healthy aging and Alzheimer's disease spectrum: a theoretically driven factor analysis *Journal of the International Neuropsychological Society, 18*(6), 1071	Not investigating relationship of CR indicator to age-associated cognitive outcome; Testing validity of CR construct
Park et al (2014) The impact of sustained engagement on cognitive function in older adults: the Synapse Project. *Psychological Science, 25*(1), 103	Intervention study (cognitive training)
Payne et al (2012) The effects of print exposure on sentence processing and memory in older adults: Evidence for efficiency and reserve. *Neuropsychology, development and cognition Section B, Aging, Neuropsychology and Cognition, 19*(1-2), 122	Not measuring effect of CR proxy on relevant outcome (investigating potential mechanisms by which print exposure might influence sentence processing/comprehension)
Perquin et al (2013) Lifelong exposure to multilingualism: new evidence to support cognitive reserve hypothesis. *PLoS One, 8*(4): e62030	Outcome (risk of clinical cognitive impairment)
Pillai et al (2012) Higher education is not associated with greater cortical thickness in brain areas related to literacy or intelligence in normal aging or mild cognitive impairment. *Journal of Clinical and Experimental Neuropsychology, 34*(9), 925	Outcome (neuroimaging outcome measure)

Reed et al (2011) Cognitive activities during adulthood are more important than education in building reserve. *Journal of the International Neuropsychological Society, 17*(4), 615	Sample (includes dementia patients and normal cognition); Not measuring CR with proxy indicator
Reed et al (2010) Measuring cognitive reserve based on decomposition of episodic memory variance. *Brain, 133*(8), 2196	Not measuring CR proxy indicator – alternative approach to CR measurement
Rentz et al (2007) Intelligence quotient adjusted memory impairment is associated with abnormal single photon emission computed tomography perfusion. *Journal of the International Neuropsychological Society*, *13*(5), 821	Not measuring CR with proxy indicator – alternative approach to CR measurement
Roe et al (2007) Education and Alzheimer disease without dementia: support for the cognitive reserve hypothesis. *Neurology*, *683*(3), 223	Sample includes participants with and without dementia analysed as one group
Roldan-Tapia et al (2012) Cognitive reserve, age and their relation to attentional and executive functions. *Applied Neuropsychology: Adult, 19*(1), 2	Sample includes participants outside of age range
Sanchez et al (2011) Study of sociodemographic variables linked to lifestyle and their possible influence on cognitive reserve. *Journal of Clinical and Experimental Neuropsychology*, *33*(8), 874	Outcome (cognitive function associated with AD in patient group – normal cognition as controls only)
Santos-Galduroz et al (2009) Cognitive performance of young and elderly subjects on the free recall memory test: effect of presentation order on recall order. *Brazilian Journal of Medical and Biological Research*, *42*(10), 988	Outcome and predictors not relevant – effect of task-specific conditions on performance
Seinfeld et al (2013) Effects of music learning and piano practice on cognitive function, mood and quality of life in older adults. *Frontiers in Psychology*, *4*, 810	Intervention study (cognitive training)
Siedlecki et al (2009) Construct validity of cognitive reserve in a multi-ethnic cohort: the Northern Manhattan Study. *Journal of the International Neuropsychological Society, 15*(4), 558	Not investigating association of CR with outcome of interest; Testing construct validity of CR
Sole-Padulles et al (2009) Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer's disease. *Neurobiology of Aging*, *30*(7), 1114	Outcome (neuroimaging measures)
Steffener et al (2011) Supporting performance in the face of age-related neural changes: testing mechanistic roles of cognitive reserve. *Brain Imaging Behavior*, *5*(3), 212	Neuroimaging outcome measure
Stern et al (2005) Brain networks associated with cognitive reserve in healthy young and old adults. *Cerebral Cortex*, *15*(4), 394	Neuroimaging outcome measure
Stern et al (2008) A common neural network for cognitive reserve in verbal and object working memory in young but not old. *Cerebral Cortex*, *18*(4), 959	Neuroimaging outcome measure
Tupler et al (2007) Predicting memory decline in normal elderly: genetics, MRI and cognitive reserve. *Neurobiology of Aging*, *28*(11), 1644	Not measuring CR with proxy indicator
Zahodne et al (2013) Quantifying cognitive reserve in older adults by decomposing episodic memory variance: replication and extension. *Journal of the International Neuropsychological Society*, *19*(8), 854	Alternative approach to measuring CR (not using proxy indicator)
Zendel et al (2012) Musicians experience less age-related decline in central auditory processing. *Psychology and Aging*, *27*(2), 410	Sample includes participants outside of age range

Zimmerman et al (2012) Sleep onset/maintenance difficulties and cognitive function in non-demented older adults: the role of cognitive reserve. *Journal of the International Neuropsychological Society*, *18*(3), 461	Outcomes associated with sleep disorder rather than normal ageing

Note: AD = Alzheimer's disease; CR = cognitive reserve; MCI = mild cognitive impairment

Articles excluded based on title/abstract	
Citation	***Reason for Exclusion***
Cognitive reserve (2006). *Harvard Mental Health Letter*, July 2006	Not original study (letter)
Aalbers et al (2013) The Mediterranean diet as a prevention strategy for dementia as a multicausal genetic syndrome. *The American Journal of Clinical Nutrition*, *97*(6), 1411	Content not relevant
Ahles et al (2010) Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. *Journal of Clinical Oncology*, *28*(29), 4434	Outcome (cognition association with breast cancer treatment)
Akbaraly et al (2009) Leisure activities and the risk of dementia in the elderly: results from the Three-City study. *Neurology*, *73*(11), 854	Outcome (dementia)
Albanese et al (2012) No association between gain in body mass index across the life course and midlife cognitive function and cognitive reserve – the 1946 British Birth Cohort Study. *Alzheimer's & Dementia*, *8*(6), 470	Content not relevant
Alchanatis et al (2005) Sleep apnea related cognitive deficits and intelligence: an implication of cognitive reserve theory. *Journal of Sleep Research*, *14*(1), 69	Population/condition (sleep apnea)
Allen et al (2005) The aging brain: the cognitive reserve hypothesis and hominid evolution. *American Journal of Human Biology*, *17*(6), 673	Review article
Alosco et al (2012) Cognitive reserve moderates the relationship between heart failure and cognitive impairment. *Journal of Clinical and Experimental Neuropsychology*, *34*(1), 1	Population/condition (heart failure)
Amato et al (2013) Cognitive reserve and cortical atrophy in multiple sclerosis: a longitudinal study. *Neurology*, *80*(19), 1728	Population/condition (MS)
Andel et al (2006) The effect of education and occupational complexity on rate of cognitive decline in Alzheimer's patients. *Journal of the International Neuropsychological Society*, *12*(1), 147	Population/condition (AD)
Andrews et al (2012) Age differences in simulated driving performance: compensatory processes. *Accident Analysis & Prevention*, *45*, 660	Content not relevant
Ansado et al (2012) Load-dependent posterior-anterior shift in aging in complex visual selective attention situations. *Brain Research*, *1454*, 14	Content not relevant

Antoniou et al (2013) Foreign language training as a cognitive therapy for age-related cognitive decline: a hypothesis for future research. *Neuroscience and Biobehavioral Reviews*, *37*(10), 2689	Interventions rather than CR indicators
Apolinario et al (2013) Estimating premorbid cognitive abilities in low-educated populations. *PLoS One*, *8*(3), e60084	Content not relevant
Armstrong et al (2012) Role of education and IQ in cognitive reserve in Parkinson's disease-mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders Extra*, *2*(1), 343	Population/condition (PD)
Arneric et al (2014) Tailoring chronic pain treatments for the elderly: are we prepared for the challenge? *Drug Discovery Today*, *19*(1), 8	Content not relevant
Baclet-Roussel et al (2010). Contribution of various MRI techniques to the characterization of Mild Cognitive Impairment. *Psychologie & Neuropsychologie du viellissement, 8*(1), 53	Non-English language
Bain (2006) A review of the "State of the Art" on mild cognitive impairment: the fourth annual symposium. *Alzheimer's & Dementia, 2*(3), 246	Review article
Barnett et al (2006) Cognitive reserve in neuropsychiatry. *Psychological Medicine*, *36*(8), 1053	Review article
Bartres-Faz et al (2011) Structural and functional imaging correlates of cognitive and brain reserve hypotheses in healthy and pathological aging. *Brain Topography, 24*(3-4), 340	Review article
Barulli et al (2013) Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. *Trends in Cognitive Sciences, 17*(10), 502	Review article
Beeri et al (2009) Memory activation in healthy nonagenarians. *Neurobiology of Aging*, *32*(3), 515	Content not relevant
Benedict et al (2010) Cognitive reserve moderates decline in information processing speed in multiple sclerosis patients. *Journal of the International Neuropsychological Society*, *16*(5), 829	Population/condition (MS)
Benedict et al (2011) Risk factors for and management of cognitive dysfunction in multiple sclerosis. *Nature Reviews Neurology, 7*(6), 332	Population/condition (MS)
Bennett et al (2005) Education modifies the association of amyloid but not tangles with cognitive function. *Neurology*, *65*(6), 953	Not original study (comment)
Bennett et al (2006) The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study. *Lancet Neurology*, *5*(5), 406	Outcome (cognition associated with AD pathology)
Bennett et al (2011) Datasets for special series on cognitive reserve. *Journal of the International Neuropsychological Society*, *17*(4), 587	Not original study (datasets)
Bennett et al (2014) Cognitive and social lifestyle: links with neuropathology and cognition in late life. *Acta Neuropathologica, 127*(1), 137	Review article
Bezerra et al (2012) School attainment in childhood is an independent risk factor of dementia in late life: results from a Brazilian sample. *International Psychogeriatrics*, *24*(1), 55	Outcome (dementia)

Bialystok et al (2012) Bilingualism: consequences for mind and brain. *Trends in Cognitive Sciences, 16*(4), 240	Review article
Bieliauskas et al (2007) Cognitive reserve and neuropsychological functioning in patients infected with hepatitis C. *Journal of the International Neuropsychological Society, 13*(4), 687	Population/condition (Hepatitis C)
Boles-Ponto et al (2006) Global cerebral blood flow in relation to cognitive performance and reserve in subjects with mild memory deficits. *Molecular Imaging and Biology, 8*(6) 363	Population/condition (MCI)
Bonner-Jackson et al (2013) Cognitive reserve and brain reserve in prodromal Huntington's disease. *Journal of the International Neuropsychological Society, 19*(7), 739	Population/condition (Huntington's disease)
Booth et al (2013) Active cognitive reserve influences the regional atrophy to cognition link in multiple sclerosis. *Journal of the International Neuropsychological Society, 19*(10), 1128	Population/condition (MS)
Bornstein et al (2006) Early-life risk factors for Alzheimer disease. *Alzheimer's Disease and Associated Disorders, 20*(1), 63	Review article
Borroni et al (2012) Reserve mechanisms in neurodegenerative disease: from bedside to bench and back again. *Current Medicinal Chemistry, 19*(36), 6112	Review article
Bracco et al (2007) Pattern and progression of cognitive decline in Alzheimer's disease: role of premorbid intelligence and ApoE genotype. *Dementia and Geriatric Cognitive Disorders, 24*(6), 483	Population/condition (AD)
Broglio et al (2012) Cognitive decline and aging: the role of concussive and sub-concussive impacts. *Exercise and Sport Sciences Reviews, 40*(3), 138	Review article
Bruandet et al (2008) Cognitive decline and survival in Alzheimer's disease according to education level. *Dementia and Geriatric Cognitive Disorders, 25*(1), 74	Population/condition (AD)
Bugiani (2011) Alzheimer's disease: ageing-related or age related? New hypotheses from an old debate. *Neurological Sciences, 32*(6), 1241	Review article
Campdelacreu (2014) Parkinson disease and Alzheimer disease: environmental risk factors. *Neuropsychologia, 29*(9), 541	Review article
Cankurtaran et al (2008) Risk factors and type of dementia: vascular or Alzheimer? *Archives of Gerontology and Geriatrics, 47*(1), 25	Outcome (dementia)
Carnero et al (2007) Education provides cognitive reserve in cognitive deterioration and dementia. *Neurologia, 22*(2), 78	Non-English language
Carro et al (2006) Serum insulin-like growth factor I in brain function. *Keio Journal of Medicine, 55*(2), 59	Content not relevant
Caserta et al (2009) Normal brain aging clinical, immunological, neuropsychological and neuroimaging features. *International Review of Neurobiology, 84*, 1	Review article
Cavedo et al (2012) Norms for imaging markers of brain reserve. *Journal of Alzheimer's Disease, 31*(3), 623	Content not relevant
Chang et al (2013) Lower cognitive reserve in the aging human immunodeficiency virus infected brain. *Neurobiology of Aging, 34*(4), 1240	Population/condition (HIV)

Chertkow et al (2010) Multilingualism (but not always bilingualism) delays the onset of Alzheimer disease: evidence from a bilingual community. *Alzheimer's Disease and Associated Disorders, 24*(2), 118	Population/condition (AD)
Cho et al (2013) Changes in subcortical structures in early- versus late-onset Alzheimer's disease. *Neurobiology of Aging*, 34(7), 1740-1747.	Content not relevant
Choo et al (2011) Relationship of amyloid-B burden with age-at-onset in Alzheimer disease. *American Journal of Geriatric Psychiatry, 19*(7), 627	Population/condition (AD)
Corsentino et al (2009) Depressive symptoms moderate the influence of the apolipoprotein epsilon e4 allele on cognitive decline in a sample of community dwelling older adults. *American Journal of Geriatric Psychiatry, 17*(2), 155	Content not relevant (influence of depression not CR)
Craik et al (2010) Delaying the onset of Alzheimer's disease: bilingualism as a form of cognitive reserve. *Neurology, 75*(19), 1726	Population/condition (AD)
Croft et al (2007) Early adolescent outcomes of institutionally-deprived and non-deprived adoptees: II language as a protective factor and vulnerable outcome. *Journal of Child Psychology and Psychiatry, 48*(1), 31	Content not relevant
Crooks et al (2008) Social network, cognitive function and dementia incidence among elderly women. *American Journal of Public Health, 98*(7), 1221	Outcome (dementia)
Daffner (2010) Promoting successful cognitive aging: a comprehensive review. *Journal of Alzheimer's Disease, 19*(4), 1101	Review article
Dartigues et al (2013) Relationship between educational level and dementia: social factor and age-related chronic disease. *Revue d'Epidemiologie et de Sante Publique, 61*(Suppl. 3), S195	Non-English language
Dawson et al (2007) Applicability of neural reserve theory in mild traumatic brain injury. *Brain Injury, 21*(9), 943	Population/condition (TBI)
De la Fuente-Fernandez, (2006) Impact of neuroprotection on incidence of Alzheimer's disease. *PLoS One, 20*(1), e52	Review article
De la Serna et al (2013) Cognitive reserve as a predictor of two year neuropsychological performance in early onset first-episode schizophrenia. *Schizophrenia Research, 143*(1), 125	Population/condition (schizophrenia)
Deary et al (2006) Physical fitness and lifetime cognitive change. *Neurology, 67*(7), 1195	Not measuring CR with proxy indicator
Degen et al (2014) Training-induced cerebral changes in the elderly. *Restorative Neurology and Neuroscience, 32*(1), 213	Review article
Depp et al (2012) Successful cognitive aging. *Current Topics in Behavioral Neuroscience, 10*, 35	Review article
Devanand et al (2013) Lessons from epidemiologic research about risk factors, modifiers, and progression of late onset Alzheimer's disease in New York city at Columbia University Medical Center. *Journal of Alzheimer's Disease, 33*(Suppl. 1), S447	Review article
Donohoe et al (2009) Influence of NOS1 on verbal intelligence and working memory in both patients with schizophrenia and healthy control subjects. *Archives of General Psychiatry, 66*(10), 1045	Population/condition (schizophrenia)
Dorasiwamy et al (2009) Does meditation enhance cognition and brain longevity? *Annals of the New York Academy of Sciences, 1172*, 63	Content not relevant

Dos Santos et al (2010) Incidental encoding strategies did not improve contextual memory in Parkinson's disease. *Neurorehabilitation and Neural Repair, 24*(5), 450	Content not relevant
Draganski et al (2013) Impact of brain aging and neurodegeneration on cognition: evidence from MRI. *Current Opinion in Neurology, 26*(6), 640	Review article
Dumurgier et al (2010) Inverse association between CSF AB42 levels and years of education in mild form of Alzheimer's disease: the cognitive reserve theory. *Neurobiology of Disease, 40*(2), 456	Population/condition (AD)
Elbaz et al (2013) Motor function in the elderly: evidence for the reserve hypothesis. *Neurology, 81*(5), 417	Non-cognitive outcome (motor function)
Engelman et al (2010) Propositional density and cognitive function in later life: findings from the Precursors study. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 65*(6), 706	Outcome (AD)
Esiri et al (2012) Cognitive reserve, cortical plasticity and resistance to Alzheimer's disease. *Alzheimer's Research and Therapy, 4*(2), 7	Review article
Ewers et al (2013) Cognitive reserve associated with FDG-PET in preclinical Alzheimer's disease. *Neurology, 80*(13), 1194	Population/condition (preclinical AD)
Fabiani (2012) It was the best of times, it was the worst of times: a psychophysiologist's view of cognitive aging. *Psychophysiology, 49*(3), 283	Review article
Fahoum et al (2013) Epileptic discharges affect the default mode network – FMRI and intracerebral EEG evidence. *PLoS One, 8*(6), e68038.	Content not relevant
Fairjones et al (2011) Exploring the role of cognitive reserve in early-onset dementia. *American Journal of Alzheimer's Disease and Other Dementias, 26*(2), 139	Population/condition (dementia)
Farias et al (2012) Maximal brain size remains an important predictor of cognition in old age, independent of current brain pathology. *Neurobiology of Aging, 33*(8), 1758	Brain reserve indicator
Feinstein et al (2013) Sub-threshold cognitive impairment in multiple sclerosis: the association with cognitive reserve. *Journal of Neurology, 260*(9), 2256	Population/condition (MS)
Feret et al (2014) Mechanisms underlying the protective effect of brain reserve against late-life depression. *Journal of Neural Transmission*	Outcome (depression)
Ferrari et al (2014) Imaging and cognitive reserve studies predict dementia in pre-symptomatic Alzheimer's disease subjects. *Neurodegenerative Disease, 13*(2-3), 157	Review article
Fick et al (2009) Delirium in early-stage Alzheimer's disease: enhancing cognitive reserve as a possible preventive measure. *Journal of Gerontological Nursing, 35*(3), 30	Review article
Flouri et al (2012) The role of nonverbal cognitive ability in the association of adverse life events with dysfunctional attitudes and hopelessness in adolescence. *Archives of Psychiatry Nursing, 26*(5), 411	Content not relevant

Foley et al (2012) Cognitive reserve as a protective factor in older HIV-positive patients at risk for cognitive decline. *Applied Neuropsychology Adult*, *19*(1), 16	Population/condition (HIV)
Forstmeier et al (2012) Motivational reserve: motivation-related occupational abilities and risk of mild cognitive impairment and Alzheimer disease. *Psychology and Aging*, *27*(2), 353	Outcome (MCI/AD risk)
Fratiglioni et al (2004) An active and socially integrated lifestyle in late life might protect against dementia. *Lancet Neurology*, *3*(6), 343	Review article
Fuentes et al (2010) Cognitive reserve in paediatric traumatic brain injury: relationship with neuropsychological outcome. *Brain Injury*, *24*(7-8), 995	Population/condition (paediatric TBI)
Gale et al (2012) Intelligence in childhood and chronic widespread pain in middle age: the National Child Development Survey. *Pain*, *153*(12), 2339	Population/condition (chronic pain)
Galioto et al (2013) Cognitive reserve preserves cognitive function in obese individuals. *Neuropsychology, Development and Cognition. Section B: Aging, Neuropsychology and Cognition*, *20*(6), 684	Outcome (not associated with ageing – cognition associated with obesity)
Galvan et al (2007) Neurogenesis in the adult brain: implications for Alzheimer's disease. *CNS & Neurological Disorders: Drug Targets*, *6*(5), 303	Review article
Garibotto et al (2012) Education and occupation provide reserve in both ApoE e4 carrier and non-carrier patients with probable Alzheimer's disease. *Neurological Sciences*, *33*(5), 1037	Population/condition (AD)
Ghaffar et al (2012) Occupational attainment as a marker of cognitive reserve in multiple sclerosis. *PLoS One*, *7*(10), e47206	Population/condition (MS)
Giordano et al (2012) Cognitive functions and cognitive reserve in relation to blood-pressure components in a population based cohort aged 53 to 84 years. *International Journal of Hypertension*, *2012*, 274851	Outcome (non-cognitive – blood pressure)
Gleichmann et al (2011) Homeostatic disinhibition in the aging brain and Alzheimer's disease. *Journal of Alzheimer's Disease*, *24*(1), 15	Content not relevant
Glodzik et al (2012) The whole-brain N-acetylasparate correlates with education in normal adults. *Psychiatry Research*, *204*(1), 49	Non-cognitive outcome
Gollan et al (2011) Degree of bilingualism predicts age of diagnosis of Alzheimer's disease in low-education but not highly educated Hispanics. *Neuropsychologia*, *49*(14), 3826	Population/condition (AD)
Gomez de Silva et al (2011) Early physical exercise and seizure susceptibility later in life. *International Journal of Developmental Neuroscience*, *29*(8), 861	Outcome (seizures)
Grandy et al (2013) Individual alpha peak frequency is related to latent factors of general cognitive abilities. *Neuroimage*, *79*, 10	Content not relevant
Green et al (2008) Examining moderators of cognitive recover trajectories after moderate to severe traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, *89*(12 Suppl.), s16	Population/condition (TBI)
Guimaraes et al (2007) Health capital, life course, and ageing. *Gerontology*, *53*(2), 96	Content not relevant

Gunderman et al (2008) Aging and cognitive reserve. *Journal of the American College of Radiology, 5*(5), 670	Review article
Haberman et al (2011) Prominent hippocampal CA3 gene expression profile in neurocognitive aging. *Neurobiology of Aging, 32*(9), 1678	Animal study
Hall et al (2007) Education delays accelerated memory decline on a memory test in persons who develop dementia. *Neurology, 69*(17), 1657	Population/condition (dementia)
Hall et al (2009) Cognitive activities delay onset of memory decline in persons who develop dementia. *Neurology, 73*(5), 356	Population/condition (dementia)
Hanyu et al (2008) The effect of education on rCBF changes in Alzheimer's disease: a longitudinal SPECT study. *European Journal of Nuclear Medicine and Molecular Imaging, 35*(1), 2182	Population/condition (AD)
Happe et al (2012) Aging in autism spectrum disorders: a mini-review. *Gerontology, 58*(1), 70	Content not relevant
Helzner et al (2007) Leisure activity and cognitive decline in incident Alzheimer's disease. *Archives of Neurology, 64*(12), 1749	Population/condition (AD)
Hempenius et al (2013) Inclusion of frail elderly patients in clinical trials: solutions to the problems. *Journal of Geriatric Oncology, 4*(1), 26	Content not relevant
Herholz et al (2013) Non-pharmacological interventions and neuroplasticity in early stage Alzheimer's disease. *Expert Review of Neurotherapeutics, 13*(11), 1235	Review article
Herzig et al (2013) Stressing schizotypy: the modulating role of stress-relieving behaviours and intellectual capacity on functional hemispheric asymmetry. *Laterality, 18*(2), 152	Content not relevant
Hindle et al (2014) Cognitive reserve in Parkinson's disease: a systematic review and meta-analysis. *Parkinsonism and Related Disorders, 20*(1), 1	Review article
Honer et al (2012) Cognitive reserve, presynaptic proteins and dementia in the elderly. *Translational Psychiatry, 2*, e114	Content not relevant (not using proxy indicator)
Hooghiemstra et al (2012) Exercise and early-onset Alzheimer's disease: theoretical considerations. *Dementia and Geriatric Cognitive Disorders Extra, 2*, 132.	Review article
Hoyer et al (2004) Relationship between cerebral energy metabolism in parietotemporal cortex and hippocampus and mental activity during aging in rats. *Journal of Neural Transmission, 111*(5), 575	Animal study
Irvine et al (2012) Greater cognitive deterioration in women than men with Alzheimer's disease: a meta-analysis. *Journal of Clinical and Experimental Neuropsychology, 34*(9), 989	Review article
Jagust et al (2011) Lifespan brain activity, β-amyloid and Alzheimer's disease. *Trends in Cognitive Sciences, 15*(11), 520	Review article
Jankowski et al (2011) Cognitive and functional predictors and sequelae of postoperative delirium in elderly patients undergoing elective joint arthroplasty. *Anaesthesia and Analgesia, 112*(5), 1186	Population/condition (post-operative delirium)
Janzarik (2012) *Cognitive* losses in old age, cognitive reserve, structural resistance. *Nervenarzt, 83*(1), 31	Non-English language

Jellinger et al (2013) Neuropathological approaches to cerebral aging and neuroplasticity. *Dialogues in Clinical Neuroscience, 15*(1), 29	Review article
Jones et al (2006) Does educational attainment contribute to risk for delirium? A potential role for cognitive reserve. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 61*(12), 1307	Population/condition (delirium)
Jones et al (2011) Conceptual and measurement challenges in research on cognitive reserve. *Journal of the International Neuropsychological Society, 17*(4), 593	Review article
Jongen et al (2012) Cognitive impairment in multiple sclerosis. *Minerva Medica, 103*(2), 73	Review article
Juncos-Rabadan et al (2014) Prevalence and correlates of mild cognitive impairment in adults aged 50 years with subjective cognitive complaints in primary care centres. *Geriatrics and Gerontology International, 14*(3), 667	Outcome (MCI)
Kalpouzos et al (2008) Cognitive reserve and neural networks in normal aging and Alzheimer's disease. *Psychologie & Neuropsychologie du viellissement, 6*(2), 97	Non-English language
Karp et al (2004) Relation of education and occupation-based socioeconomic status to incident Alzheimer's disease. *American Journal of Epidemiology, 159*(2) 175	Outcome (AD)
Karp et al (2006) Mental, physical and social components in leisure activities equally contribute to decrease dementia risk. *Dementia and Geriatric Cognitive Disorders, 21*(2), 65	Outcome (dementia)
Karp et al (2009) Mentally stimulating activities at work during midlife and dementia risk after age 75: follow up study from the Kungsholmen project. *American Journal of Geriatric Psychiatry, 17*(3), 227	Outcome (dementia)
Karver et al (2014) Cognitive reserve as a moderator of responsiveness to an online problem-solving intervention for adolescents with complicated mild-to-severe traumatic brain injury. *Child Neuropsychology, 20*(3), 343	Population/condition (TBI)
Kemppainen et al (2008) Cognitive reserve hypothesis: Pittsburgh Compound B and flurodeoxyglucose positron emission tomography in relation to education in mild Alzheimer's disease. *Annals of Neurology, 63*(1), 112	Population/condition (AD)
Kesler et al (2010) Cognitive reserve and brain volumes in paediatric lymphoblastic leukaemia. *Brain Imaging and Behavior, 4*(3-4), 256	Population/condition (paediatric leukaemia)
Kesse-Guyot et al (2013) Mediterranean diet and cognitive function: a French study. *The American Journal of Clinical Nutrition, 97*(2), 369	Content not relevant
Kesse-Guyot et al (2013) Reply to Aalbers et al. *The American Journal of Clinical Nutrition, 97*(6), 1412	Not original study
Khandaker et al (2011) A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia. *Schizophrenia Research, 132*(2-3), 220	Content not relevant
Kilanowski et al (2010) An intervention for delirium superimposed on dementia based on cognitive reserve theory. *Aging & Mental Health, 14*(2), 232	Population/condition (delirium/dementia); study design

Kim et al (2012) Increased basal forebrain metabolism in mild cognitive impairment: an evidence for brain reserve in incipient dementia. *Journal of Alzheimer's Disease, 32*(4), 927	Population/condition (MCI/AD)
Kingma et al (2012) The power of longitudinal population-based studies for investigating the etiology of chronic widespread pain. *Pain, 153*(12), 2305	Content not relevant
Klempin et al (2007) Adult hippocampal neurogenesis and aging. *European Archives of Psychiatry and Clinical Neuroscience, 257*(5), 271	Review article
Koenen et al (2009) Childhood IQ and adult mental disorders: a test of the cognitive reserve hypothesis. *American Journal of Psychiatry, 166*(1), 50	Non-cognitive outcome (neuropsychiatric)
Koepsell et al (2008) Education, cognitive function and severity of neuropathology in Alzheimer disease. *Neurology, 70*(19 Pt2), 1732	Population/condition (AD)
Kolanowski et al (2011) Study protocol for the recreational stimulation for elders as a vehicle to resolve delirium superimposed on dementia (Reserve for DSD) trial. *Trials, 12*, 119	Not original study (study protocol)
Kontis et al (2013) Effects of age and cognitive reserve on cognitive remediation therapy outcome in patients with schizophrenia. *American Journal of Geriatric Psychiatry, 21*(2), 218	Population/condition (schizophrenia)
Krolak-Salmon (2011) Post-surgery cognitive disorders: prevention, diagnosis and treatment strategies. *Annals Francaises d'Anesthesie et de Reanimation, 30*(10), e61	Non-English language
Kumar et al (2008) The response-signal method reveals age-related changes in object working memory. *Psychology and Aging, 23*(2), 315	CR as covariate rather than predictor/key variable of interest
La Rue (2010) Healthy brain aging: role of cognitive reserve, cognitive stimulation and cognitive exercises. *Clinics in Geriatric Medicine, 26*(1), 99	Review article
Lane et al (2011) Influence of education on subcortical hyperintensities and global cognitive status in vascular dementia. *Journal of the International Neuropsychological Society, 17*(3), 531	Population/condition (dementia)
Lane et al (2013) Butyrylcholinesterase genotype and gender influence on Alzheimer's disease phenotype. *Alzheimer's & Dementia, 9*(2), e1-73	Content not relevant
Langa et al (2008) Trends in the prevalence and mortality of cognitive impairment in the United States: is there evidence of a compression of cognitive morbidity? *Alzheimer's & Dementia, 4*(2), 134	Outcome (cognitive impairment consistent with dementia)
Larson et al (2007) Cognitive sequelae in acute respiratory distress syndrome patients with and without recall of the intensive care unit. *Journal of the International Neuropsychological Society, 13*(4), 595	Population/condition (acute respiratory distress syndrome)
LeCarret et al (2005) Influence of education on the pattern of cognitive deterioration in AD patients: the cognitive reserve hypothesis. *Brain and Cognition, 57*(2), 120	Population/condition (AD)

Leeson et al (2011) IQ trajectory, cognitive reserve and clinical outcome following a first episode of psychosis: a 3-year longitudinal study. *Schizophrenia Bulletin, 37*(4), 768	Population/condition (schizophrenia)
Leeson et al (2012) The effect of cannabis use and cognitive reserve on age at onset and psychosis outcomes in first episode schizophrenia. *Schizophrenia Bulletin, 38*(4), 873	Population/condition (schizophrenia)
Leist et al (2013) Do economic recessions during early and mid-adulthood influence cognitive function in older age? *Journal of Epidemiology and Community Health*	Content not relevant
Leist et al (2013) Time away from work predicts later cognitive function: differences by activity during leave. *Annals of Epidemiology, 23*(8), 455	Content not relevant
Leon et al (2011) Development of the scale of cognitive reserve in Spanish population: a pilot study. *Revista de Neurologia, 52*(11), 653	Non-English language
Levi et al (2013) Cognitive reserve components as expressed in traumatic brain injury. *Journal of the International Neuropsychological Society, 19*(6), 664	Population/condition (TBI)
Liao et al (2005) Cognitive reserve: a SPECT study of 132 Alzheimer's disease patients with an education range of 0-19 years. *Dementia and Geriatric Cognitive Disorders, 20*(1), 8	Population/condition (AD)
Liberati et al (2012) Cognitive reserve and its implications for rehabilitation and Alzheimer's disease. *Cognitive Processing, 13*(1), 1	Review article
Lichtenstein et al (2010) Staging anti-inflammatory therapy in Alzheimer's disease. *Frontiers in Aging Neuroscience, 2*, 142	Content not relevant
Liozidou et al (2012) The role of working memory and information processing speed on Wisconsin card sorting test performance in Parkinson disease without dementia. *Journal of Geriatric Psychiatry and Neurology, 25*(4), 215	Population/condition (PD)
Liu et al (2012) Education increases reserve against Alzheimer's disease – evidence from structural MRI analysis. *Neuroradiology, 54*(9), 929	Population/condition (AD)
Liu et al (2013) Proxies of cognitive reserve and their effects on neuropsychological performance in patients with mild cognitive impairment. *Journal of Clinical Neuroscience, 20*(4), 548	Population/condition (MCI)
Lo et al (2013) Effect of cognitive reserve markers on Alzheimer pathologic progression. *Alzheimer's Disease and Associated Disorders, 27*(4), 343	Population/condition (AD)
Lojo-Seoane et al (2012) Does intellectual activity prevent cognitive impairment? Relationships between cognitive reserve and mild cognitive impairment. *Revista Espanola de Geriatria y Gerontologia, 47*(6), 270	Non-English language
Luber et al (2013) Applications of transcranial magnetic stimulation and magnetic seizure therapy in the study and treatment of disorders relating to cerebral aging. *Dialogues in Clinical Neuroscience, 15*(1), 87	Content not relevant
Mandelblatt et al (2013) Cognitive effects of cancer and its treatments at the intersection of aging: what do we know; what do we need to know? *Seminars in Oncology, 40*(6), 709	Population/condition (cancer)

Mak et al (2006) Leg length, cognitive impairment and cognitive decline in an African Caribbean population. *International Journal of Geriatric Psychiatry, 21*(3), 266	Content not relevant
Mangialasche et al (2012) Dementia prevention: current epidemiological evidence and future perspective. *Alzheimer's Research and Therapy, 4*(1), 6	Review article
Manly et al (2004) Literacy and cognitive change among ethnically diverse elders. *International Journal of Psychology, 39*(1), 47	Review article
May (2011) Experience-dependent structural plasticity in the adult human brain. *Trends in Cognitive Sciences, 15*(10), 475	Review article
McDowell et al (2007) Mapping the connections between education and dementia. *Journal of Clinical and Experimental Neuropsychology, 29*(2), 127	Outcome (dementia)
McGurn et al (2008) Childhood cognitive ability and risk of late onset Alzheimer and vascular dementia. *Neurology, 71*(14), 1051	Outcome (dementia)
Mehta et al (2009) "Below average" self-assessed school performance and Alzheimer's disease in the Aging, Demographics and Memory Study. *Alzheimer's & Dementia, 5*(5), 380	Outcome (AD)
Meng et al (2012) Education and dementia in the context of the cognitive reserve hypothesis: a systematic review with meta-analyses and qualitative analyses. *PLoS One, 7*(6), e38268.	Review article
Mevel et al (2013) Age effect on the default mode network, inner thoughts and cognitive abilities. *Neurobiology of Aging, 34*(4), 1292	Content not relevant
Miettinen et al (2011) Effect of cholinergic stimulation in early Alzheimer's disease – functional imaging during a recognition memory task. *Current Alzheimer Research, 8*(7), 753	Population/condition (AD)
Milewski et al (2008) Re: Impact of cognitive reserve on the relationship of lead exposure and neurobehavioral performance. *Neurology, 70*(14), 1221	Not original study (reply to comment)
Milgram et al (2006) Neuroprotective effects of cognitive enrichment. *Ageing Research Reviews, 5*(3), 354-69	Review article
Miller et al (2013) Effect of a computerised brain exercise program on cognitive performance in older adults. *American Journal of Geriatric Psychiatry, 21*(7), 655	Intervention study
Miller et al (2013) Environmental enrichment may protect against hippocampal atrophy in the chronic stages of traumatic brain injury. *Frontiers in Human Neuroscience, 7*, 506	Population (brain injury)
Molteni et al (2012) Load dependent brain activation assessed by time-domain near-infrared spectroscopy during a working memory task with graded levels of difficulty. *Journal of Biomedical Optics, 17*(5), 056005	Content not relevant
Monk et al (2011) Postoperative cognitive disorders. *Current Opinion in Critical Care, 17*(4), 10	Review article
Morbelli et al (2013) Metabolic networks underlying cognitive reserve in prodromal Alzheimer disease: a European Alzheimer disease consortium project. *Journal of Nuclear Medicine, 54*(6), 894	Population/condition (prodromal AD)
Moretti et al (2012) Cognitive decline in older adults with a history of traumatic brain injury. *Lancet Neurology, 11*(12), 1103	Population/condition (TBI)

Morgan et al (2012) Lower cognitive reserve among individuals with syndromic HIV-associated neurocognitive disorders. *AIDS Behavior, 16*(8), 2279	Population/condition (HIV)
Mortamais et al (2013) Education modulates the impact of white matter lesions on risk of mild cognitive impairment and dementia. *American Journal of Geriatric Psychiatry, 22*(11), 1336	Outcome (MCI/Dementia)
Mortimer et al (2005) Very early detection of Alzheimer neuropathology and the role of brain reserve in modifying its clinical expression. *Journal of Geriatric Psychiatry and Neurology, 18*(4), 218	Review article
Negash et al (2013) Cognitive and functional resilience despite molecular evidence of Alzheimer's disease pathology. *Alzheimer's & Dementia, 9*(3), e89	Population/condition (AD)
Ngandu et al (2007) Education and dementia: what lies behind the association? *Neurology, 69*(14), 1442	Outcome (dementia)
Nithianantharajah et al (2009) The neurobiology of brain and cognitive reserve: mental and physical activity as modulators of brain disorders. *Progress in Neurobiology, 89*(4), 369	Review article
Nithianantharajah et al (2011) Mechanisms mediating brain and cognitive reserve: experience-dependent neuroprotection and functional compensation in animal models of neurodegenerative diseases. *Progress in NeuroPsychopharmacology and Biological Psychiatry, 35*(2), 331	Review article
Notarianni (2013) Hypercortisolemia and glucocorticoid receptor-signalling insufficiency in Alzheimer's disease initiation and development. *Current Alzheimer Research, 10*(7), 714	Content not relevant
Nucci et al (2012) Cognitive Reserve Index questionnaire (CRIq): a new instrument for measuring cognitive reserve. *Aging Clinical and Experimental Research, 24*(3), 218	Publishing CR measure; not studying cognitive outcome
Ojala-Oksala et al (2012) Educational history is an independent predictor of cognitive deficits and long-term survival in post-acute patients with mild to moderate ischemic stroke. *Stroke, 43*(11), 2931	Population/condition (stroke)
Okereke et al (2011) Plasma beta-amyloid level, cognitive reserve and cognitive decline. *JAMA, 305*(16), 1655	Not original study
Pai et al (2005) Is cognitive reserve applicable to epilepsy? The effect of educational level on the cognitive decline after onset of epilepsy. *Epilepsia, 46*(Suppl. 1), 7	Population/condition (epilepsy)
Paradise et al (2009) Systematic review of the effect of education on survival in Alzheimer's disease. *International Psychogeriatrics, 21*(1), 25	Review article
Parente et al (2013) Investigating higher-order cognitive functions in temporal lobe epilepsy: cognitive estimation. *Epilepsy Behavior, 29*(2), 330	Population/condition (epilepsy)
Park et al (2013) The aging mind: neuroplasticity in response to cognitive training. *Dialogues in Clinical Neuroscience, 15*(1), 109	Review article
Patel et al (2013) The aggregate effects of multiple comorbid risk factors on cognition among HIV-infected individuals. *Journal of Clinical Experimental Neuropsychology, 35*(4), 421	Population/condition (HIV)

Pendlebury et al (2012) Dementia in patients hospitalised with stroke: rates, time course and clinic-pathologic factors. *International Journal of Stroke, 7*(7), 570	Population/condition (stroke)
Perls (2004) Centenarians who avoid dementia. *Trends in Neurosciences, 27*(10), 633	Review article
Perls (2004) Dementia-free centenarians. *Experimental Gerontology, 39*(11-12), 1587	Review article
Perneczky et al (2007) Male gender is associated with greater cerebral hypo metabolism in frontotemporal dementia: evidence for sex-related cognitive reserve. *International Journal of Geriatric Psychiatry, 22*(11), 1135	Population/condition (FTD)
Perneczky et al (2008) Activities of daily living, cerebral glucose metabolism, and cognitive reserve in Lewy body and Parkinson's disease. *Dementia and Geriatric Cognitive Disorders, 26*(5), 475	Population/condition (dementia/PD)
Perneczky et al (2009) Fluro-deoxy-glucose positron emission tomography correlates of impaired activities of daily living in dementia with Lewy bodies: implications for cognitive reserve. *American Journal of Geriatric Psychiatry, 17*(3), 188	Population/condition (dementia)
Perneczky et al (2011) Cognitive reserve and its relevance for the prevention and diagnosis of dementia. *Nervenarzt, 82*(3), 325	Non-English language
Perneczky et al (2012) Head circumference, apolipoprotein E genotype and cognition in the Bavarian School Sisters Study. *European Psychiatry, 27*(3), 219	Brain reserve indicator
Petkus et al (2012) History of sexual assault is associated with greater decline in executive functioning in older adults with APOE epsilon 4. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 67*(6), 653	Content not relevant
Pettigrew et al (2013) Relationship of cognitive reserve and APOE status to the emergence of clinical symptoms in preclinical Alzheimer's disease. *Cognitive Neuroscience, 4*(3-4), 136	Outcome (progression to clinical symptoms MCI/AD)
Pillai et al (2011) Association of crossword puzzle participation with memory decline in persons who develop dementia. *Journal of the International Neuropsychological Society, 17*(6), 1006	Population/condition (dementia)
Poletti et al (2011) Mild cognitive impairment and cognitive reserve in Parkinson's disease. *Parkinsonism and Related Disorders, 17*(8), 579	Population/condition (PD)
Pomara et al (2011) Plasma beta-amyloid level, cognitive reserve and cognitive decline. *JAMA, 305*(16), 1655	Not original study
Prakash et al (2011) Cognitive reserve: the warehouse within. *Industrial Psychiatry Journal, 20*(2), 79	Review article
Premi et al (2012) Nature versus nurture in frontotemporal lobar degeneration: the interaction of genetic background and education on brain damage. *Dementia and Geriatric Cognitive Disorders, 33*(6), 372	Population/condition (dementia)
Premi et al (2013) Beyond cognitive reserve: behavioural reserve hypothesis in frontotemporal dementia. *Behavioural Brain Research, 245*, 58	Population/condition (dementia)
Premi et al (2013) Cognitive reserve in granulin-related frontotemporal dementia: from preclinical to clinical stages. *PLoS One, 8*(9), e74762	Population/condition (dementia)

Preuss et al (2009) Depressive disorders in dementia and mild cognitive impairments: is comorbidity a cause or a risk factor? *Fortschritte der Neurologie-Psychiatrie, 77*(7), 399	Non-English language
Prince et al (2012) Dementia incidence and mortality in middle-income countries, and associations with indicators of cognitive reserve: a 10/66 Dementia Research Group population-based cohort study. *Lancet, 380*(9836), 50	Outcome (dementia)
Qiu et al (2007) The epidemiology of the dementias: an update. *Current Opinion in Psychiatry, 20*(4), 380	Review article
Querbes et al (2009) Early diagnosis of Alzheimer's disease using cortical thickness: impact of cognitive reserve. *Brain, 132*(8), 2036	Population/condition (AD)
Rajender et al (2011) Study of neurocognitive endophenotypes in drug-naïve obsessive-compulsive disorder patients, their first degree relatives and healthy controls. *Acta Psychiatrica Scandinavica, 124*(2), 152	Population/condition (OCD)
Rami et al (2011) Cognitive reserve questionnaire: scores obtained in a healthy elderly population and in one with Alzheimer's disease. *Revista de Neurologia, 52*(4), 195	Non-English language
Ravaglia et al (2005) Incidence and etiology of dementia in a large elderly Italian population. *Neurology, 64*(9), 1525	Outcome (dementia)
Redolat et al (2012) Potential benefits and limitations of enriched environments and cognitive activity on age-related behavioural decline. *Current Topics in Behavioural Neuroscience, 10*, 293.	Review article
Reichman et al (2012) History and experience: the direction of Alzheimer's disease. *Menopause, 19*(7), 724	Review article
Rentz et al (2010) Cognition, reserve and amyloid deposition in normal ageing. *Annals of Neurology, 67*(3), 353-364	Outcome (cognition associated with AD pathology)
Rentz et al (2011) Face-name associative memory performance is related amyloid burden in normal elderly. *Neuropsychologia, 49*(9), 2776	CR as covariate rather than predictor or key variable of interest
Richards et al (2005) A life course approach to cognitive reserve: a model for cognitive aging and development? *Annals of Neurology, 58*(4), 617	Review article
Robertson, I.H. (2013) A noradrenergic theory of cognitive reserve: implications for Alzheimer's disease. *Neurobiology of Aging, 34*(1), 298	Review article
Robertson, I.H. (2014) Right hemisphere role in cognitive reserve. *Neurobiology of Aging, 35*(6), 1375	Review article
Rodrigue et al (2009) Beta-amyloid deposition and the aging brain. *Neuropsychology Review, 19*(4), 436	Review article
Roe et al (2008) Alzheimer disease and cognitive reserve: variation of education effect with carbon labelled Pittsburgh Compound B uptake. *Archives of Neurology, 65*(11), 1467	Outcome (cognition associated with AD pathology)
Roe et al (2008) Interaction of neuritic plaques and education predicts dementia. *Alzheimer Disease & Associated Disorders, 22*(2), 188	Outcome (dementia)
Roe et al (2010) Alzheimer disease identification using amyloid imaging and reserve variables: proof of concept. *Neurology, 75*(1), 42	Content not relevant (not looking at relationship of CR indicator to cognitive outcome)

Roe et al (2011) Cerebrospinal fluid biomarkers, education, brain volume and future cognition. *Archives of Neurology, 68*(9), 1145	Outcome (incident cognitive impairment)
Rolstad et al (2009) Biomarkers in relation to cognitive reserve in patients with mild cognitive impairment – proof of concept. *Dementia and Geriatric Cognitive Disorders, 27*(2), 194	Population/condition (MCI)
Rolstad et al (2009) Cognitive reserve in relation to abeta42 in patients concerting from MCI to dementia – a follow up report. *Dementia and Geriatric Cognitive Disorders, 28*(2), 110	Population/condition (MCI/dementia)
Rolstad et al (2010) High education may offer protection against tauopathy in patients with mild cognitive impairment. *Journal of Alzheimer's Disease, 21*(1), 221	Population/condition (MCI)
Ropacki et al (2007) The influence of cognitive reserve on neuropsychological functioning following coronary artery bypass grafting (CABG). *Archives of Clinical Neuropsychology, 22*(1), 73	Outcome not associated with normal aging
Roselli et al (2009) Rate of MMSE score change in Alzheimer's disease: influence of education and vascular risk factors. *Clinical Neurology and Neurosurgery, 111*(4), 327	Population/condition (AD)
Ruiz-Contreras et al (2012) Low diversity and low frequency of participation in leisure activities compromise working memory efficiency in young adults. *Acta Psychologia (Amst), 139*(1), 91	Population (young adults)
Sabbath et al (2012) Occupational solvent exposure and cognition: does the association vary by education? *Neurology, 78*(22), 1754	Outcome not associated with normal ageing
Sabia et al (2011) High alcohol consumption in middle aged adults is associated with poorer cognitive performance only in low socio-economic group. Results from GAZEL cohort study. *Addiction, 106*(1), 93	Outcome (not associated with normal ageing)
Sakamoto et al (2013) Protective effects of higher cognitive reserve for neuropsychological and daily functioning among individuals infected with hepatitis C. *Journal of NeuroVirology, 19*(5), 442	Population/condition (Hepatitis C)
Salmond et al (2006) Cognitive reserve as a resilience factor against depression after moderate/severe head injury. *Journal of Neurotrauma, 23*(7), 1049	Population/condition (head injury); Non-cognitive outcome
Sanchez-Rodriguez et al (2011) Cognitive reserve and lifestyle in Spanish individuals with sporadic Alzheimer's disease. *American Journal of Alzheimer's Disease and Other Dementias, 26*(7), 542	Population/condition (AD)
Sanders et al (2012) Non-native language use and risk of incident dementia in the elderly. *Journal of Alzheimer's Disease, 29*(1), 99	Outcome (dementia)
Santamamrina et al (2009) Influence of cognitive reserve on neuropsychological performance in epileptic patients. *Medicina Clinica (Barcelona), 132*(12), 459	Non-English language
Sattler et al (2012) Cognitive activity, education and socioeconomic status as preventive factors for mild cognitive impairment and Alzheimer's disease. *Psychiatry Research, 196*(1), 90	Outcome (MCI/AD)
Satz et al (2011) Brain and cognitive reserve: Mediator(s) and construct validity, a critique. *Journal of Clinical and Experimental Neuropsychology, 33*(1), 121	Review article

Scarmeas & Stern (2004) Cognitive reserve implications for diagnosis and prevention of Alzheimer's disease. *Current Neurology and Neuroscience Reports, 4*(5), 374	Review article
Scarpazza et al (2013) Education protects against cognitive changes associated with multiple sclerosis. *Restorative Neurology and Neuroscience, 31*(5), 619	Population/condition (MS)
Scazufca et al (2008) Risk factors across the life course and dementia in a Brazilian population: results from the Sao Paulo Ageing & Health Study (SPAH). *International Journal of Epidemiology, 37*(4), 879	Outcome (dementia)
Scherer et al (2012) Neurofunctional (re)organisation underlying narrative discourse processing in aging: evidence from fNIRS. *Brain and Language, 121*(2), 174.	Content not relevant
Schmidt et al (2008) Sex differences in Alzheimer's disease. *Neuropsychiatry, 22*(1), 1	Non-English language
Schmidtt et al (2012) Decision making after pediatric traumatic brain injury: trajectory of recovery and relationship with age and gender. *International Journal of Developmental Neuroscience, 30*(3), 225	Population/condition (paediatric TBI)
Schmidtt et al (2012) Novel risk markers and long-term outcomes of delirium: the successful aging after elective surgery (SAGES) study design and methods. *Journal of the American Medical Directors Association, 13*(9), 818	Not original study (protocol)
Schwartz et al (2013) Cognitive reserve and patient reported outcomes in multiple sclerosis. *Multiple Sclerosis, 19*(1), 87	Population/condition (MS)
Schwartz et al (2013) Cognitive reserve and symptom experience in multiple sclerosis: a buffer to disability progression over time? *Archives of Physical Medicine and Rehabilitation, 94*(10), 1971	Population/condition (MS)
Schweizer et al (2012) Bilingualism as a contributor to cognitive reserve: evidence from brain atrophy in Alzheimer's disease. *Cortex, 48*(8), 991	Population/condition (AD)
Seo et al (2011) Effects of demographic factors on cortical thickness in Alzheimer's disease. *Neurobiology of Aging, 32*(3), 200	Population/condition (AD)
Serra et al (2011) Neuroanatomical correlates of cognitive reserve in Alzheimer's disease. *Rejuvenation Research, 14*(2), 143	Population/condition (AD)
Shapiro et al (2014) Cognitive reserve protects against apathy in individuals with Human Immunodeficiency Virus. *Archives of Clinical Neuropsychology, 29*(1), 110	Population/condition (HIV)
Simon et al (2012) Cognitive intervention in amnestic Mild Cognitive Impairment: a systematic review. *Neuroscience and Biobehavioral Reviews, 36*(4), 1163	Review article
Singh-Manoux et al (2008) Socioeconomic status moderates the association between carotid intima-media thickness and cognition in midlife: evidence from the Whitehall II study. *Atherosclerosis, 197*(2), 541	Outcome (cognition associated with heart disease)
Singh-Manoux et al (2009) Cognition and incident coronary heart disease in late midlife: the Whitehall II study. *Intelligence, 37*(6), 529	Outcome (cognition association with heart disease)
Sitskoorn et al (2004) Memory profiles of patients with schizophrenia. *Psychiatry Research, 128*(1), 27	Population/condition (schizophrenia)

Slegers et al (2009) Effects of computer training and internet usage on cognitive abilities in older adults: a randomised controlled study. *Aging Clinical and Experimental Research, 21*(1), 43	Intervention study
Smith (2013) Everyday technologies across the continuum of dementia care. *Conference Proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2013*, 7040	Content not relevant
Soldan et al (2013) Relationship of cognitive reserve and cerebrospinal fluid biomarkers to the emergence of clinical symptoms in preclinical Alzheimer's disease. *Neurobiology of Aging, 34*(12), 2827	Outcome (AD clinical symptoms)
Sosa-Ortiz et al (2012) Epidemiology of dementias and Alzheimer's disease. *Archives of Medical Research, 43*(8), 600	Review article
Soto-Anari et al (2013) Level of reading skills as a measure of cognitive reserve in elderly adults. *Revista de Neurologia, 56*(2), 79	Non-English language
Spiegel (2012) A case of postoperative cognitive decline, with a highly elevated C-reactive protein, status post left ventricular assist device insertion: a review of the neuroinflammatory hypothesis of delirium. *Innovations in Clinical Neuroscience, 9*(1), 35	Content not relevant
Spitznagel et al (2005) Cognitive reserve and anosognosia in questionable and mild dementia. *Archives of Clinical Neuropsychology, 20*(4), 505	Population/condition (dementia)
Spreng et al (2011) Relationship between occupation attributes and brain metabolism in frontotemporal dementia. *Neuropsychologia, 49*(13), 2699	Population/condition (dementia)
Staff (2012) Reserve, brain changes, and decline. *Neuroimaging Clinics of North America, 22*(1), 99	Review article
Starr & Lonie (2011) Estimated pre-morbid IQ effects on cognitive and functional outcomes in Alzheimer's disease: a longitudinal study in a treated cohort. *BMC Psychiatry, 8*, 27	Population/condition (AD)
Steffener & Stern (2012) Exploring the neural basis of cognitive reserve in aging. *Biochimica et Biophysica Acta (BBA) – Molecular Basis of Disease 1822*(3), 467	Review article
Stern (2006) Cognitive reserve and Alzheimer's disease. *Alzheimer Disease & Associated Disorder, 20*(2), 112	Review article
Stern (2009) Cognitive reserve. *Neuropsychologia, 47*(10), 2015	Review article
Stern (2012) Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology, 11*(11), 1006	Review article
Stern (2013) Cognitive reserve: implications for assessment and intervention. *Folio Phoniatrica et Logopaedica, 65*(2), 49	Review article
Studenski et al (2006) From bedside to bench: does mental and physical activity promote cognitive vitality in late life? *Science's SAGE KE, 2006*(10), pe21	Review article
Suchy et al (2011) Instrumental activities of daily living among community-dwelling older adults: discrepancies between self-report and performance are mediated by cognitive reserve. *Journal of Clinical and Experimental Neuropsychology, 33*(1), 92	Non-cognitive outcome (IADL)
Suchy et al (2011) Practice effect and beyond: reaction to novelty as an independent predictor of cognitive decline among older adults. *Journal of the International Neuropsychological Society, 17*(1), 101	Not measuring CR indicator in relation to cognitive outcome

Summers et al (2013) The Tasmanian Healthy Brain Project (THBP): a prospective longitudinal examination of the effect of university level education in older adults in preventing age-related cognitive decline and reducing the risk of dementia. *International Psychogeriatrics, 25*(7), 1145	Not original study (study protocol)
Sumowski et al (2009) Cognitive reserve moderates the negative effect of brain atrophy on cognitive efficiency in multiple sclerosis. *Journal of the International Neuropsychological Society, 15*(4), 606	Population/condition (MS)
Sumowski et al (2009) Cognitive reserve protects against cognitive dysfunction in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology, 31*(8), 913	Population/condition (MS)
Sumowski et al (2010) Intellectual enrichment is linked to cerebral efficiency in multiple sclerosis: functional magnetic resonance imaging evidence for cognitive reserve. *Brain, 133*(2), 362	Population/condition (MS)
Sumowski et al (2010) Intellectual enrichment lessens the effect of brain atrophy on learning and memory in multiple sclerosis. *Neurology, 74*(24), 1942	Population/condition (MS)
Sumowski et al (2010) Premorbid cognitive leisure independently contributes to cognitive reserve in multiple sclerosis. *Neurology, 75*(16), 1428	Population/condition (MS)
Sumowski et al (2013) Brain reserve and cognitive reserve in multiple sclerosis: what you've got and how you use it. *Neurology, 80*(24), 2186	Population/condition (MS)
Sumowski et al (2013) Cognitive reserve in multiple sclerosis. *Multiple Sclerosis Journal, 19*(9), 1122	Review article
Sumowski et al (2013) Education attenuates the negative impact of traumatic brain injury on cognitive status. *Archives of Physical Medicine and Rehabilitation, 94*(12), 2562	Population/condition (TBI)
Takeda (2013) Memory and cognitive impairment of the elderly. *Nihon Rinsho, 71*(10), 1755	Non-English language
Tate et al (2011) Intracranial volume and dementia: some evidence in support of the cerebral reserve hypothesis. *Brain Research, 1385*, 151	Population/condition (dementia)
Teixeira et al (2012) Non-pharmacological interventions on cognitive functions in older people with mild cognitive impairment (MCI). *Archives of Gerontology and Geriatrics, 54*(1), 175	Population/condition (MCI)
Tognoni et al (2005) From mild cognitive impairment to dementia: a prevalence study in the district of Tuscany, Italy. *Acta Neurologica Scandinavica, 112*(2), 65	Outcome (dementia)
Tsuchida et al (2012) Working memory capacity affects the interference control of distractors at auditory gating. *Neuroscience Letters, 516*(1), 62	Content not relevant
Tucker & Stern (2011) Cognitive reserve in aging. *Current Alzheimer Research, 8*(4), 354	Review article
Vadikolias et al (2012) Mild cognitive impairment: effect of education on the verbal and nonverbal tasks performance decline. *Brain and Behavior, 2*(5), 620	Population/condition (MCI)

Valenzuela & Sachdev (2009) Harnessing brain and cognitive reserve for the prevention of dementia. *Indian Journal of Psychiatry, 51*(Suppl.1), S16	Review article
Van Veluw et al (2012) Prefrontal cortex cytoarchitecture in normal ageing and Alzheimer's disease: a relationship with IQ. *Brain Structure and Function, 217*(4), 797	Non-cognitive outcome
Vance & Struzick (2007) Addressing risk factors of cognitive impairment in adults aging with HIV: a social work model. *Journal of Gerontological Social Work, 49*(4), 51	Review article
Vance & Wright (2009) Positive and negative neuroplasticity: implications for age-related cognitive declines. *Journal of Gerontological Nursing, 35*(6), 11	Review article
Vance (2013) Prevention, rehabilitation, and mitigation strategies of cognitive deficits in aging with HIV: implications for practice and research. *ISRN Nursing,* 2013.	Population/condition (HIV)
Vance (2013) The cognitive consequences of stigma, social withdrawal and depression in adults aging with HIV. *Journal of Psychosocial Nursing and Mental Health Services, 51*(5), 18	Population/condition (HIV)
Vance et al (2008) Mental stimulation, neural plasticity, and aging: directions for nursing research and practice. *Journal of Neuroscience Nursing, 40*(4), 241	Review article
Vance et al (2010) How neuroplasticity and cognitive reserve protect cognitive functioning. *Journal and Psychosocial Nursing & Mental Health Services, 48*(4), 23	Review article
Vance et al (2010) The future of cognitive remediation training in older adults. *Journal of Neuroscience Nursing, 42*(5), 255	Review article
Vance et al (2011) Comorbidities and cognitive functioning: Implications for nursing research and practice. *Journal of Neuroscience Nursing, 43*(4), 215	Review article
Vance et al (2011) Sleep and cognition on everyday functioning in older adults: implications for nursing practice and research. *Journal of Neuroscience Nursing, 43*(5), 261	Review article
Vance et al (2012) An overview of non-pathological geroneuropsychology: Implications for nursing practice and research. *The Journal of Neuroscience Nursing: Journal of the American Association of Neuroscience Nurses, 44*(1), 43	Review article
Vance et al (2012) Neuroplasticity and successful cognitive aging: a brief overview for nursing. *Journal of Neuroscience Nursing, 44*(4)	Review article
Vance et al (2012) Neuropsychology and cognitive health in healthy older adults: a brief overview for psychiatric nurses. *Journal of Psychosocial Nursing and Mental Health Services, 50*(6), 30	Review article
Vance et al (2013) The role of neuroplasticity and cognitive reserve in aging with HIV: Recommendations for protection and rehabilitation. *Journal of Neuroscience Nursing, 45*(5), 306	Review article
Verma & Howard (2012) Semantic memory and language dysfunction in early Alzheimer's disease: a review. *International Journal of Geriatric Psychiatry, 27*(12), 1209	Review article

Verret et al (2013) Transient enriched housing before amyloidosis onset sustains cognitive improvement in Tg2576 mice. *Neurobiology of Aging, 34*(1), 211	Animal study
Villeneuve et al (2010) Cognitive reserve and neuronal changes associated with aging. *Psychologie & Neuropsychiatrie du vieillissement, 8*(2), 133	Non-English language
Villeneuve et al (2011). The nature of episodic memory deficits in MCI with and without vascular burden. *Neuropsychologia, 49*(11), 3027	Population/condition (MCI)
Viloria (2011) Predementia Alzheimer's disease: benefits of early diagnosis. *Revista Espanola de Geriatria y Gerontologia, 46*(S1), 47	Non-English language
Whalley et al (2004) Cognitive reserve and the neurobiology of cognitive aging. *Ageing Research Reviews, 3*(4), 369	Review article
Willis & Hakim (2013) Stroke prevention and cognitive reserve emerging approaches to modifying risk and delaying onset of dementia. *Frontiers in Neurology, 4*, 13	Review article
Wilson et al (2009) Elderly women with large social networks are less likely to develop dementia. *Evidence Based Mental Health, 12*(1), 22	Not original study (comment)
Wilson et al (2013) Neural reserve, neuronal density in the locus coerleus and cognitive decline. *Neurology, 80*(13), 1202	Not measuring CR indicator (MRI as brain reserve indicator)
Wood et al (2011) "Brain training" improves cognitive performance and survival in a transgenic mouse model of Huntington's disease. *Neurobiology of Disease, 42*(3), 427	Animal study
Woodard et al (2009) Semantic memory activation in amnestic mild cognitive impairment. *Brain, 132*(8), 2068	Population/condition (MCI)
Xiong et al (2009) Does meditation enhance cognition and brain plasticity? *Annals of the New York Academy of Sciences, 1172*, 63	Content not relevant
Yaffe et al (2011) Association of plasma beta-amyloid level and cognitive reserve with subsequent cognitive decline. *JAMA, 305*(3), 261	Outcome (cognition associated with AD pathology)
Yeo et al (2011) Alzheimer's disease and intelligence. *Current Alzheimer Research, 8*(4), 345	Review article
Yoshizawa et al (2013) Characterising the normative profile of (18) F-FDG PET brain imaging: sex difference, aging effect and cognitive reserve. *Psychiatry Research, 221*(1), 78	Content not relevant
Zieren et al (2013) Education modifies the relation of vascular pathology to cognitive function: cognitive reserve in cerebral autosomal dominant artheriopathy with subcortical infarcts and leukoencephalopathy. *Neurobiology of Aging, 34*(2), 400	Population/condition
Zigman et al (2004) Incidence and prevalence of dementia in elderly adults with mental retardation without down syndrome. *American Journal of Mental Retardation, 109*(2), 126	Population/condition

Note: AD = Alzheimer's disease; CR = cognitive reserve; HIV = human immunodeficiency virus; MCI = mild cognitive impairment; MS = multiple sclerosis; PD = Parkinson's disease; TBI = traumatic brain injury

Appendix B: Health screening questionnaire

1. Have you ever had a stroke or T.I.A. (transient ischemic attack)? Yes/No
2. Have you ever been seen by a neurologist of neurosurgeon? Yes/No
    a. *If yes*: was this for a back or neck problem? Yes/No
    b. *If yes*: was this for a tension headache? Yes/No
3. Have you had a cancer other than skin cancer diagnosed within the last 3 years? Yes/No
4. Do you have shortness of breath while sitting still? Yes/No
5. Do you use home oxygen? Yes/No
6. Do you have difficulty understanding conversations because of your hearing, even if you wear a hearing aid? Yes/No
7. Do you have trouble with your vision that prevents you from reading ordinary print, even when you have glasses on? Yes/No
8. Have you had heart surgery? Yes/No
9. Have you ever been resuscitated? Yes/No
10. Do you drink beer, wine or other alcoholic beverages every day or less often? Every day/Less often
    a. *If yes:* How many drinks do you have each day?
11. Have you ever had a problem due to abuse of drugs or medications? Yes/No
    a. *If yes:* Was this in the past 5 years? Yes/No
12. Have you ever been treated for alcohol or drug abuse? Yes/No
    a. *If yes:* Was this within the past 5 years? Yes/No
13. Do you have diabetes that requires insulin to control?
14. Do you have hypertension that is not well controlled? Yes/No
15. Have you ever had a head injury with loss of consciousness greater than 5 minutes? Yes/No
16. Have you ever been unconscious for more than 1 hour, other than during surgery? Yes/No
17. Have you ever required overnight hospitalisation because of a head injury? Yes/No
18. Have you ever had encephalitis or meningitis? Yes/No
19. Have you ever had a heart attack? Yes/No

    a. *If yes*: Did you have any change in your memory, ability to talk or solve problems 24 hours after your heart attack? Yes/No

20. Are you currently taking medication for a psychiatric condition? Yes/No
21. In the last 5 years have you been hospitalised for a psychiatric condition? Yes/No
22. Have you ever had seizures? Yes/No
23. Do you have Parkinson's disease? Yes/No
24. Have you ever had brain surgery? Yes/No
25. Have you ever undergone surgery to clear arteries to the brain? Yes/No
26. Have you ever had any illness that caused a permanent decrease in your memory or other mental functions? Yes/No
27. Have you ever received electro-convulsive therapy? Yes/No
28. Have you ever been diagnosed as learning disables? Yes/No
29. Did you ever receive additional classes in school because of a learning problem? Yes/No
30. Have you ever been diagnosed as having a brain tumour? Yes/No
31. Do you have difficulty using your hands? Yes/No
32. Have you ever had major surgery with general anaesthesia? Yes/No
    a. *If yes:* Did you have any change in your memory, ability to talk or solve problems 1 week after surgery? Yes/No
33. Do you have multiple sclerosis, cerebral palsy, or Huntington's disease? Yes/No
34. Are you receiving kidney dialysis? Yes/No
35. Do you have a liver disease? Yes/No
36. Do you have lupus? Yes/No
37. Are you able to write your name? Yes/No
38. Are you aware if any of your immediate biological relatives (your biological parents, brothers or sisters, or children) have been told by a doctor that they have Alzheimer's disease or any other form of dementia?
    a. *If yes*: What is the relationship of that relative to you?
39. I would like to record all of the medications that you take on a regular basis, like every day or every week. This will prescription and non-prescription medications, over-the-counter medicines, vitamins and herbal and alternative medicines. Would you be able to get those medications and read

out the names of them to me? [record name, dosage and frequency of each medication verbatim]

Appendix C: List of excluded medications

Generic Name	Trade Name(s)
Amisulpiride	Solian
Aripiprazole	Abilify
Chlorpromazine	Thorazine; Largactil
Clozapine	Clozaril
Fluphenazine	Fluphenazine
Haloperidol	Haldol
Iloperidone	Fanapt
Olanzapine	Olanzapine Apotex
Olanzapine	Olanzapine Glenmark
Olanzapine	Olanzapine Mylan
Olanzapine	Olanzapine Neopharma
Olanzapine	Olanzapine Teva
Olanzapine	Olazax
Olanzapine	Olazax Disperzi
Olanzapine	Zalasta
Olanzapine Pamoate	Zypadhera
Olanzapine	Zyprexa
Paliperidone	Invega
Paliperidone Palmitate	Xeplion
Perphenazine (generic)	Perphenazine
Pimozide	Orap
Quetiapine	Seroquel
Risperidone	Risperdal
Thioridazine (generic)	Thioridazine
Thiothixene	Navane
Trifluoperazine	Stelazine
Sertindole	Serdolect
Sulperide	Dolmatil
Ziprasidone	Geodon
Zotepine	Zoleptil
Haloperidol decanoate	Haldol
Flupenthixol decanoate	Depixol
Fluphenazine decanoate	Modecate
Pipothiazine palmitate	Piportil
Zuclopenthixol decanoate	Clopixol
Risperidone	Risperdal Consta
Carbamazepine	Tegretol
Divalproex sodium (valproic acid)	Depakote
Gabapentin	Neurontin
Lamotrigine	Lamictal
Lithium carbonate	Eskalith, Lithobid
Lithium citrate	Lithium citrate
Oxcarbazepine	Trileptal
Topiramate	Topamax
Levetiracetam	Keppra
Levetiracetam	Levetiracetam Accord

Levetiracetam	Levetiracetam Activas
Levetiracetam	Levetiracetam Ratiopharm
Levetiracetam	Levetiracetam Sun
Levetiracetam	LevetiracetamTeva
Levetiracetam	Matever
Retigabine	Trobalt
Lacosamide	Vimpat

Appendix D: Ethical approval letter

COLÁISTE NA TRÍONÓIDE, BAILE ÁTHA CLIATH | TRINITY COLLEGE DUBLIN
Ollscoil Átha Cliath | The University of Dublin

4th April 2012

F.A.O. Ian Robertson

School of Psychology Research Ethics Committee

Dear Ian,

I am pleased to inform you that your application entitled "Cognitive function and lifestyle in older adults" has been approved by the School of Psychology Research Ethics Committee.

It is not routine policy of the Committee to issue duplicate or replacement letters confirming ethical approval. It is therefore the responsibility of the applicant to keep the approval letter safe.

Yours sincerely,

SCHOOL OF PSYCHOLOGY
Áras an Phairsaigh
Trinity College
Dublin 2

Dr. Tim Trimble
Chair
School of Psychology Research Ethics Committee

Scoil na Síceolaíochta,
Dámh na nEolaíochtaí Sóisialta agus Daonna,
Áras an Phiarsaigh, Coláiste na Tríonóide,
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Appendix E: Information sheet and consent form

TRINITY COLLEGE DUBLIN
COLÁISTE NA TRÍONÓIDE, BAILE ÁTHA CLIATH

TRINITY COLLEGE
Institute of Neuroscience

NEIL
Neuro-Enhancement for Independent Lives
Memory Research Unit

Study Information Sheet:
For the attention of Research Participants

Cognitive Function and Lifestyle in Older Adults

What is the project?

We would like to invite you to participate in a study that aims to understand how mental processes such as memory and attention are influenced by various aspects of peoples' lives.

If you agree to take part you will be asked to complete some questionnaires at home – to provide us with some background information about your life (for example, your occupation, your family and your sleep habits). We would also like you to ask a friend or relative to complete a short questionnaire about how they find your day to day memory – this is optional.

You will then be invited to Trinity College to complete some more questionnaires and some tasks that provide us with information about your lifestyle, your mood and mental processes like memory and attention. Some of these are paper and pen tests, and a few are computer based tests. You do not need to be familiar with a computer to complete the tasks; they only involve pressing one or two buttons in response to instructions. Our researchers will also ask you some questions about various aspects of your life that have been shown to impact on our memory as we get older.

All of the information that you provide will be treated in the strictest confidence. You will be assigned a study ID code, and all of the information you provide will be stored only under this ID code, not under your name or any contact details. You are free to decline to provide some or all of the information requested in the questionnaires or at any time during the session. The information we collect during this study will never be made available to anyone other than members of the NEIL research team or their assistants.

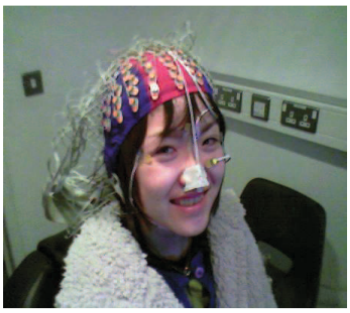
When you attend Trinity College Dublin, we will also take some basic physical measures and a measure of the electrical activity in your brain using electroencephalography (EEG). We will measure your height and weight, grip strength and the time that it takes you to walk a short distance. We will also ask you to provide a sample of your saliva, to be stored anonymously for future medical research.

Grip Strength

We will use a hydraulic hand dynamometer (pictured right) to measure your grip strength. You will be required to squeeze the handle of this dynamometer for a few seconds. There are no risks associated with using this machine, and any participant with pain or swelling in their wrists, or any other problems with their wrists, will not be asked to take this test.

EEG

We will use electroencephalogram (EEG) to take a measure of the electrical activity in your brain. We will take a short measure, for three minutes while you sit with your eyes closed, and for three minutes while you sit with your eyes open. The recording of EEG involves a special cap (see picture below).



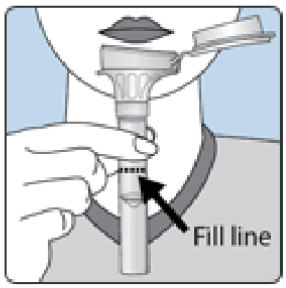
Gel is used to form a link between the small electrodes and your scalp. The experience is very comfortable but you will get some gel in your hair. Please note that we do not have hair-washing facilities at the testing venue, but will provide 'wet wipes' which will allow you to remove some of the gel after the recording. If you would prefer not to have the EEG for this reason, you are free to decline this part of the assessment session.

We request that you do not consume alcohol for 24 hours prior to EEG testing.

Saliva Sample

We will ask you to provide a saliva sample, from which DNA will be extracted and stored anonymously to be used in future medical research. Separate consent is required for the provision of a saliva sample. If you agree to provide this saliva sample and have DNA extracted and stored for use in future research, please sign the saliva collection consent form.

Providing this saliva sample involves spitting into a small container, as shown in the picture on the right. This container will then be sealed and packaged, to be sent to a repository, where DNA will be extracted from the sample and stored for future research. Saliva samples and DNA extracted from samples are stored under a unique sample ID code, which is different from your study ID code, and cannot be linked to your name or other identifying information.



There are no known risks associated with any of the procedures in neurologically healthy adults and you are free to decline any of the tasks or measurements that you do not wish to complete.

What happens to my data?

All of your data is stored securely under a unique study ID code. Only the research team will be able to link your name to the information you provide during the study. The file linking your name to your study ID number will be kept separately from your data, in a secure location. This information will be used only to contact you for follow up assessment or sub-studies.

Your saliva sample and DNA extracted from this sample are stored under a unique sample ID code, which cannot be linked to your name or other identifying information.

Data will be placed in the NEIL Memory Research Unit database for analysis. Your name or other identifying information will not be in this database, and details linking your name to your data will never be released.

What are my rights if I join the study?

Participation in the study is entirely voluntary and if you agree to participate you have the following rights:

1. The information from this study will be kept strictly confidential and will not be made available to any other people.

2. We will aim to publish our results in scientific journals but any information we have will be completely anonymous and presented as a group.

3. As participation is completely voluntary, you are free to withdraw from the study at any time. You are also free to withdraw your data at the conclusion of your participation should you so wish.

4. You are entitled to request access to information we store about you, as per the terms of the Data Protection Act.

For queries related to your appointment, please contact the Memory Research Unit:

Phone: (01) 896 4506
Email: neilmru@tcd.ie

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TRINITY COLLEGE DUBLIN
COLÁISTE NA TRÍONÓIDE, BAILE ÁTHA CLIATH

TRINITY COLLEGE
Institute of Neuroscience

NEIL
Neuro-Enhancement for Independent Lives
Memory Research Unit

TRINITY COLLEGE DUBLIN
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Memory Research Unit

Study Consent Form
For the attention of Research Participants

Cognitive Function and Lifestyle in Older Adults

You have received this consent form because you indicated that you wish to take part in research at the NEIL Memory Research Unit in Trinity College Dublin. Our research aims to examine how different aspects of people's lives affect their memory. If you consent to take part in this research, you will first be asked to answer some questions about your health over the phone. You may then be asked to complete a questionnaire at home and to have a close friend or relative complete a short questionnaire about your day to day memory (this is optional).

You will also be invited to attend a testing session at Trinity College Dublin. During this session, you will be asked to complete some questionnaires about your lifestyle and your mood, some pen and paper tasks and some computerised tasks. We will also measure your height and weight, your grip strength and your walking speed. We will also take a short measure of the electrical activity in your brain using an electroencephalogram (EEG). We have provided information about this procedure in the attached study information sheet.

We will also request to anonymously store a sample of your saliva, and DNA extracted from this saliva, for use in future medical research. **Separate consent is required** for both the provision of this saliva sample; and for the extraction, analysis and storage of DNA data from the sample. **Please indicate your consent by signing the saliva collection consent form.**

The assessment session will take no longer than 3 hours and there will be regular breaks during the session. You are free to terminate the session at any time and you can decline to provide some or all of the information requested.

You will be given the opportunity to take part in annual follow up assessments which will be of a shorter duration. You can choose not to take part in this follow up assessment if you wish. You are free to withdraw your participation from the study at any time. **Please indicate if you wish to take part in follow up assessments by ticking the appropriate box below**.

Participant ID:_____

Trinity College Institute of Neuroscience, Lloyd Institute, Trinity College Dublin, Dublin 2

You will also be offered the opportunity to take part in sub-studies following your initial session. If you are invited to take part in research you will be told what kind of tests you will be expected to complete. You are free to decline any invitation to participate in research. You can also indicate that you do not want to be contacted to take part in sub-studies. **If you consent to being contacted about taking part in sub-studies, please tick the appropriate box below.**

The information we collect will never be made available to anyone other than members of the NEIL research team or their assistants. If you indicate that you are willing to take part in further sub-studies, you agree to allow members of the NEIL research team or their assistants to contact you from time to time and invite you to participate in research or to update your records.

Please note that the measures we use are for research purposes only, and do not provide a clinical assessment for people who are worried about their memory. However, if we are concerned that your test results might warrant clinical investigation, we will tell you, and recommend that you visit your GP. If you are worried about your memory, please speak to your family doctor.

What are my rights if I join the study?

Participation in the study is entirely voluntary and if you agree to participate you have the following rights:

1. The information from this study will be kept strictly confidential and will not be made available to any other people.

2. We will aim to publish our results in scientific journals but any information we have will be completely anonymous and presented as a group.

3. As participation is completely voluntary, you are free to withdraw from the study at any time. You are also free to withdraw your data at the conclusion of your participation should you so wish.

4. You are entitled to request access to information we store about you, as per the terms of the Data Protection Act.

Participant ID:_____

Trinity College Institute of Neuroscience, Lloyd Institute, Trinity College Dublin, Dublin 2

Terms of Consent

Please tick the appropriate boxes to indicate your consent

I, the undersigned, give my informed consent to:

1. Take part in the Cognitive Function and Lifestyle in Older Adults Study ☐
2. Take part in follow up assessments ☐
3. Be contacted regarding taking part in further sub-studies ☐

Once I have signed this consent I understand that:

- I am confirming that I have read and understood this form and the attached study information sheet.
- I will be assigned a unique study ID code, under which all of my data will be stored.
- I consent to provide information to the researchers involved. I understand that I can decline to provide some or all of the information requested. I understand that this information will never be made available to anyone other than members of the NEIL research team or their assistants.
- Any data obtained through my participation in this research will be treated as confidential and processed only in accordance with the Data Protection Acts, and that they will be used only for the purposes of research. I understand that I can request any information stored about me, under the terms of the Data Protection act.
- I may withdraw my participation at any time during the study.
- I may request for my data to be removed from the study database at any time, and my request will be honoured.
- I will not be requested to participate in any study that could be foreseen to be detrimental to a person's well being, under normal circumstances, and that every study that I will be invited to participate in will have received prior approval from the relevant ethics committees of Trinity College Dublin.

Please sign here

Full Name: _____ **Signed:** _____ **Date:** _____

If you consent to participate in this research, we will contact you by phone to ask you some questions about your health. **Please indicate which times would suit you to be contacted by phone by ticking the boxes overleaf:**

Participant ID:_____

Trinity College Institute of Neuroscience, Lloyd Institute, Trinity College Dublin, Dublin 2

Please tick the boxes below to indicate what times would suit you to be contacted by phone:

Monday	☐	Morning	☐	Afternoon	☐	Evening	☐
Tuesday	☐	Morning	☐	Afternoon	☐	Evening	☐
Wednesday	☐	Morning	☐	Afternoon	☐	Evening	☐
Thursday	☐	Morning	☐	Afternoon	☐	Evening	☐
Friday	☐	Morning	☐	Afternoon	☐	Evening	☐
Saturday	☐	Morning	☐	Afternoon	☐	Evening	☐
Sunday	☐	Morning	☐	Afternoon	☐	Evening	☐

For queries related to your appointment, please contact the Memory Research Unit:

Phone: (01) 896 4506
Email: neilmru@tcd.ie

Caoimhe Hannigan	Dr Sabina Brennan	Prof Ian Robertson
hannigc@tcd.ie	brennas1@tcd.ie	iroberts@tcd.ie
(01) 8964505	(01) 8968414	(01) 8962684

Participant ID:_____

Trinity College Institute of Neuroscience, Lloyd Institute, Trinity College Dublin, Dublin 2

Appendix F: NEIL Memory Research Unit study protocol

		T1 Screen (Phone)	T1 Questionnaire	T1 Assessment	T2 Phone Assessment	T2 Questionnaire	T2 Assessment
Explain Study		X			X		
Obtain Consent		X					X
Inclusion/exclusion criteria		X					
Health							
Medical history	Health Screening Questionnaire (Christensen et al, 1992)	X			X		
Medication list	Self-report (verbatim from labels)	X			X		
Family history AD/Dementia	Self-report item	X			X		
Self-rated health	Self-report items		X		X		
Frailty	Fried Frailty Index			X			X
Cognitive function							
Self-rated memory	Self-report items		X		X		
Subjective memory complaints/failures	MAC-Q (Crook et al, 1992)					X	
	PRMQ (Smith et al, 2000)					X	
Informant rating of memory performance/ complaints/ failures	IQCODE (Jorm, 1994)		X			X	
	Proxy PRMQ (Smith et al, 2000)					X	
	Self-report items					X	
Reading ability/ literacy	WRAT-3 Reading Subtest (Wilkenson, 1993)			X			
Pre-morbid IQ	NART (Nelson, 1982)			X			
Overall function	MMSE (Folstein et al, 1975)			X			X
	MoCA (Nasreddine et al, 2005)			X			X
Episodic Memory	WMS-IV Logical Memory subtest (Wechsler, 2009)			X			X
	Buschke & Grober FSRT (Grober & Buschke, 1987)			X			X

	ACAD word and shape recognition task (Di Rosa et al 2014)				X				X
Working Memory	WMS-III Letter-Number Sequencing subtest (Wechsler, 1997)				X				X
Prospective Memory	TILDA Experimental Task				X				X
Processing Speed	CTT1 (D'Elia et al, 1994)				X				X
	Choice Reaction Time experimental task (Brennan, 2011)				X				X
Executive Function	CTT2 (D'Elia et al, 1994)				X				X
	Verbal (animal) fluency task				X				X
	CAMDEX Visual Reasoning subtest (Roth et al, 1998)				X				X
Attention	SART experimental task (Robertson et al, 1997)				X				X
	ACAD Shapes-SART (SSART) (Di Rosa et al, 2014)				X				X
Visuo-Spatial	Landmark Spatial Bias Task (Bellgrove et al, 2005)								X
Demographics									
Age	Self-report item	X		X		X		X	
Sex	Self-report item	X							
Marital status	Self-report item			X				X	
Occupational status (current)	Self-report item			X				X	
Occupational history	Item adapted from CRIq (Nucci et al, 2012)			X					
Educational attainment	Self-report items (years, highest level completed)			X				X	
Caregiving	Self-report items			X				X	
Behavioural/lifestyle									
Smoking	Self-report items			X		X			
Alcohol use	Self-report items			X		X			
	CAGE (Mayfield et al, 1974)								
Sleep	Pittsburgh Sleep Quality Index Buysse et al, 1989)			X				X	
	Stanford Sleepiness Scale (Hoddes et al, 1973)				X				X
Physical activity	IPAQ Short Form (Craig et al, 2003)				X				X

Leisure activities	Leisure Activities Scale (House et al, 1982)	X			X	
	Lifetime Cognitive Activity Scale (Wilson et al, 2013)				X	
Boredom-proneness	Self-report item (Conroy et al, 2010)		X			X
Psychosocial						
Self-rated mental health	Self-report item	X		X		
Depression	CES-D (Radloff, 1977)		X			X
Anxiety	HADS-A anxiety subscale (Zigmond & Snaith, 1983)		X			X
Perceived stress	4-item PSS (Cohen et al, 1983)		X			X
Quality of life	CASP-12 (Wiggins et al, 2008)		X			X
	Self-report life satisfaction item		X			X
Social networks	Berkman-Syme SNI (Berkman & Syme, 1979)		X			X
	Lubben Social Network Scale 18-item (Lubben et al, 2003)				X	
Physical						
Height	Standing body height – Seca© stadtiometer		X			X
Weight	Weight - Seca© electronic scale		X			X
Dominant hand	Self-report		X			X
Walking Speed	Timed walk (16ft)		X			X
Grip Strength	Baseline Hydraulic Hand Dynamometer – 2 measures per hand		X			X
Physiological						
EEG	Resting state (3 mins eyes open, 3 mins eyes closed)		X			X

Note: ACAD = Automated Cognitive Assessment Delivery; CAMDEX = Cambridge Mental Disorders of the Elderly Examination; CES-D = Centre for Epidemiologic Studies Depression Scale; CTT= Colour Trails Test; FCSRT = Free and Cued Selective Reminding Scale; HADS-A = Hospital Anxiety and Depression Scale; IPAQ = International Physical Activity Questionnaire; IQCODE = Informant Questionnaire for Cognitive Decline in the Elderly; MAC-Q = Memory Assessment Clinic Questionnaire; MMSE = Mini Mental State Examination; MoCA = Montreal Cognitive Assessment; NART = National Adult Reading Test; PRMQ = Prospective Retrospective Memory Questionnaire; PSS = Perceived Stress Scale; SART = Sustained Attention to Response Task; SNI = Social Network Index; TILDA = The Irish Longitudinal Study of Ageing; WMS = Wechsler Memory Scale; WRAT-3 = Wide Range Achievement Test

Appendix G: Background Questionnaire

TRINITY COLLEGE DUBLIN | THE UNIVERSITY OF DUBLIN
COLÁISTE NA TRÍONÓIDE, BAILE ÁTHA CLIATH

NEIL Neuro-Enhancement for Independent Lives

About this Questionnaire

This questionnaire is designed to provide us with some information about aspects of your life that may be related to how your memory functions as you get older. We greatly value your participation in our research, and we hope that you will find this questionnaire interesting to complete.

Your answers are extremely important to us. Please answer all questions honestly. All of your responses will be treated in the strictest confidence. If you would prefer not to answer any question, please skip it and move on to the next item.

If you are unsure of how to complete any item, please leave it blank and we can help you to complete it when you visit the Memory Research Unit.

How to fill in this questionnaire:
Please answer the questions by:

Ticking a box like this ☐

Or writing in a box like this: ☐

Sometimes you will find an instruction telling you which questions to answer next, like this:

Yes ☐
No ☐ ***Go to Question 3***

How to return this questionnaire
Please complete this questionnaire at home, and bring it with you to your appointment at the Memory Research Unit.

Thank you for volunteering.

Participant ID: _____

The following questions are designed to provide us with some basic information about your background.

1. **Are you male or female?**
   - Male ☐
   - Female ☐

2. **What is your date of birth?**
   Please enter your date of birth _____/_____/_____
   DD MM YYYY

3. **What is your age?**
   Please enter your age ☐

4. **Are you....?**
   - Married ☐
   - Living with a partner as if married ☐
   - Single (never married) ☐
   - Separated ☐
   - Divorced ☐
   - Widowed ☐

5. **What is the highest level of education you have completed?**
   - Some primary (not complete) ☐
   - Primary or equivalent ☐
   - Intermediate/junior/group certificate or equivalent ☐
   - Leaving certificate or equivalent ☐
   - Diploma/certificate ☐
   - Primary degree ☐
   - Postgraduate/higher degree ☐
   - None ☐

6. **In total, how many years of full time education have you completed?**
   Years ☐

Participant ID: _____

7. Which of the following best describes your current situation?

Retired	☐
Employed	☐
Self-employed	☐
Unemployed	☐
Permanently sick or disabled	☐
Looking after home or family	☐
In education or training	☐
Other	☐

If 'other', please specify: _____

8. What is the name or title of your current/most recent occupation?

_____

Participant ID: _____

We would like to collect some information about the types of occupations you have had during your life.

For **each job you have had during your life**, please **tell us the name of that job** and **indicate the number of years** you spent working in that occupation. Please include your current/most recent occupation.

If you have had more than 8 occupations, please list the occupations in which you have spent the longest periods of time working in.

Occupation	**Years**
1.	
2.	
3.	
4.	
5.	
6.	
7.	
8.	

Participant ID: _____

The following questions are designed to provide us with some general information about your health. Please tick one box to indicate your response to each of the questions below.

1. **Would you say that your health is...?**
   - Excellent ☐
   - Very good ☐
   - Good ☐
   - Fair ☐
   - Poor ☐

2. **In general, compared to other people your age, would you say that your health is...?**
   - Excellent ☐
   - Very good ☐
   - Good ☐
   - Fair ☐
   - Poor ☐

3. **Would you say that your emotional or mental health is...?**
   - Excellent ☐
   - Very good ☐
   - Good ☐
   - Fair ☐
   - Poor ☐

4. **In the past year, have you lost 10 pounds (4.5kg) or more in weight when you weren't trying to, for example, because of an illness?**
   - Yes ☐
   - No ☐

Participant ID: _____

We are interested in people's own views about their memory, and their ability to remember things during their day to day lives.

Please select one answer from the options provided for each of the questions below.

1. **How would you rate your day-to-day memory at the present time? Would you say it is...?**
   - Excellent ☐
   - Very good ☐
   - Good ☐
   - Fair ☐
   - Poor ☐

2. **How often would you find that you are absent minded, for example, forgetting where you put your glasses or keys, or finding yourself in a room having forgotten why you came in there? Would you say that you are absent minded in this sort of way....?**
   - All of the time ☐
   - Most of the time ☐
   - Some of the time ☐
   - None of the time ☐

Participant ID: _____

We are interested in collecting information about smoking and alcohol use, in order to examine the effects these behaviours may have on memory and related processes as we get older.

Please provide us with some information about your smoking behaviours and alcohol use by answering the questions below. All of your responses are treated in the strictest of confidence.

1. **Have you ever smoked cigarettes, cigars, cigarillos or a pipe daily for a period of at least one year?**
   Yes ☐
   No ☐ ***Go to Question 6***

2. **Do you smoke at the present time?**
   Yes ☐ ***Go to Question 4***
   No ☐ ***Go to Question 3***

3. **How old were you when you stopped smoking?**
   Age ☐

4. **For how many years have you been/did you smoke altogether?**
   Number of years ☐

5. **How many cigarettes/cigars/cigarillos/pipes do/did you smoke on average per day?**
   Number per day ☐

6. **Do you drink alcohol?**
   Yes ☐
   No ☐ ***Go to Page 8***

Participant ID: _____

7. **During the last six months, how often have you drunk any alcoholic beverages, like beer, cider, wine, spirits or cocktails?**

Almost every day	☐
Five or six days a week	☐
Three or four days a week	☐
Once or twice a week	☐
Once or twice a month	☐
Less than once a month	☐
Not at all in the last six months	☐

8. **On average, how many units of alcohol do you consume per week?**
   (1 unit = ½ pint beer, a pub measure of spirits. A bottle of wine is 9 units)

   Units ☐

9. **Have you ever felt that you should cut down on drinking?**

   Yes ☐
   No ☐

10. **Have people ever annoyed you by criticising your drinking?**

    Yes ☐
    No ☐

11. **Have you ever felt bad or guilty about drinking?**

    Yes ☐
    No ☐

12. **Have you ever taken a drink first thing in the morning to steady your nerves or get rid of a hangover?**

    Yes ☐
    No ☐

Participant ID: _____

We are interested in people's habits and the quality of their sleep.

The following questions relate to your usual sleep habits during the past month only. Our answers should indicate the most accurate reply for the majority of days and nights in the past month.

Please answer all questions.

1. **During the past month, what time have you usually gone to bed at night?**
   Bed time ☐

2. **During the past month, how long (in minutes) has it usually taken you to fall asleep each night?**
   Number of minutes ☐

3. **During the past month, what time have you usually gotten up in the morning?**
   Getting up time ☐

4. **During the past month, how many hours of actual sleep did you get at night? (This may be different from the number of hours you spent in bed).**
   Hours of sleep per night ☐

For each of the remaining questions, please tick one best response. Please answer all questions.

Participant ID: _____

5. **During the past month, how often have you had trouble sleeping because you...**

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
Cannot get to sleep within 30 minutes	☐	☐	☐	☐
Wake up in the middle of the night or early morning	☐	☐	☐	☐
Have to get up to use the bathroom	☐	☐	☐	☐
Cannot breathe comfortably	☐	☐	☐	☐
Cough or snore loudly	☐	☐	☐	☐
Feel too cold	☐	☐	☐	☐
Feel too hot	☐	☐	☐	☐
Have bad dreams	☐	☐	☐	☐
Have pain	☐	☐	☐	☐
Other reasons	☐	☐	☐	☐

Please describe 'other reasons'

6. **During the past month, how would you rate your sleep quality overall?**

Very good ☐
Fairly good ☐
Fairly bad ☐
Very bad ☐

7. **During the past month, how often have you had to take medicine to help you sleep (prescribed or "over-the-counter")?**

Not during the past month ☐
Less than once a week ☐
Once or twice a week ☐
Three or more times a week ☐

Participant ID: _____

8. **During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?**

- ☐ Not during the past month
- ☐ Less than once a week
- ☐ Once or twice a week
- ☐ Three or more times a week

9. **During the past month, how much of a problem has it been for you to keep enough enthusiasm to get things done?**

- ☐ No problem at all
- ☐ Only a very slight problem
- ☐ Somewhat of a problem
- ☐ A very big problem

10. **Do you have a bed partner or room-mate?**

- ☐ No bed partner or room-mate
- ☐ Partner/room-mate in other room
- ☐ Partner in same room, but not same bed
- ☐ Partner in same bed

11. **If you have a room-mate or bed partner, please ask him/her how often in the past month you have had...**

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
Loud snoring	☐	☐	☐	☐
Long pauses between breaths while asleep	☐	☐	☐	☐
Legs twitching or jerking while you sleep	☐	☐	☐	☐
Episodes of disorientation or confusion during sleep	☐	☐	☐	☐
Other restlessness while you sleep	☐	☐	☐	☐

Please describe 'other restlessness while you sleep'

Participant ID: _____

The next questions ask about how you feel about different aspects of your life.

1. **For each of the statements below, please indicate the extent to which they apply to your situation, the way you feel now. Please tick the box beside the most appropriate answer.**

	Yes	More or less	No
I feel a general sense of emptiness.	☐	☐	☐
I miss having people around.	☐	☐	☐
I often feel rejected.	☐	☐	☐
There are plenty of people I can rely on when I have problems.	☐	☐	☐
There are many people I can trust completely.	☐	☐	☐
There are enough people I feel close to.	☐	☐	☐

2. **How often do you find that you are bored, or have time on your hands that you don't know how to fill?**

Very often ☐
Quite often ☐
Not that often ☐
Not at all ☐

Participant ID: _____

The next few questions ask about caregiving.

1. **In the last 12 months, have you provided unpaid care to a relative or friend to help them take care of themselves?**

   Yes ☐

   No ☐ ***Go to Page 15***

2. **Are you currently providing unpaid help to a relative or friend, or was this something you did in the past 12 months but are no longer doing?**

   Currently doing so ☐

   In the past 12 months, but no longer doing ☐

3. **What is the relationship of the person you care for to you?**

   Spouse/Partner ☐

   Child/Adopted Child ☐

   Step-Child ☐

   Child in law (daughter in law/son in law) ☐

   Parent ☐

   Parent in law ☐

   Brother or Sister ☐

   Brother in law/Sister in law ☐

   Grandparent ☐

   Grandparent-in-law ☐

   Other blood relative ☐

   Other in-law ☐

   Grandchild ☐

   Non-relative ☐

4. **Where do you and the person you care for live?**

   In the same household ☐

   Within 20 minutes of your home ☐

   Between 20 minutes and 1 hour from your home ☐

   A 1-2 hour drive from your home ☐

   More than 2 hours away ☐

Participant ID: _____

5. **In total, how long have you provided care for this person?**

   Years ☐

   Months ☐

6. **Thinking of all of the kinds of help you provide for the person you care for, about how many hours do you spend in an average week, doing these things?**

   Hours ☐

Participant ID: _____

We would like to ask you some questions about participation in social activities.

1. How often, if at all, do you do any of the following activities?

Please tick one box per line.	Daily/ Almost Daily	Once a week or more	Twice a month or more	About once a month	Every few months	About once or twice a year	Less than once a year	Never
Watch television.	☐	☐	☐	☐	☐	☐	☐	☐
Go out to films, plays and concerts.	☐	☐	☐	☐	☐	☐	☐	☐
Attend classes and lectures.	☐	☐	☐	☐	☐	☐	☐	☐
Travel for pleasure.	☐	☐	☐	☐	☐	☐	☐	☐
Work in the garden, or your home, or on a car.	☐	☐	☐	☐	☐	☐	☐	☐
Read books or magazines for pleasure.	☐	☐	☐	☐	☐	☐	☐	☐
Listen to music, radio.	☐	☐	☐	☐	☐	☐	☐	☐
Spend time on hobbies or creative activities.	☐	☐	☐	☐	☐	☐	☐	☐
Play cards, bingo, games in general.	☐	☐	☐	☐	☐	☐	☐	☐
Go to the pub.	☐	☐	☐	☐	☐	☐	☐	☐
Eat out of the house.	☐	☐	☐	☐	☐	☐	☐	☐
Participate in sport activities or exercise.	☐	☐	☐	☐	☐	☐	☐	☐
Visits to or from family or friends, either in person or talking on the phone.	☐	☐	☐	☐	☐	☐	☐	☐
Do voluntary work.	☐	☐	☐	☐	☐	☐	☐	☐

Appendix H: Data cleaning logs

Table A.H.1: Chapter 3 Dataset; Chapter 4 Dataset 1: Invalid data

Variable	ID	Describe how problem with data identified	Value	Action taken
CTdiff	00956	Descriptive stats – out of range score[1]	-224	Recoded to missing
CTdiff	00730	Descriptive stats – out of range score[1]	-50	Recoded to missing
CTdiff	00420	Descriptive stats – out of range score[1]	-25	Recoded to missing
CTdiff	00228	Descriptive stats – out of range score[1]	-23	Recoded to missing
CTdiff	00361	Descriptive stats – out of range score[1]	-16	Recoded to missing
CTdiff	00885	Descriptive stats – out of range score[1]	-14	Recoded to missing
CTdiff	00004	Descriptive stats – out of range score[1]	-19	Recoded to missing
CTdiff	00927	Descriptive stats – out of range score[1]	-8	Recoded to missing
CTdiff	00514	Descriptive stats – out of range score[1]	-7	Recoded to missing
CT2time	00956	Descriptive stats – out of range score[1]	61	Recoded to missing
CT2time	00730	Descriptive stats – out of range score[1]	95	Recoded to missing
CT2time	00420	Descriptive stats – out of range score[1]	56	Recoded to missing
CT2time	00228	Descriptive stats – out of range score[1]	33	Recoded to missing
CT2time	00361	Descriptive stats – out of range score[1]	68	Recoded to missing
CT2time	00885	Descriptive stats – out of range score[1]	94	Recoded to missing
CT2time	00004	Descriptive stats – out of range score[1]	91	Recoded to missing
CT2time	00927	Descriptive stats – out of range score[1]	75	Recoded to missing
CT2time	00514	Descriptive stats – out of range score[1]	68	Recoded to missing
CT1time	00956	Descriptive stats – out of range score[1]	285	Recoded to missing
CT1time	00730	Descriptive stats – out of range score[1]	145	Recoded to missing
CT1time	00420	Descriptive stats – out of range score[1]	81	Recoded to missing
CT1time	00228	Descriptive stats – out of range score[1]	56	Recoded to missing
CT1time	00361	Descriptive stats – out of range score[1]	84	Recoded to missing
CT1time	00885	Descriptive stats – out of range score[1]	108	Recoded to missing
CT1time	00004	Descriptive stats – out of range score[1]	100	Recoded to missing
CT1time	00927	Descriptive stats – out of range score[1]	83	Recoded to missing
CT1time	00514	Descriptive stats – out of range score[1]	75	Recoded to missing
CT2time	00677	Descriptive stats – out of range score[2]	250	Recoded to 240
CT2time	01159	Descriptive stats – out of range score[2]	252	Recoded to 240
CT2time	00633	Descriptive stats – out of range score[2]	260	Recoded to 240
CT2time	00666	Descriptive stats – out of range score[2]	265	Recoded to 240
CT2time	00953	Descriptive stats – out of range score[2]	266	Recoded to 240
CT2time	00273	Descriptive stats – out of range score[2]	298	Recoded to 240
CT2time	00595	Descriptive stats – out of range score[2]	332	Recoded to 240

Note: CTdiff = Colour Trails Test difference score; CT1time = time to complete Colour Trails Test 1; CT2time = time to complete Colour Trails Test 2
[1]Negative value for CTT difference score (CTT2 – CTT1) indicates invalid data; [2]Considered out of range based on normative data

Table A.H.2: Chapter 3 Dataset: Multivariate outliers

Identification methods	ID	Reason for outlier	Action
MD^2 $p < 0.001$	00135	MV outlier	Case removed from analysis
MD^2 $p < 0.001$	00206	MV outlier	Case removed from analysis
MD^2 $p < 0.001$	00229	MV outlier	Case removed from analysis
MD^2 $p < 0.001$	00258	MV outlier	Case removed from analysis
MD^2 $p < 0.001$	00265	MV outlier	Case removed from analysis
MD^2 $p < 0.001$	00285	MV outlier	Case removed from analysis
MD^2 $p < 0.001$	00330	MV outlier	Case removed from analysis
MD^2 $p < 0.001$	00375	MV outlier	Case removed from analysis

MD^2 p < 0.001	00397	MV outlier	Case removed from analysis
MD^2 p < 0.001	00400	MV outlier	Case removed from analysis
MD^2 p < 0.001	00490	MV outlier	Case removed from analysis
MD^2 p < 0.001	00598	MV outlier	Case removed from analysis
MD^2 p < 0.001	00670	MV outlier	Case removed from analysis
MD^2 p < 0.001	00730	MV outlier	Case removed from analysis
MD^2 p < 0.001	00810	MV outlier	Case removed from analysis
MD^2 p < 0.001	00848	MV outlier	Case removed from analysis
MD^2 p < 0.001	00892	MV outlier	Case removed from analysis
MD^2 p < 0.001	00943	MV outlier	Case removed from analysis
MD^2 p < 0.001	00986	MV outlier	Case removed from analysis
MD^2 p < 0.001	01092	MV outlier	Case removed from analysis
MD^2 p < 0.001	01166	MV outlier	Case removed from analysis
MD^2 p < 0.001	01194	MV outlier	Case removed from analysis
MD^2 p < 0.001	01207	MV outlier	Case removed from analysis
MD^2 p < 0.001	01219	MV outlier	Case removed from analysis

Note: MD^2 p < 0.001 = Cases for which the probability associated with Mahalanobis D2 (MD2) value was 0.0001 and therefore considered to be multivariate outliers

Table A.H.3: Chapter 3 Dataset: Results of Mardia's test of multivariate skewness and kurtosis

	Multivariate skewness		Multivariate kurtosis	
Imputed Dataset	γ1	*p*	γ2	*p*
1	295.41	<.001	1706.47	<.001
2	298.63	<.001	1709.31	<.001
3	297.26	<.001	1706.71	<.001
4	294.33	<.001	1702.16	<.001
5	293.72	<.001	1706.73	<.001
6	298.04	<.001	1708.80	<.001
7	298.08	<.001	1709.36	<.001
8	300.59	<.001	1710.48	<.001
9	299.94	<.001	1710.76	<.001
10	299.09	<.001	1708.08	<.001

Table A.H.4: Chapter 3 Dataset: Results of Henze-Zirekler's multivariate normality tests

Imputed Dataset	HZ	*p*
1	1.00	<.001
2	1.00	<.001
3	1.00	<.001
4	1.00	<.001
5	1.00	<.001
6	1.00	<.001
7	1.00	<.001
8	1.00	<.001
9	1.00	<.001
10	1.00	<.001

Table A.H.5: Chapter 3 Dataset: Results of Royston's multivariate normality tests

Imputed Dataset	H	*p*
1	2808.85	<.001
2	2818.91	<.001
3	2820.13	<.001
4	2811.89	<.001
5	2815.02	<.001
6	2808.20	<.001
7	2818.25	<.001
8	2831.26	<.001
9	2836.17	<.001
10	2812.28	<.001

Table A.H.6: Chapter 4 Dataset 2: Invalid data

Variable	**ID**	**Describe how problem with data identified**	**Value**	**Action taken**
CTdiff	00004	Descriptive stats – out of range score[1]	-9	Recoded to missing
CTdiff	00228	Descriptive stats – out of range score[1]	-23	Recoded to missing
CT1time	00004	Descriptive stats – out of range score[1]	100	Recoded to missing
CT1time	00228	Descriptive stats – out of range score[1]	56	Recoded to missing
CT2time	00004	Descriptive stats – out of range score[1]	91	Recoded to missing
CT2time	00228	Descriptive stats – out of range score[1]	33	Recoded to missing
F1_CT2time	00291	Descriptive stats – out of range score[2]	252	Recoded to 240

Note: CTdiff = Colour Trails Test difference score (time 1); CT1time = time to complete Colour Trails Test 1 (time 1); CT2time = time to complete Colour Trails Test 2 (time 1); F1_CT2time = time to complete Colour Trails Test 2 (time 2)
[1]Negative value for CTT difference score (CTT2 – CTT1) indicates invalid data; [2]Considered out of range based on normative data

Table A.H.7: Chapter 6 Sample 1: Invalid data

Variable	**ID**	**Describe how problem with data identified**	**Value**	**Action taken**
CTdiff	00956	Descriptive stats – out of range score[1]	-224	Recoded to missing
CTdiff	00730	Descriptive stats – out of range score[1]	-50	Recoded to missing
CTdiff	00420	Descriptive stats – out of range score[1]	-25	Recoded to missing
CTdiff	00228	Descriptive stats – out of range score[1]	-23	Recoded to missing
CTdiff	00361	Descriptive stats – out of range score[1]	-16	Recoded to missing
CTdiff	00885	Descriptive stats – out of range score[1]	-14	Recoded to missing
CTdiff	00004	Descriptive stats – out of range score[1]	-19	Recoded to missing
CTdiff	00927	Descriptive stats – out of range score[1]	-8	Recoded to missing
CTdiff	00514	Descriptive stats – out of range score[1]	-8	Recoded to missing
CT2time	00956	Descriptive stats – out of range score[1]	61	Recoded to missing
CT2time	00730	Descriptive stats – out of range score[1]	95	Recoded to missing
CT2time	00420	Descriptive stats – out of range score[1]	56	Recoded to missing
CT2time	00228	Descriptive stats – out of range score[1]	33	Recoded to missing
CT2time	00361	Descriptive stats – out of range score[1]	68	Recoded to missing
CT2time	00885	Descriptive stats – out of range score[1]	94	Recoded to missing
CT2time	00004	Descriptive stats – out of range score[1]	91	Recoded to missing
CT2time	00927	Descriptive stats – out of range score[1]	75	Recoded to missing
CT2time	00514	Descriptive stats – out of range score[1]	68	Recoded to missing
CT1time	00956	Descriptive stats – out of range score[1]	285	Recoded to missing
CT1time	00730	Descriptive stats – out of range score[1]	145	Recoded to missing
CT1time	00420	Descriptive stats – out of range score[1]	81	Recoded to missing

CT1time	00228	Descriptive stats – out of range score[1]	56	Recoded to missing
CT1time	00361	Descriptive stats – out of range score[1]	84	Recoded to missing
CT1time	00885	Descriptive stats – out of range score[1]	108	Recoded to missing
CT1time	00004	Descriptive stats – out of range score[1]	100	Recoded to missing
CT1time	00927	Descriptive stats – out of range score[1]	83	Recoded to missing
CT1time	00514	Descriptive stats – out of range score[1]	75	Recoded to missing
CT2time	00677	Descriptive stats – out of range score[2]	250	Recoded to 240
CT2time	01159	Descriptive stats – out of range score[2]	252	Recoded to 240
CT2time	00633	Descriptive stats – out of range score[2]	260	Recoded to 240
CT2time	00666	Descriptive stats – out of range score[2]	265	Recoded to 240
CT2time	00953	Descriptive stats – out of range score[2]	266	Recoded to 240
CT2time	00273	Descriptive stats – out of range score[2]	298	Recoded to 240
CT2time	00595	Descriptive stats – out of range score[2]	332	Recoded to 240

Note: CTdiff = Colour Trails Test difference score; CT1time = time to complete Colour Trails Test 1; CT2time = time to complete Colour Trails Test 2
[1]Negative value for CTT difference score (CTT2 – CTT1) indicates invalid data; [2]Considered out of range based on normative data

Table A.H.8: Chapter 6 Sample 2: Invalid data

Variable	ID	Describe how problem with data identified	Value	Action taken
CTdiff	00956	Descriptive stats – out of range score[1]	-224	Recoded to missing
CTdiff	00730	Descriptive stats – out of range score[1]	-50	Recoded to missing
CTdiff	00420	Descriptive stats – out of range score[1]	-25	Recoded to missing
CTdiff	00228	Descriptive stats – out of range score[1]	-23	Recoded to missing
CTdiff	00361	Descriptive stats – out of range score[1]	-16	Recoded to missing
CTdiff	00885	Descriptive stats – out of range score[1]	-14	Recoded to missing
CTdiff	00004	Descriptive stats – out of range score[1]	-19	Recoded to missing
CTdiff	00927	Descriptive stats – out of range score[1]	-8	Recoded to missing
CTdiff	00514	Descriptive stats – out of range score[1]	-8	Recoded to missing
CT2time	00956	Descriptive stats – out of range score[1]	61	Recoded to missing
CT2time	00730	Descriptive stats – out of range score[1]	95	Recoded to missing
CT2time	00420	Descriptive stats – out of range score[1]	56	Recoded to missing
CT2time	00228	Descriptive stats – out of range score[1]	33	Recoded to missing
CT2time	00361	Descriptive stats – out of range score[1]	68	Recoded to missing
CT2time	00885	Descriptive stats – out of range score[1]	94	Recoded to missing
CT2time	00004	Descriptive stats – out of range score[1]	91	Recoded to missing
CT2time	00927	Descriptive stats – out of range score[1]	75	Recoded to missing
CT2time	00514	Descriptive stats – out of range score[1]	68	Recoded to missing
CT1time	00956	Descriptive stats – out of range score[1]	285	Recoded to missing
CT1time	00730	Descriptive stats – out of range score[1]	145	Recoded to missing
CT1time	00420	Descriptive stats – out of range score[1]	81	Recoded to missing
CT1time	00228	Descriptive stats – out of range score[1]	56	Recoded to missing
CT1time	00361	Descriptive stats – out of range score[1]	84	Recoded to missing
CT1time	00885	Descriptive stats – out of range score[1]	108	Recoded to missing
CT1time	00004	Descriptive stats – out of range score[1]	100	Recoded to missing
CT1time	00927	Descriptive stats – out of range score[1]	83	Recoded to missing
CT1time	00514	Descriptive stats – out of range score[1]	75	Recoded to missing
F1_CTdiff	00206	Descriptive stats – out of range score[1]	-1	Recoded to missing
F1_CT2time	00206	Descriptive stats – out of range score[1]	79	Recoded to missing
F1_CT1time	00206	Descriptive stats – out of range score[1]	80	Recoded to missing

Note: CTdiff = Colour Trails Test difference score (time 1); CT1time = time to complete Colour Trails Test 1 (time 1); CT2time = time to complete Colour Trails Test 2 (time 1); F1_CT2time = time to complete Colour Trails Test 2 (time 2)
[1]Negative value for CTT difference score (CTT2 – CTT1) indicates invalid data; [2]Considered out of range based on normative data

Appendix I: Model 1 Parameter Estimates

Parameter	*B*	SE	*p*	*β*
	Measurement Model			
Loadings				
CR → Education[1]	1.00			0.41
CR → NART	3.92	0.42	<.001	0.87
CR → WRAT-3	1.94	0.24	<.001	0.74
CR → OCC	11.65	1.94	<.001	0.31
CR → Leisure activity	1.05	0.36	.004	0.17
EXEC → Visual reasoning[1]	1.00			0.41
EXEC → LNS	3.21	0.40	<.001	0.55
EXEC → Category fluency	5.63	0.83	<.001	0.46
EXEC → CTT difference	2.47	2.66	.352	0.04
EXEC → CTT 2 time	-37.32	5.34	<.001	-0.51
MEM → LMI immediate recall[1]	1.00			0.91
MEM → LMII delayed recall	1.07	0.05	<.001	0.92
MEM → LMII recognition	0.48	0.03	<.001	0.58
Uniquenesses				
Education	9.16	0.63		0.84
NART	9.21	1.63		0.25
WRAT-3	5.69	1.51		0.46
Occupational complexity	2374.81	160.11		0.91
Leisure activity	63.64	4.17		0.97
Visual reasoning	1.10	0.07		0.83
LNS	5.40	0.46		0.70
Category fluency	26.65	1.66		0.79
CTT difference	781.87	73.97		0.99
CTT 2 time	873.50	83.89		0.74
LMI immediate recall	1.31	0.24		0.18
LMII delayed recall	1.23	0.27		0.15
LMII recognition	2.74	0.22		0.66
	Structural Model			
Paths				
Age → EXEC	-8.04	1.20	<.001	-0.56
Age → MEM	-0.22	0.12	.058	-0.08
CR → EXEC	1.70	0.29	<.001	0.60
CR → MEM	0.02	0.03	.511	0.03
Co-variances				
Age ↔ CR	3.45	0.49	<.001	0.57
EXEC ↔ MEM	-0.04	0.06	.528	-0.03
Disturbances (Variances)				
Age	31.98	2.65		0.69
CR	1.16	0.26		0.64
EXEC	0.22	0.05		1.00
MEM	5.97	0.49		1.00

Note: CR = cognitive reserve; CTT = Colour Trails Test; EXEC = executive function; LMI = WMS-IV Logical Memory I subtest; LMII = WMS-IV Logical Memory II subtest; LNS = WMS-II Letter Number Sequencing subtest; MEM = memory; NART = National Adult Reading Test; OCC = occupational complexity; WRAT-3 = Wide Range Achievement Test-3 Reading subtest.
[1]Parameter fixed at 1.0 to identify variance of latent variable

Appendix J: Model 2 Parameter Estimates

Parameter	*B*	SE	*p*	*β*
	Measurement Model			
Loadings				
CR → Education[1]	1.00			0.41
CR → NART	3.87	0.42	<.001	0.86
CR → WRAT-3	1.94	0.24	<.001	0.74
CR → OCC	11.67	1.94	<.001	0.31
CR → Leisure activity	1.05	0.40	.004	0.18
EXEC → Visual reasoning[1]	1.00			0.41
EXEC → LNS	3.19	0.39	<.001	0.55
EXEC → Category fluency	5.58	0.82	<.001	0.46
EXEC → CTT difference	2.51	2.63	.339	0.04
EXEC → CTT 2 time	-37.07	5.26	<.001	-0.51
MEM → LMI immediate recall[1]	1.00			0.91
MEM → LMII delayed recall	1.07	0.05	<.001	0.92
MEM → LMII recognition	0.48	0.03	<.001	0.58
INT → Age*Education[1]	1.00			0.45
INT → Age*NART	3.53	0.68	<.001	0.80
INT → Age*WRAT-3	1.77	0.38	<.001	0.76
INT → Age*OCC	9.60	2.96	.001	0.26
INT → Age*Leisure activity	1.02	0.82	.217	0.17
Uniquenesses				
Education	9.14			0.83
NART	9.58			0.26
WRAT-3	5.62			0.45
OCC	2,371.52			0.91
Leisure activity	63.62			0.97
Visual reasoning	1.10			0.83
LNS	5.40			0.70
Category fluency	26.70			0.79
CTT difference	781.81			0.99
CTT 2 time	873.96			0.74
LMI immediate recall	1.32			0.18
LMII delayed recall	1.22			0.15
LMII recognition	2.74			0.66
Age*Education	408.09			0.80
Age*NART	702.00			0.36
Age*WRAT-3	236.55			0.43
Age*OCC	128,641.21			0.93
Age*Leisure activity	3,484.78			0.97
	Structural Model			
Paths				
Age → EXEC	-7.99	1.19	<.001	-0.56
Age → MEM	-0.22	0.12	.058	-0.08
CR → EXEC	1.70	0.29	<.001	0.60
CR → MEM	0.02	0.03	.509	0.03
INT → EXEC	2.58	2.24	.248	0.12
INT → MEM	-0.21	0.19	.269	-0.05
Co-variances				
Age ↔ CR	3.47	0.49	<.001	0.57

Age ↔ INT	1.91	3.79	.613	0.03
CR ↔ INT	0.65	1.11	.559	0.57
EXEC ↔ MEM	-0.04	0.06	.525	-0.03
Disturbances (Variances)				
Age	31.97			0.69
CR	1.16			0.64
EXEC	0.23			1.00
MEM	5.97			1.00
INT	99.79			0.98

Note: CR = cognitive reserve; CTT = Colour Trails Test; EXEC = executive function; INT = Age x CR Interaction; LM1 = Logical Memory I; LM2 = Logical Memory II; LNS = WMS-II Letter Number Sequencing subtest MEM = memory; NART = National Adult Reading Test; OCC = Occupational complexity; WRAT-3 = Wide Range Achievement Test-3 Reading subtest
[1]Parameter fixed at 1.0 to identify variance of latent variable